

Resistance Training with Vascular Occlusion: Metabolic Adaptations in Human Muscle

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ABSTRACT

BURGOMASTER, K. A., D. R. MOORE, L. M. SCHOFIELD, S. M. PHILLIPS, D. G. SALE, and M. J. GIBALA. Resistance Training with Vascular Occlusion: Metabolic Adaptations in Human Muscle. *Med. Sci. Sports Exerc.*, Vol. 35, No. 7, pp. 1203–1208, 2003. Two recent studies have reported increases in strength and whole muscle cross-sectional area after low-intensity resistance training (LIT) with vascular occlusion (OCC) that are greater than LIT alone (e.g., 22,25). The OCC stress might be expected to induce metabolic alterations that are consistent with compromised oxygen delivery rather than an increase in strength *per se*, but this has not been studied. **Purpose:** We examined the effect of LIT and LIT+OCC on resting metabolites in m. biceps brachii and elbow flexor strength. **Methods:** Eight men (19.5 ± 0.4 yr) performed 8 wk of LIT at ~50% of one-repetition maximum (2 sessions per week; 3–6 sets, 8–10 repetitions, final set to failure); one arm trained with OCC and the other without (CON). **Results:** Biopsies obtained before and 72 h after the final training bout revealed that resting [glycogen] was higher ($P \leq 0.05$) in both arms after LIT (CON: 452 ± 20 vs 325 ± 28 , OCC: 501 ± 12 vs 332 ± 28 mmol·kg⁻¹ dry weight) and the increase was larger in the OCC arm ($P \leq 0.05$). Resting [ATP] was lower ($P \leq 0.05$) after LIT in both arms (CON: 20.5 ± 0.5 vs 22.8 ± 0.7 , OCC: 18.2 ± 0.6 vs 23.1 ± 0.5 mmol·kg⁻¹ dry weight), and the decrease was larger in the OCC arm ($P \leq 0.05$). Maximal isotonic and isokinetic elbow flexor strength increased ($P \leq 0.05$) after training to a similar extent in both arms. **Conclusion:** We conclude that [glycogen] was increased and [ATP] was decreased in resting human muscle, 72 h after an 8-wk LIT protocol. OCC potentiated the metabolic changes, perhaps by inducing an ischemic stimulus that enhanced muscle glucose transport and adenine nucleotide catabolism after LIT, but did not augment the increases in strength. **Key Words:** ADENINE NUCLEOTIDE METABOLISM, FATIGUE, GLYCOGEN, ISCHEMIA, STRENGTH

Relatively brief bouts of resistive-type exercise performed repeatedly over 8–12 wk produce gains in muscle strength and size (14,16). Low-intensity resistance training (LIT; 40–50% of one-repetition maximum, 1-RM) has been shown to increase strength in previously untrained subjects, but it is generally recommended that individuals train with loads $\geq 70\%$ of 1-RM in order to optimize gains in strength and stimulate muscle hypertrophy (11). Recently, two studies reported that LIT combined with moderate vascular occlusion produced gains in strength that were greater than LIT alone and comparable to that achieved after conventional high-intensity resistance training (22,25). Takarada and colleagues (25) reported increases in elbow flexor strength and cross-sectional area in a group of novice, older women after 16 wk of elbow flexor LIT (50% 1-RM) combined with vascular occlusion that were greater than in a group that performed LIT alone and comparable to a group that followed a HIT protocol (80% 1-RM). Another study

(22) reported greater increases in maximal isometric knee extensor torque in one leg after 2 and 4 wk of LIT with tourniquet occlusion compared with the contra lateral leg that performed only LIT. Finally, periodic application of an occlusive stimulus was shown to be effective for ameliorating disuse atrophy in the knee extensor muscles postsurgery (24).

