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RESEARCH ARTICLE | *Physical Activity and Inactivity*

Microvascular adaptations to resistance training are independent of load in resistance-trained young men

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Holloway TM, Morton RW, Oikawa SY, McKellar S, Baker SK, Phillips SM. Microvascular adaptations to resistance training are independent of load in resistance-trained young men. *Am J Physiol Regul Integr Comp Physiol* 315: R267–R273, 2018. First published June 13, 2018; doi:10.1152/ajpregu.00118.2018.—Resistance training promotes microvasculature expansion; however, it remains unknown how different resistance training programs contribute to angiogenesis. Thus, we recruited experienced resistance-trained participants and determined the effect of 12 wk of either high-repetition/low-load or low-repetition/high-load resistance training performed to volitional fatigue on muscle microvasculature. Twenty men performed either a high-repetition [20–25 repetitions, 30–50% of 1-repetition maximum (1RM); $n = 10$] or a low-repetition (8–12 repetitions, 75–90% of 1RM; $n = 10$) resistance training program. Muscle biopsies were taken before and after resistance training, and immunohistochemistry was used to assess fiber type (I and II)-specific microvascular variables. High-repetition/low-load and low-repetition/high-load groups were not different in any variable before resistance training. Both protocols resulted in an increase in capillarization. Specifically, after resistance training, the capillary-to-fiber ratio, capillary contacts, and capillary-to-fiber perimeter exchange index were elevated, and sharing factor was reduced. These data demonstrate that resistance training performed to volitional failure, using either high repetition/low load or low repetition/high load, induced similar microvascular adaptations in recreationally resistance-trained young men.

capillary; health; resistance training; skeletal muscle

INTRODUCTION

Resistance training represents a powerful stimulus responsible for increases in muscle mass and strength in both young (10, 13) and old (6, 21) persons. Investigations to date have focused on two forms of resistance training: high repetition/low load and low repetition/high load, the former being associated with greater gains in muscle endurance and the later greater gains in strength and hypertrophy (15). The association of these seemingly divergent skeletal muscle adaptations remains despite more recent evidence that resistance training promotes adaptations commonly considered hallmark for endurance training (e.g., angiogenesis). In support, the expansion of microvascular networks has recently been demonstrated following high-load resistance training in young (10, 14) and older (9, 25) untrained men. Furthermore, resistance training in these studies resulted in improvements in fiber-specific indexes of oxidative potential [e.g., capillary-fiber perimeter exchange (CFPE) index] despite employing a training mode that most closely represents low-repetition/high-load resistance training [80% 1-repetition maximum (1RM), 8–10 repetitions] previously only connected with gains in muscle size and strength. Consequently, whereas an increase in capillarization is a core adaptation to endurance/aerobic training, it remains unclear whether resistance training that is more "aerobic" in nature (e.g., high repetition/low load) would result in superior capillary adaptations. Furthermore, it is unknown whether previous resistance training would augment this result as it does with hypertrophy, such that resistance-trained individuals demonstrate a reduced hypertrophic response because of an attenuated capacity to adapt to training (13, 23).

Therefore, the main objective of this study was to investigate whether resistance training with high repetition/low load vs. low repetition/high load would result in comparable microvasculature adaptations in skeletal muscle of previously resistance-trained young men. We hypothesized that microvascular expansion would occur to a greater degree in high-repetition/low-load training compared with low-repetition/high-load training.

METHODS

Subject characteristics. Twenty healthy young (22 ± 2 yr) men who previously participated in resistance training over the past 2 yr (4 ± 2 training sessions/wk) provided written informed consent and were included in this study. This study was reviewed and approved by the Hamilton Integrated Research Ethics Board and conformed to the Tri-Council policy statement on the use of human subjects in research. Participants were a subset of a larger project (13) investigating whether load or systemic hormones mediated gains in resistance training in healthy young men. The trial was registered at https://clinicaltrials.gov as NCT02139865. Inclusion in the current study was dependent on the availability of tissue for immunohistochemical and whole muscle homogenate analysis.