The mechanisms responsible for the purported increases in muscle strength and size after LIT combined with vascular occlusion, as compared with LIT alone, remain speculative. Takarada and colleagues (24,25) suggested that the application of moderate occlusive pressure might produce an intramuscular environment that is similar to that created during heavy-resistance exercise training. Specifically, these authors hypothesized that the occlusive stimulus might produce a transient ischemia and/or alterations in metabolite concentrations, which could lead to an increased recruitment of fast-twitch muscle fibers and hence greater increases in muscle strength and size as compared with LIT alone (24,25). There is little direct evidence to support this hypothesis, however, and recent evidence (30) suggests that the molecular responses to mechanical strain (which would be similar between LIT and LIT with occlusion) are unique from those induced by metabolic strain (which could be different between LIT and LIT with occlusion). Thus, from the perspective of the myocyte, it is plausible that the occlusive stress might induce metabolic alterations that are consistent with compromised oxygen delivery rather than an increase in strength *per se*.

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The potential metabolic changes induced by LIT—with or without vascular occlusion—have not been explored. However, there is equivocal evidence to suggest that conventional heavy resistance training (6,15,26,27) and acute exercise performed under conditions of reduced oxygen availability (20,21) can alter the resting metabolic profile of skeletal muscle. It is also known that patients with peripheral arterial disease, who develop ischemia during exercise, display abnormal muscle metabolic adaptations in response to exercise training (10). Our purpose, therefore, was to assess the effect of LIT on resting energy metabolites in human muscle and, secondly, to determine whether OCC during LIT augmented any potential training-induced adaptations. We hypothesized that (i) LIT would induce an increase in resting [glycogen], due to repeated, transient increases in muscle glucose transport during recovery from exercise (6,19); (ii) LIT would decrease resting [ATP], due to the chronic effect of intense exercise on adenine nucleotide catabolism (8,23); and (iii) vascular occlusion would augment the changes in [glycogen] and [ATP] induced by LIT, due to the additional stress of reduced oxygen delivery on muscle glucose uptake (4) and adenine nucleotide catabolism (21) during recovery. Finally, we assessed changes in elbow flexor strength after LIT and LIT+OCC, in an attempt to confirm the recent observations made by Shinohara et al. (22) and Takarada et al. (25).

METHODS

Subjects. Eight healthy men with a mean (\pm SE) age, height, and body mass of 19.5 ± 0.4 yr, 180 ± 1 cm, and 84.0 ± 4.5 kg, respectively, volunteered to take part in the study. The subjects were “recreationally active” individuals from the undergraduate student population at McMaster University who took part in aerobic activities two to three times per week (e.g., running, cycling, and basketball) but had no formal weight-training experience. After a screening procedure for preexisting medical conditions that might preclude their participation, the subjects were informed of the procedures and risks inherent to the study, and all provided written consent. The experimental protocol was approved by the McMaster University and Hamilton Health Sciences Corporation Research Ethics Board.

Overview of experimental procedures. Subjects initially performed a familiarization trial before the experimental protocol in order to become oriented with all testing procedures and training devices. Subjects were instructed in the proper use of the resistance exercise equipment and also performed several muscle actions using a light load ($<25\%$ of estimated 1-RM) in order to mimic the type of actions to be performed during testing and training. The experimental protocol consisted of (i) baseline measurements of resting muscle energy metabolites in the biceps brachii and elbow flexor strength, (ii) an 8-wk elbow flexor resistance-training program, and (iii) posttraining strength and muscle metabolite measurements that were conducted in an identical manner to the baseline measurements. All testing and training procedures were performed on each arm separately. One

arm was randomly assigned to an “occluded” condition (OCC) such that all training was performed with an occlusion cuff (see below), whereas the other arm performed exercise without occlusion (CON).

Baseline measurements. Subjects reported to the laboratory and rested in an upright, seated position while the upper portion of each arm was anesthetized (1% w/v lignocaine hydrochloride with epinephrine, Antigen Pharmaceuticals Ltd., Ireland) and prepared for the extraction of a single, needle-biopsy sample from the biceps brachii muscle of each arm using manual suction. The biopsy samples were immediately frozen in liquid nitrogen for subsequent analyses of metabolites. Subjects reported back to the laboratory ~72 h after muscle tissue extraction for baseline strength tests.

Assessment of muscular strength. Muscular strength was first assessed by measuring the maximal elbow flexor torque produced by each arm during three, single-maximal repetitions on an isokinetic dynamometer (Biodex Medical Systems Inc., Shirley, NY). Torque production was assessed during both the concentric and eccentric phases of the movement at a velocity of $60^\circ \cdot \text{s}^{-1}$, and the highest value recorded during any of the three repetitions was taken as the peak torque. A velocity of $60^\circ \cdot \text{s}^{-1}$ was selected in order to mimic the protocol employed by Takarada et al. (25). During testing, subjects were stabilized with belts placed over the chest and distal portion of the upper arm, and the rotational axis of the dynamometer was positioned to be coaxial with the elbow axis.

At least 30 min after the assessment of maximal isokinetic elbow flexor torque, maximal isotonic strength was determined using a single-arm curl exercise performed with a cable pulley that was attached to an adjustable weight stack. Subjects were seated in an upright position on a preacher bench, and were instructed to keep both feet flat on the floor and the upper arm flat on the upper pad in order to minimize extraneous movements and isolate work to the elbow flexors. The arm moved through a joint angle from approximately 170° to 70° ($180^\circ =$ full extension). Subjects began with a load that was estimated to be equivalent to 50% 1-RM and continued making single attempts using progressively higher loads (2.5- to 5.0-lb increments) until the peak load was determined. On average, subjects performed four to five attempts, each separated by a 1-min rest interval.

Training protocol. Approximately 48 h after the baseline strength tests, subjects commenced an 8-wk, periodized resistance training protocol, with two sessions performed each week. Training consisted of unilateral elbow flexor resistance exercise using a load equivalent to ~50% of their concentric 1-RM. Subjects performed single-arm curl exercise using the same device that was employed for isotonic strength testing (described above). A metronome was employed, and subjects were instructed to complete the concentric and eccentric phase of the arm curl movement in 2.0 s each. Subjects completed three sets of exercise during the first 2 wk of training: the first two sets consisted of 10 repetitions, followed by a third set to failure, with a 1-min rest interval between sets. Beginning at week 3, the number

of sets performed increased by one set per week until week 5 when a maximum of six sets in total were performed throughout the remainder of the study. For these sessions, a 5-min rest period was permitted between the third and fourth set, and the final set was always performed to failure (i.e., during week 3, the fourth set was performed to failure; during week 4, the fourth set consisted of 10 repetitions; and the fifth set was performed to failure; and during weeks 5–8, the fourth and fifth set consisted of 10 repetitions, and the sixth set was performed to failure). Maximal isotonic strength was reassessed after 2, 4, and 6 wk of training, and loads were adjusted to maintain a training intensity equivalent to ~50% 1-RM.

For all training sets, the OCC arm was exercised first, and the number of repetitions performed by the CON arm was matched to that completed by the OCC arm. All training sessions were supervised by one of the investigators who was familiar with the equipment and its proper use. For the OCC condition, an occlusion cuff (12-cm width) was placed around the upper-arm approximately 2 cm proximal to the biceps brachii, and pneumatically inflated to 100 mm Hg. A cuff pressure of 100 mm Hg was employed in order to restrict venous blood flow outflow and cause pooling of blood in capacitance vessels distal to the cuff, ultimately restricting arterial blood inflow (25). The cuff remained in place and inflated throughout the first set of three sets during each training session. During weeks 3–8 when more than three sets were performed, the cuff was deflated during the 5-min recovery interval after the third set, and then re-inflated and kept in place for the duration of the remaining sets.