Resistance exercise protocols. Participants were randomized to one of two exercise interventions (high repetition or low repetition). The high-repetition/low-load intervention consisted of three sets of 20–25 repetitions/set, such that the load varied between 30 and 50% of the participant's 1RM. The low-repetition/high-load intervention consisted of three sets of 8–12 repetitions/set, which corresponded to 75–90% of 1RM. Importantly, for both the high repetition/low load and low repetition/high load, each set was performed to volitional failure. Briefly, participants completed 12 wk of full-body resistance training 4 days/wk, the details of which are reported elsewhere (13). 1RM testing was done at baseline and after 3, 6, 9, and 12 wk of

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training in both groups. To optimize muscle mass gains, both the high-repetition/low-load and low-repetition/high-load groups were supplemented with 30 g of whey protein (BioPRO; Daviso Foods, Le Sueur, MN) two times daily, immediately following resistance training (or in the morning on nontraining days) and before sleep.

Muscle biopsy. Muscle biopsies (50–80 mg) were obtained at baseline and after 12 wk of high-repetition/low-load and low-repetition/high-load resistance training. Under fasting conditions and after local anesthesia (1% lidocaine), percutaneous needle biopsies (5-mm Bergstrom needle customized for manual suction) were collected from the vastus lateralis, ~15 cm above the patella (2). Physical activity was avoided for 72 h before the baseline biopsy, and, to prevent acute effects of the last training session, biopsies were performed 72 h later. Biopsy samples were embedded in optimal cutting temperature compound (OCT), frozen in liquid nitrogen-cooled isopentane (Sigma-Aldrich, Dorset, UK), and stored at −80°C for further histochemical analysis. A separate sample was snap-frozen in liquid nitrogen for Western blotting.

Fiber type-specific capillary content. Immunohistochemical staining was performed on OCT-mounted biopies to determine muscle fiber cross-sectional area (CSA) and fiber type-specific skeletal muscle capillarization. Briefly, previously OCT-mounted tissue was cut into 5-μm-thick cryosections using a cryostat at −20°C. Both pre- and postresistance training samples from a given subject were mounted on the same glass slide. To measure fiber type-specific CSA (μm^2) and capillarization, slides were taken from the −80°C freezer and thawed for 30 min at room temperature. After fixation for 5 min with acetone (VWR Scientific), samples were air-dried for 15 min and then incubated for 45 min with CD31 (1:50, M082329; DAKO, Glostrup, Denmark). This was followed by washing (3 × 5 min, 0.05% Tween-PBS) and a 45-min incubation with goat anti-mouse biotin (1:200, VECTBA-2000; Vector Laboratories, Burlingame, CA). Subsequent incubations with Avidin Texas Red (1:400, VECTA-2006; Vector Laboratories) and antibodies against myosin heavy chain (MHC)-I (1:25, A4.840, DSHB) and laminin (1:50, L9393 polyclonal rabbit anti-laminin; Sigma) were performed for 45 min followed by washes. Fluorescent secondary GAMIgM AlexaFluor488 and GARIgG AlexaFluor350 (A-10680 and A-11046, respectively; Thermo Fischer Scientific) were applied for 30 min followed by final washing. Slides were mounted with ProLong Gold (Thermo Fischer Scientific). The staining procedure resulted in images with laminin in blue, MHC-I in green, and CD31 in red.

Images were captured with a Nikon Eclipse 90i microscope at a magnification of ×20 taken with a Photometrics Cool SNAP HQ2 fluorescent camera (Nikon Instruments, Melville, NY), and images were analyzed with ImageJ (National Institutes of Health). For analyses, a minimum of 30 fibers was counted per fiber type, excluding longitudinal fibers. Muscle fiber CSA was determined for each fiber separately using ImageJ software. The following variables were generated after manual counting of capillaries: capillary contacts (CC; no. of capillaries in contact with each fiber), capillary-to-fiber ratio (C/Fi; no. of CC ÷ the mean sharing factor for each fiber), sharing factor (SF; no. of fibers sharing each capillary), capillary density (CD; no. of capillaries/mm^2), and CFPE index (no. of capillaries/1,000-μm perimeter) (8). Averages were calculated separately for type I and II fibers for each subject and time point, with the exception of CD. Representative immunohistochemistry images are shown in Fig. 1.

Western blotting. After muscle homogenization, protein concentration was measured with the Bradford assay (3), and samples, along with a control sample, were prepared at a concentration of 1 μg/μl. Muscle homogenates were separated on criterion gel %TRIS-gels by electrophoresis using SDS-PAGE and transferred to 0.2-μm nitrocellulose membranes (Bio-Rad). Membranes were incubated overnight at 4°C with the following commercially available antibodies: endothelial nitric oxide synthase (eNOS, 1:1,000, ab5589; Abcam), vascular endothelial growth factor (VEGF, 1:1,000, ab46154; Abcam), and oxidative phosphorylation (OXPHOS) (MitoSciences, Eugene, OR).