Posttraining measurements. Posttraining strength tests were conducted on the final training day (i.e., the second training session of week 8), at least 30 min before the actual training session. This strategy was employed so that the posttraining strength measurements did not interfere with the final muscle biopsy procedure, and also to allow a defined period of rest between the final training session and the biopsy trial. Subjects reported back to the laboratory 72 h after the final training session so that posttraining biopsy samples could be obtained from each arm.

Muscle analyses. Samples of frozen wet muscle were subsequently freeze-dried, powdered, dissected free of non-muscle elements, and stored at -80°C . Aliquots of freeze-dried muscle were extracted with 0.5 M perchloric acid, neutralized with 2.2 M KHCO_3 , and assayed for glycogen, ATP, PCr, and creatine using standard enzymatic methods (7,18). All pre- and posttraining samples from a given subject were analyzed at the same time, and all metabolite measurements were adjusted to the highest total creatine value in order to account for differences in blood or connective tissue between samples.

Nutritional considerations. In an attempt to minimize any potential diet-induced variability in resting muscle metabolite measurements, we instructed subjects to consume the same types and quantities of food for ~36 h before the pre- and posttraining biopsy procedures. Subjects were also asked to record all food intake during these times, and

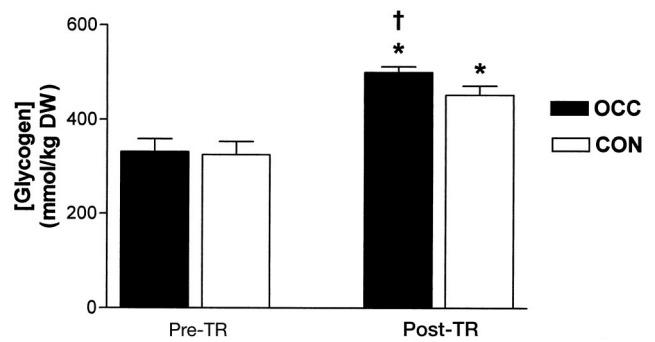


FIGURE 1—Resting muscle glycogen concentration in the occluded arm (OCC) and nonoccluded arm (CON) at baseline (PreTR) and after 8 wk of low-intensity resistance exercise training (PostTR). DW = dry weight. All values are means \pm SE ($N = 8$). * $P \leq 0.05$ vs PreTR for same arm; † $P \leq 0.05$ vs CON PostTR.

compliance was assessed by performing dietary analyses on the individual food records maintained by the subjects. After the pretraining biopsy procedure, the individual food records were photocopied and returned to the subjects 2–3 d before the posttraining biopsy, and subjects were instructed to replicate their individual pattern of food intake. Pre- and posttraining food diaries were analyzed for total energy intake and proportion of energy derived from carbohydrates, fats, and protein (Nutritionist Five, First Data Bank Inc., San Bruno, CA). These analyses confirmed that there was no difference between trials in the total amount of energy consumed or macronutrient proportions (pre- vs posttraining: 50 ± 3 vs $52 \pm 2\%$ CHO, 34 ± 3 vs $33 \pm 1\%$ fat, and 16 ± 3 vs $15 \pm 1\%$ protein).

Statistical analyses. Muscle metabolite and strength data were analyzed using a two-factor (time \times condition) repeated measures analysis of variance. Significant interactions were subsequently analyzed using Tukey's honestly significant difference *post hoc* test. Significance level was set at $P \leq 0.05$. Data are presented as means \pm SE.

RESULTS

Muscle glycogen. The resting intramuscular concentration of glycogen was similar between arms at baseline and increased after training in both arms (Fig. 1). However, the increase in glycogen was greater in the OCC arm compared with CON (169 ± 26 vs 127 ± 29 $\text{mmol}\cdot\text{kg}^{-1}$ dry weight, respectively, $P \leq 0.05$).

Muscle ATP, phosphocreatine, and creatine. There were no differences between arms in the resting concentrations of ATP, PCr, or creatine. However, resting [ATP] was lower after training in both arms (Fig. 2), and the net decrease was larger in the OCC arm compared with CON (4.9 ± 0.5 vs 2.3 ± 0.5 $\text{mmol}\cdot\text{kg}^{-1}$ dry weight, $P \leq 0.05$). Resting [PCr] and [creatinine] were not different in either arm after training (Table 1).

Muscular strength. Maximal isokinetic concentric elbow flexor torque was similar between limbs at baseline and increased by 9.6 and 10.5% for the CON and OCC arms, respectively (main effect for time, $P \leq 0.05$), with no

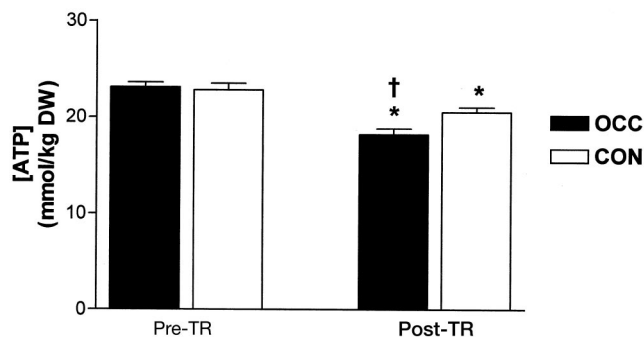


FIGURE 2—Resting muscle adenosine triphosphate (ATP) concentration of the occluded arm (OCC) and nonoccluded arm (CON) at baseline (PreTR) and after 8 wk of low-intensity resistance exercise training (PostTR). DW = dry weight. All values are means \pm SE ($N = 8$). * $P \leq 0.05$ vs PreTR for same arm; † $P \leq 0.05$ vs CON PostTR.

differences between conditions (Fig. 3). Similarly, maximal isotonic elbow flexor strength was not different between limbs at baseline and increased by 23 and 22% for the CON and OCC arms, respectively (main effect for time, $P \leq 0.05$), with no differences between conditions (Fig. 4).

DISCUSSION

The present study demonstrated that 8 wk of elbow flexor LIT altered the resting metabolic profile of human biceps brachii muscle and that application of moderate vascular occlusion during LIT augmented the metabolic changes. Consistent with our hypotheses, the two primary, novel findings from the present study were: (i) resting muscle [glycogen] was increased after LIT and vascular occlusion potentiated this effect; and (ii) resting [ATP] was lower after LIT and vascular occlusion potentiated this effect. In addition, our data indicate that isotonic resistance training using an intensity equivalent to 50% 1-RM was effective for increasing isotonic and isokinetically assessed elbow flexor strength in young, untrained men; however, OCC did not augment this response.

The effect of LIT and vascular occlusion on resting muscle [glycogen]. It is well established that contractile activity can stimulate muscle glucose uptake and thus substrate availability for glycogen resynthesis during recovery (12,19). We did not directly assess muscle glucose uptake in the present study; however, the observed increases in muscle [glycogen] after LIT were likely due in part to chronic, transient increases in the translocation of GLUT-4 transporters to the sarcolemma, which promoted glucose uptake after exercise. Notably, the application of the occlusive stimulus during LIT enhanced muscle glycogen storage, possibly due to alterations in glucose transport induced

TABLE 1. Resting intramuscular phosphocreatine and creatine.

	Occluded Arm (OCC)		Nonoccluded Arm (CON)	
	PreTR	PostTR	PreTR	PostTR
Phosphocreatine	98.2 \pm 6.8	96.5 \pm 7.6	92.3 \pm 2.7	100.7 \pm 6.3
Creatine	48.0 \pm 6.2	49.4 \pm 5.9	53.9 \pm 4.7	45.5 \pm 5.7

All values are means \pm SE ($N = 8$) in millimoles per kilogram dry weight; TR, training.