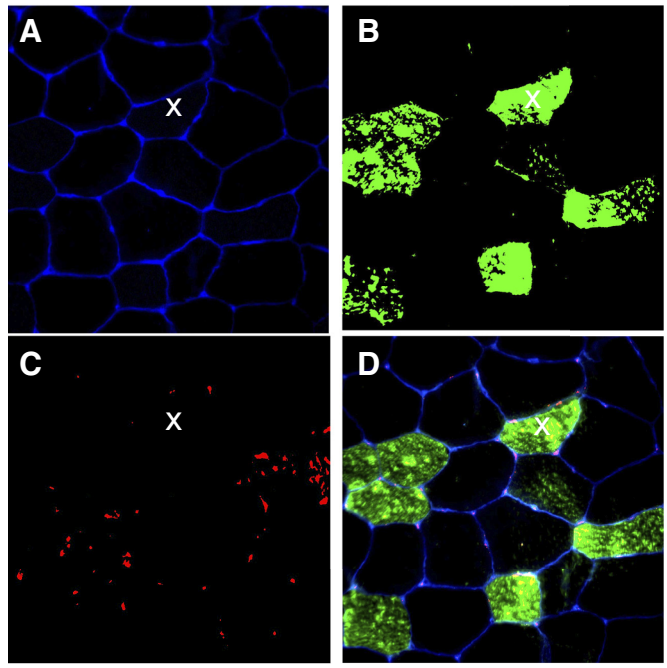

Fig. 1. Representative images of muscle fiber type-specific analyses. *A*: laminin (blue). *B*: myosin heavy chain (MHC)-I (green). *C*: CD31 (red); *D*: MHC-I (green) + laminin (blue) + CD31 (red). "x" depicts the same fiber followed throughout. Color enhancement of different channels has been performed for visual clarity (i.e., after recording and analysis).

After incubation, membranes were washed for 2 × 15 min in 0.05% PBS-Tween 20 and 1 × 15 min with PBS and then were incubated for 1 h at room temperature with the applicable secondary antibodies. A control sample was loaded on each gel, and samples were detected from the same Western blot by cutting gels and transferring to a single membrane where possible to limit variability. Equal loading of protein was verified using Ponceau staining. All samples for a given protein were detected on the same membrane using chemiluminescence and the FluorChem HD imaging system (Alpha Innotech, Santa Clara, CA).

Statistics. All data are expressed as means ± SE. Muscle characteristics were analyzed using repeated-measures ANOVA with time (before vs. after training) and training intervention (high repetition/low load and low repetition/high load) as factors. A Student's *t*-test was used to determine if individual percent changes were significantly different between groups postresistance training. Statistical significance was set at $P < 0.05$. All data were analyzed and graphed using GraphPad Prism for Mac version 7.0 (San Diego, CA). Results are presented as box-and-whisker plots including the median (lines) with interquartile range (boxes) ± range (minimum and maximum), where + indicates mean.

RESULTS

Participant characteristics. Twenty males completed the study (10/group; Table 1). Participants did not differ in age (high repetition/low load: 23 ± 2, low repetition/high load: 22 ± 1), total body mass (high repetition/low load: 87 ± 4, low repetition/high load: 86 ± 2 kg), or body mass index (high repetition/low load: 26.2 ± 2, low repetition/high load: 26.5 ± 2 kg/m^2) at baseline. Subjects self-reported resistance training for at least the past 2 yr [4 ± 2 yr, training 2 sessions/wk (range 3–6 days/wk)] (13), including at least one weekly dedicated lower-body session.

Table 1. *Participant and skeletal muscle characteristics before and after 12 wk of HR or LR resistance training*

	High Repitition/Low Load (n = 10)		Low Repitition/High Load (n = 10)		Individual % Change, HR	Individual % Change, LR	P Values, % Change
	Pre	Post	Pre	Post			
Age, yr	23 ± 2		22 ± 1				
Strength characterization (1RM), kg							
Bench press	91 ± 6	100 ± 6*	95 ± 6	110 ± 5*	10 ± 2.2	16 ± 2.6†	0.03
Shoulder press	81 ± 5	104 ± 8*	85 ± 6	110 ± 5*	30 ± 8.3	37 ± 4.7	0.97
Knee extension	71 ± 5	103 ± 5*	79 ± 6	108 ± 6*	45 ± 9.4	42 ± 4.5	0.43
Leg press	307 ± 26	422 ± 22*	363 ± 32	499 ± 35*	38 ± 13	38 ± 5.8	0.85
Muscle characterization							
Fiber CSA							
Type I	6,097 ± 857	8,126 ± 525*	6,066 ± 276	7,099 ± 318*	36 ± 15	25 ± 6.8	0.55
Type II	6,836 ± 739	8,319 ± 99*	7,599 ± 711	9,247 ± 570*	19 ± 9	25 ± 6.9	0.61
SF							
Type I	2.77 ± 0.06	2.66 ± 0.04*	2.72 ± 0.03	2.64 ± 0.03*	−4 ± 1.2	−3 ± 1.7	0.58
Type II	2.88 ± 0.04	2.68 ± 0.02*	2.76 ± 0.05	2.69 ± 0.04*	−6.4 ± 1.0	−2.5 ± 0.8†	0.012
CD	260 ± 35	289 ± 311	287 ± 5	308 ± 31	32 ± 18	25 ± 10	0.93
Fat-free mass (DXA), kg	63 ± 2	64 ± 3	64 ± 3	66 ± 3	2 ± 1	3 ± 1	0.21

Values are means ± SE. HR, high repetition/low load; LR, low repetition/high load; Pre, before; Post, after; 1RM, 1-repetition maximum; CSA, cross-sectional area; SF, sharing factor (no. of fibers sharing each capillary); CD, capillary density (no. of capillaries/mm^2); DXA, dual X-ray absorptiometry. *Significant main effect of time ($P < 0.02$). †Significant difference from HR.

Strength characteristics and body composition. As previously reported (13), both high-repetition/low-load and low-repetition/high-load resistance training resulted in significant strength gains in bench press ($P = 0.04$), shoulder press ($P = 0.0002$), knee extension ($P = 0.0001$), and leg press ($P = 0.001$). Whereas most indexes of strength were similar between groups after training, low-repetition/high-load individuals displayed slightly greater bench press strength gains (%change, Table 1). In this smaller cohort of data from the original study (13), increases in total fat-free mass by dual X-ray absorptiometry did not reach significance (high repetition/low load: 2 ± 1%, low repetition/high load 3 ± 1%, $P = 0.59$; Table 1).

Fiber CSA and capillarization. First, we aimed to characterize the effect of 12 wk of high-repetition/low-load and low-repetition/high-load resistance training on muscle morphology. Muscle fiber CSA increased as a result of both low-repetition/high-load and high-repetition/low-load training interventions in both type I and II fibers (CSA main effect of time: type I, $P = 0.02$ and type II, $P = 0.008$; Table 1), with no difference between groups (CSA interaction effect: type I, $P = 0.69$ and type II, $P = 0.70$), consistent with the entire cohort as previously reported (13). Furthermore, following both high-repetition/low-load and low-repetition/high-load resistance training, C/Fi (main effect of time: type I, $P = 0.0001$ and type II, $P = 0.0001$; Fig. 2, *A* and *B*), CC (main effect of time: type I, $P = 0.02$ and type II $P = 0.0002$; Fig. 2, *D* and *E*), and CFPE index (main effect of time: type I, $P = 0.03$ and type II, $P = 0.001$; Fig. 2, *G* and *H*) increased as a result of training with no difference between groups (interaction effects C/Fi: type I, $P = 0.33$ and type II, $P = 0.07$; CC: type I, $P = 0.51$ and type II, $P = 0.21$; CFPE: type I, $P = 0.26$ and type II, $P = 0.39$; Fig. 2). Training reduced SF in both groups (main time effect: type I, $P = 0.02$ and type II, $P = 0.0001$; Table 1). CD remained unchanged as a result of training (CD main effect of time: $P = 0.20$, interaction effect: $P = 0.74$). These data demonstrate that resistance training performed to volitional failure, using either high repetition/low load and low repetition/high load, induced similar microvascular adaptations in resistance training-experienced young men. However, interaction effects were close to significance for some variables (e.g., interaction effect C/Fi: type II fibers, $P = 0.07$); therefore, we elected to further analyze the capillarization data to determine the potential for subtle group differences to exist by comparing individual percent changes with a Student's *t*-test. Although most parameters were not different between groups, low repetition/high load displayed slightly less reduction in SF, and gains in C/Fi, among type II fibers (Table 1 and Fig. 2*C*).

eNOS and VEGF content. Because of the similar effect of high-repetition/low-load and low-repetition/high-load resistance training on microvascular expansion, we next characterized the effects on angiogenic factors. The protein content of both VEGF and eNOS was increased as a result of resistance training in both groups (main effect of time: VEGF, $P = 0.001$ and eNOS, $P = 0.03$), with no group differences (Fig. 3).