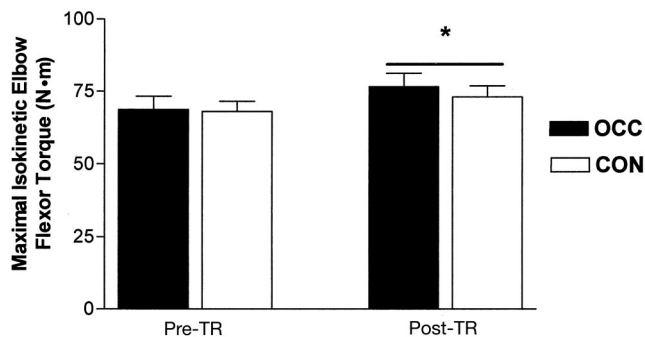


FIGURE 3—Maximal isokinetic concentric elbow flexor torque generated at baseline (PreTR) and after 8 wk of low-intensity resistance exercise training (PostTR) with the occluded (OCC) and nonoccluded arm (CON). All values are means \pm SE ($N = 8$). * $P \leq 0.05$ vs PreTR (main effect for time).

as a result of compromised oxygen delivery. In support of this interpretation, Cartee and colleagues (2) showed that hypoxia stimulated muscle glucose transport by increasing the GLUT-4 translocation, and subsequent studies have confirmed that muscle glucose uptake is enhanced in response to hypoxic conditions (1,5,9). There is also evidence to suggest that the mechanism by which hypoxia stimulates glucose uptake is independent to that of contraction-mediated glucose uptake (4,5,28,29), and thus contractile activity and hypoxia may provide additive stimuli for increased rates of muscle glucose uptake (4,5). Although vascular occlusion does not precisely mimic the stress of hypoxia, it is nonetheless plausible that a reduced rate of oxygen delivery during LIT+OCC potentiated glucose transport during recovery and contributed to the larger increase in resting [glycogen] after training.

In addition to glucose uptake, the rate of muscle glycogen resynthesis after exercise is also determined by the activity of the rate-limiting enzyme glycogen synthase and the availability of blood-borne glucose (3). To our knowledge, no study has directly examined the effect of resistance exercise and ischemia on glycogen synthase activity during recovery in humans. However, Laughlin et al. (13) reported a marked activation of this enzyme during recovery from brief, repeated episodes of hypoxemia in rodent hearts. It is possible,

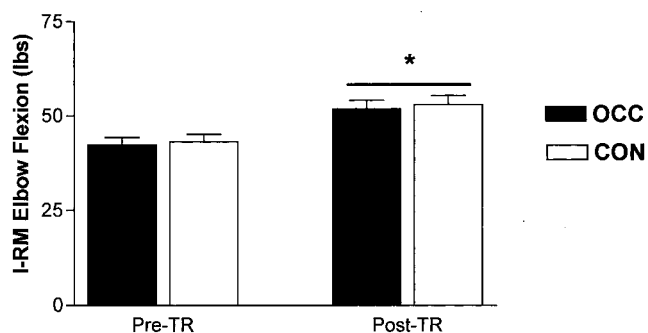


FIGURE 4—Maximal isotonic concentric elbow flexor strength generated at baseline (PreTR) and after 8 wk of low intensity resistance exercise training (PostTR) with the occluded (OCC) and nonoccluded arm (CON). All values are means \pm SE ($N = 8$). * $P \leq 0.05$ vs PreTR (main effect for time).

therefore, that the higher resting glycogen concentration observed posttraining in the OCC arm was also influenced by differences in glycogen synthase activity after exercise. We feel it is unlikely that differences in the availability of blood glucose after exercise markedly influenced the rate of glycogen resynthesis during recovery, because nutritional intake was virtually identical during the 36 h before each biopsy trial.