Mitochondrial content. To further asses the effects of both high-repetition/low-load and low-repetition/high-load resistance training programs, we measured the content of OXPHOS protein complexes. Resistance training did not result in changes in any of the complexes (I–V) in either high-repetition/low-load or low-repetition/high-load groups ($P > 0.05$; Fig. 4).

DISCUSSION

In the current study, we provide evidence that 12 wk of both high-repetition/low-load and low-repetition/high-load resistance training results in microvascular expansion in previously resistance-trained healthy young men. C/Fi, CC, and CFPE index all increased, and SF was reduced as a result of both high-repetition/low-load and low-repetition/high-load resistance training in both fiber types. Furthermore, protein contents of VEGF and eNOS increased as a result of training with no between-group differences. Altogether, these data demonstrate that, even in previously resistance-trained young healthy men, both high-repetition/low-load and low-repetition/high-load resistance training results in microvascular expansion.

We, and others, have previously shown both high-repetition/low-load and low-repetition/high-load resistance training augment muscle size to a similar degree, whereas greater strength gains (1RM) are generally observed as a result of low-repeti-

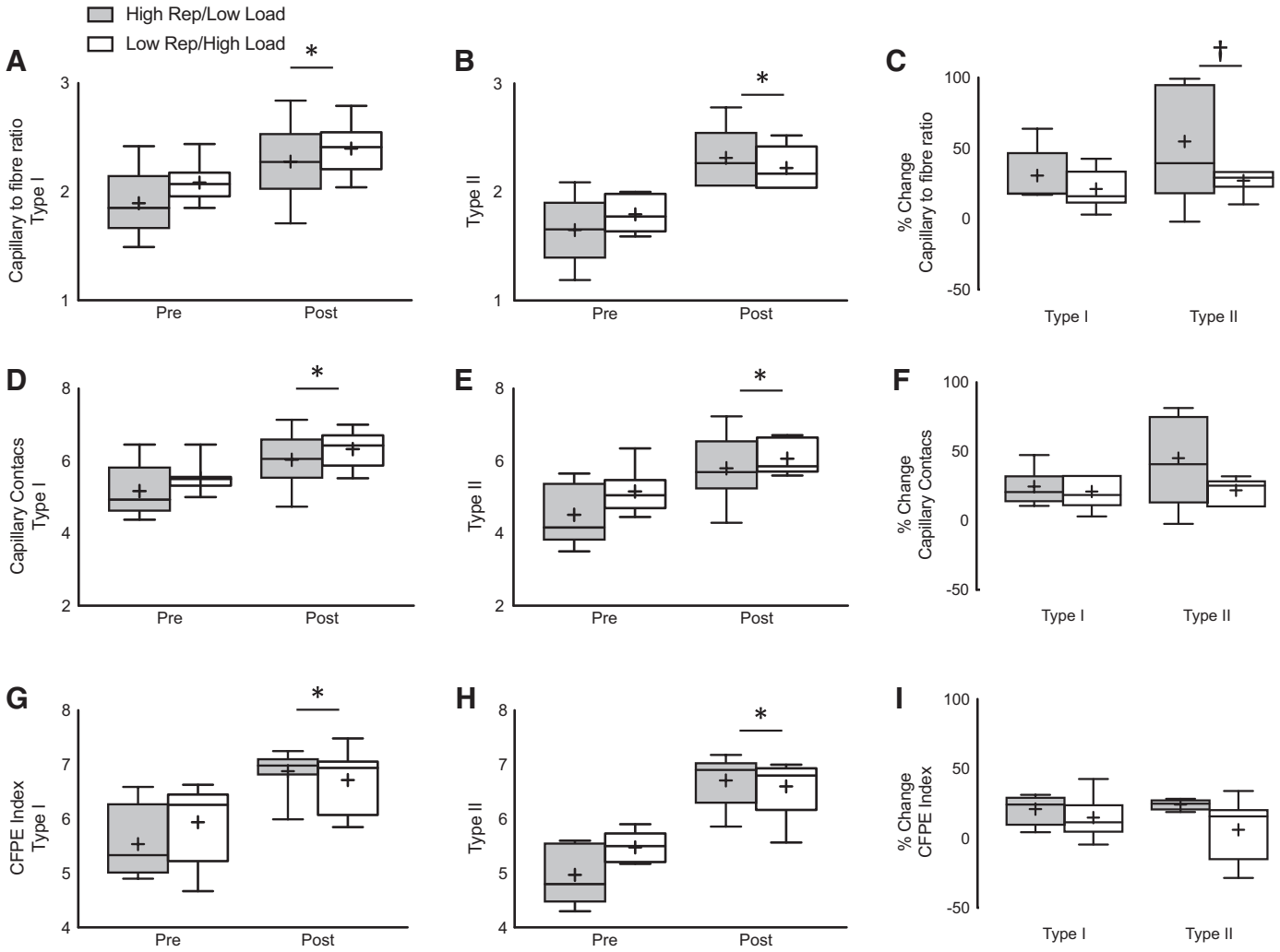

Fig. 2. Fiber type-specific capillary-fiber index ratio (C/Fi; *A* and *B*), capillary contacts (CC; *D* and *E*), and capillary-fiber perimeter exchange (CFPE) index (*G* and *H*) before (Pre) and after (Post) 12 wk of high-repetition/low-load ($n = 10$ men) or low-repetition/high-load ($n = 10$) resistance training and individual percent change in C/Fi (*C*), CC (*F*), and CFPE index (*I*) after training in type I and II fibers. C/Fi, CC, and CFPE were significantly elevated as a result of both training programs. Data are presented as medians (lines) with interquartile ranges (boxes) ± range (minimum and maximum), where + indicates the mean. *Significant main effect of time ($P < 0.02$) from baseline. †Significantly different from high repetition/low load.

tion/high-load training (5, 13, 18). This result has been attributed to greater neural adaptations, or specificity of training, such that low-repetition/high-load training relates more closely to 1RM testing, thereby further improving 1RM compared with high-repetition/low-load training (12). Whereas low-repetition/high-load training may have an advantage at improving 1RM, it is important to note that high-repetition/low-load training elevates 1RM as well (35 vs. 28%, respectively) as presented in a recent meta-analysis (18). The current data, taken together with our previous data that demonstrate similar hypertrophic responses, suggest emphasis should be placed on adapting resistance training programs to suit the needs of the individual with the knowledge similar benefit will arise with either high-repetition/low-load and low-repetition/high-load training.

Capillarization. The capillary represents the key integrator of metabolic stimuli determining the match between demand and delivery of required oxygen and nutrients to skeletal muscle; thus, we aimed to investigate whether differential adaptations would occur as a result of low-repetition/high-load or high-repetition/low-load resistance training on capillarization. We demonstrate that both resistance training programs resulted in angiogenesis in our resistance-trained young men. Although subtle differences are demonstrated in the comparisons of percent change, where high repetition/low load resulted in a greater reduction in SF (type II fibers) and an increase in C/Fi (type II fibers), these adaptations do not appear to translate into differences in overall strength gains, since both groups responded similarly, with the exception of bench press.

Previous evidence that prolonged resistance training resulted in microvascular expansion (10) may have been a result of the training-naïve status of the participants; however, based on our current results, it appears that, whether or not subjects are resistance trained, capillary adaptation occurs. Recent evidence has demonstrated that the microvascular environment plays a critical role in the muscle's ability to adapt to exercise stimuli, such that greater capillary content is associated with a greater hypertrophic response to resistance training (19). Furthermore, because skeletal muscle represents the main site for postprandial glucose disposal, there is little doubt that capillary density determines indexes of metabolic health. Recently, this was