The effect of LIT and vascular occlusion on resting muscle [ATP]. In most exercise situations, the rate of ATP provision is precisely matched to ATP degradation such that the concentration of ATP remains constant. However, during strenuous exercise, the rate of ATP hydrolysis exceeds the rate of ATP resynthesis, resulting in an accumulation of adenosine diphosphate (ADP) and production of adenosine-monophosphate (AMP) through the near-equilibrium myokinase reaction (17). AMP can be deaminated by AMP deaminase, resulting in the formation of inosine 5'-mono-phosphate (IMP) and ammonia, and subsequent breakdown of IMP to inosine and hypoxanthine results in a loss of adenine nucleotides from the muscle (8). Replacement of purine nucleotides lost from the muscle is a relatively slow, energy-consuming process and appears to continue for several days after intense exercise (8). The lower [ATP] measured in both arms after LIT in the present study may therefore have been due to the stress of chronic training, or the acute residual effects of the final training bout, which was performed 72 h before tissue extraction. Stathis et al. (23) reported a 19% decrease in resting [ATP] after a 7-wk sprint-training program and suggested that the reduction in [ATP] was primarily attributable to the acute effects of the previous exercise session. We also detected a larger net decrease in resting [ATP] in the OCC arm, which suggests that exercise with vascular occlusion placed a greater stress on the adenine nucleotide pool as compared with LIT alone. This interpretation is supported by previous studies that revealed larger decreases in resting [ATP] and increases in [IMP] during strenuous exercise under hypoxia (20,21).

Muscular strength adaptations after LIT and vascular occlusion. Our data are consistent with previous studies (reviewed in ref. 11), which demonstrated that training with loads as low as 50% 1-RM was effective for increasing muscular strength in previously untrained subjects. However, in contrast to two recent reports that suggested moderate vascular occlusion has an additive effect on strength gains after LIT (22,25), we observed no differences in strength between the OCC and CON groups after training. We cannot readily explain this discrepancy, although it could be related to methodological differences between studies. Our training protocol was virtually identical to the one described by Takarada et al. (25) with respect to the mode, intensity, timing of muscle actions, recovery interval, number of training bouts per week, occlusive cuff pressure,

and the fact that the total amount of work done was matched between arms for a given training session. However, our protocol differed in that our subjects trained for only 8 wk (instead of 16 wk), and even though the number of sets progressed from 3 to 6 over the course of the training protocol, the total number of sets performed by our subjects was lower than in the study by Takarada et al. (25) and subjects in that study performed every set to failure (96 sets in total), whereas our subjects performed either one or two sets to failure each session (24 sets to failure in total). Thus, even though we assessed elbow flexor strength using one method that was identical to the study by Takarada et al. (25) (i.e., isokinetic dynamometer at $60^{\circ}\cdot\text{s}^{-1}$), it is possible that differences between studies in the overall volume of training between may explain our lack of congruent findings. In addition, those authors (25) studied older women, whereas we examined young men. However, our failure to reproduce the purported benefit of occlusion on strength gains after LIT cannot be solely attributed to differences in subject age. Shinohara et al. (22) reported greater gains in strength in a group of young men after only 2 and 4 wk of LIT plus occlusion, as compared with LIT alone, although that study involved isometric training and testing of the knee extensor muscles. Irrespective of the changes in muscle strength, the primary focus of our study was muscle metabolic adaptations and we clearly demonstrated that vascular occlusion augmented the changes in substrate concentrations induced by LIT.

CONCLUSION

In summary, the results from the present study demonstrate that, 72 h after the cessation of an 8-wk elbow flexor LIT, the resting concentration of glycogen was increased in biceps brachii muscle, whereas resting [ATP] was reduced. Moreover, the application of moderate vascular occlusion augmented the metabolic changes induced by LIT, such that glycogen storage was enhanced and resting [ATP] was further reduced. Isotonic and isokinetically assessed muscular strength was increased after LIT in both arms; however, there was no additional effect of vascular occlusion. Future studies should be designed to elucidate the mechanisms that account for the observed metabolic alterations induced by LIT and occlusion. Specifically, potential alterations in glucose transport, glycogen resynthesis, and adenine nucleotide metabolism induced by LIT plus vascular occlusion warrant further investigation.

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