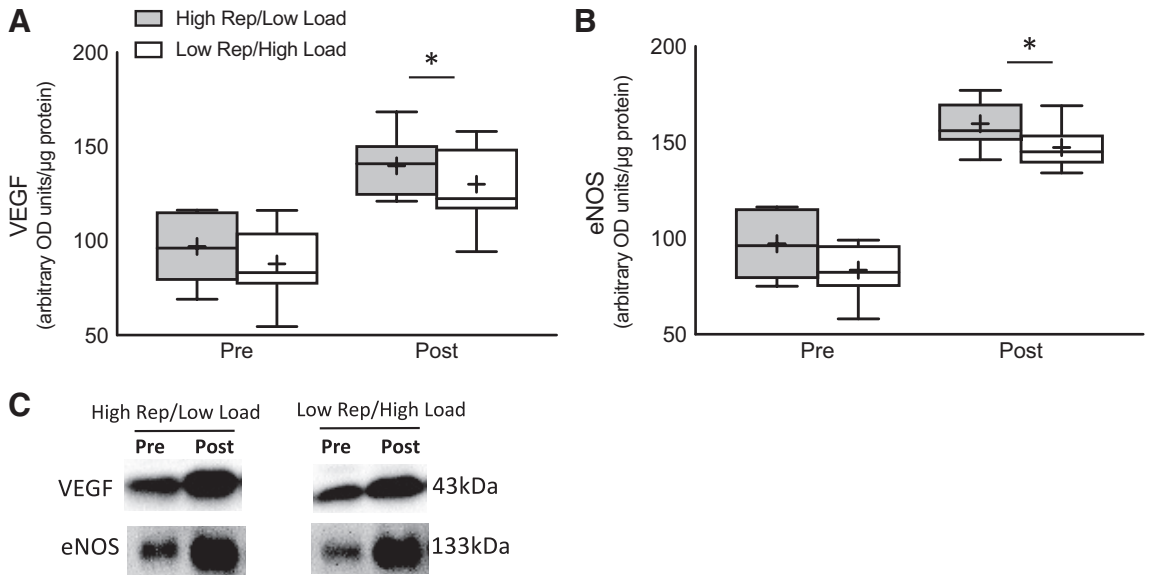

Fig. 3. Western blot analysis of vascular endothelial growth factor (VEGF; *A*) and endothelial nitric oxide synthase (eNOS; *B*) before (Pre) and after (Post) 12 wk of high-repetition/low-load ($n = 10$) or low-repetition/high-load ($n = 10$) resistance training. *A*: 12 wk of both high-repetition/low-load and low-repetition/high-load resistance training resulted in significant increase in VEGF protein in whole muscle homogenate. *B*: 12 wk of both high-repetition/low-load and low-repetition/high-load resistance training resulted in significant increase in eNOS protein in whole muscle homogenate. *C*: representative blots. Data are presented as medians (lines) with interquartile ranges (boxes) ± range (minimum and maximum), where + indicates the mean. *Significant main effect of time ($P < 0.05$).

demonstrated by Snijders and colleagues (20) who saw an attenuated rise in postprandial plasma insulin following an oral glucose tolerance test in older persons with higher capillary density. Therefore, the knowledge that both high-load/low-repetition and low-load/high-repetition training stimulates capillarization provides further support for the inclusion of resistance training to fatigue, regardless of load, in programs aimed at microvascular expansion.

Mitochondrial content. Mitochondrial content by OXPHOS Western blotting did not change following either the high-load/low-repetition and low-load/high-repetition training program in the current study. While the effect of endurance training on mitochondrial biogenesis is evident and has been demonstrated in both young (17) and older muscle (11), the effect of resistance training on mitochondrial biogenesis/content is less clear. A previous study in young healthy resistance exercise-

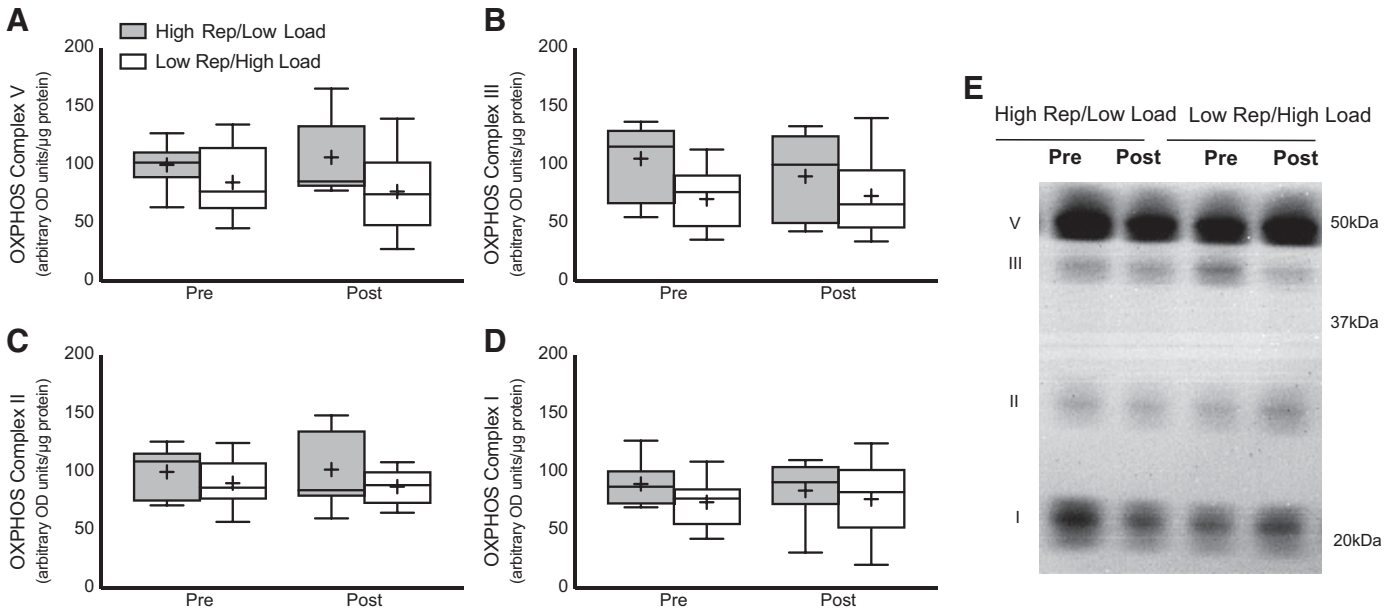

Fig. 4. Mitochondrial content of whole muscle homogenate before (Pre) and after (Post) 12 wk of high-repetition/low-load ($n = 10$) or low-repetition/high-load ($n = 10$) resistance training. *A–D*: 12 wk of both high-repetition/low-load and low-repetition/high-load resistance training resulted in no change in oxidative phosphorylation (OXPHOS) protein contents. *E*: representative blot. Data are presented as medians (lines) with interquartile ranges (boxes) ± range (minimum and maximum), where + indicates the mean.

accustomed males demonstrated an acute bout of high-repetition/low-load resistance exercise performed to volitional fatigue increased mitochondrial protein synthesis rate during both early and later postexercise recovery (4). Chronically, however, the effect of resistance training is less clear, with no long-term data on high repetition/low load and equivocal data on low repetition/high load. Long-term studies on low repetition/high load used untrained men and relied on measures of citrate synthase activity as a marker of mitochondrial content with some positive (22), but mostly equivocal, results (16, 24, 26, 27).

Studies have demonstrated that high-repetition/low-load resistance training results in greater ATP turnover compared with low repetition/high load (1, 7); therefore, it is possible that this enhanced metabolic stress would result in further mitochondrial adaptation. However, in the current study, we were unable to detect a difference between high-repetition/low-load and low-repetition/high-load training programs in terms of mitochondrial adaptation. This result may be because of the training status of our subjects, since the stimulatory effects of resistance exercise on mitochondrial protein synthesis are absent in resistance-trained, but not untrained, muscle. Previous work has demonstrated, before resistance training, both myofibrillar and mitochondrial protein synthesis are stimulated with resistant exercise, whereas, after training, resistance exercise stimulates myofibrillar protein synthesis alone (27). Further work using stable isotopes such as deuterated water to look at cumulative changes to both high-repetition/low-load and low-repetition/high-load resistance training would provide further insight into the effect of resistance training on mitochondria.

In conclusion, we present novel evidence that skeletal muscle capillarization is augmented as a result of both low-repetition/high-load and high-repetition/low-load resistance training in previously resistance-trained young men. Further investigations should focus on whether formally/elite resistance-trained subjects would demonstrate the same results, since the training status of the subjects in the current study was recreational in nature. These findings provide further evidence to support the use of resistance exercise training as a therapeutic tool to increase muscle mass and expand muscle microvasculature.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

T.M.H., R.W.M., S.Y.O., and S.M.P. conceived and designed research; T.M.H., R.W.M., S.Y.O., and S.M. performed experiments; T.M.H., S.M., and S.M.P. analyzed data; T.M.H., S.K.B., and S.M.P. interpreted results of experiments; T.M.H. prepared figures; T.M.H. drafted manuscript; T.M.H., R.W.M., S.Y.O., S.M., S.K.B., and S.M.P. edited and revised manuscript; T.M.H., R.W.M., S.Y.O., S.M., S.K.B., and S.M.P. approved final version of manuscript.

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