THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontolog A Biol Sci Med Sci*, 2015, 1024–1029
doi:10.1093/gerona/glu313
Advance Access publication February 2, 2015

OXFORD

Research Article

Day-to-Day Changes in Muscle Protein Synthesis in Recovery From Resistance, Aerobic, and High-Intensity Interval Exercise in Older Men

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Received September 6 2014; Accepted December 17 2014.

Decision Editor: Stephen Kritchevsky, PhD

Abstract

Background. Resistance exercise (RE) and aerobic exercise are recommended for older adults for fitness and strength. High-intensity interval exercise (HIIT) is an understudied but potent potential alternative to aerobic exercise. This study aimed to determine how each mode of exercise affected the integrated day-to-day response of muscle protein synthesis.

Methods. Sedentary men (n = 22; 67 ± 4 years; body mass index: 27.0 ± 2.6 kg m^{-2} [mean ± *SEM*]) were randomly assigned to perform RE, aerobic exercise, or HIIT. Participants consumed a stable isotope tracer (D_2O) for 9 days. Daily saliva samples were taken to measure tracer incorporation in body water. Muscle biopsies were obtained on Days 5–8 of D_2O consumption to measure tracer incorporation into muscle at rest, 24 hours, and 48 hours following each exercise bout: RE (3 × 10 repetitions: leg extensor and press, 95% 10RM), HIIT (10 × 1 minute, 95% maximal heart rate [HR_{max}]), or aerobic exercise (30 minutes, 55%–60% HR_{max}).

Results. Myofibrillar protein fractional synthetic rate was elevated, relative to rest, at 24 and 48 hours following RE and HIIT. The increase in myofibrillar fractional synthetic rate was greater following RE versus HIIT at both time points. HIIT was the only mode of exercise to increase sarcoplasmic protein fractional synthetic rate 24-hour postexercise (2.30 ± 0.34% d^{-1} vs 1.83 ± 0.21% d^{-1}).

Conclusions. This study shows that in older men, changes in muscle protein synthesis in response to certain exercises are long lasting and that HIIT significantly increases myofibrillar and sarcoplasmic fractional synthetic rate in this population.

Key Words: Exercise—Metabolism—Muscle—Sarcopenia

The global increase in the population of older adults demands solutions to reduce the risk of age-related disability associated with inactivity. Sarcopenia, the age-associated decline in muscle mass and strength, is measurable beginning in the fifth decade of life (1) and is accompanied by an increased risk of disability, falls, and fractures (2) and a higher incidence of metabolic diseases, such as type 2 diabetes (3). Exercise currently stands as the most viable strategy to counteract age-related declines in skeletal muscle mass and function and to alleviate the risk of disability (1).

Resistance exercise (RE) effectively bolsters muscle mass and strength and is commonly recommended for older adults to counteract sarcopenia (1). Physical activity recommendations for older

persons also include the regular practice of aerobic exercise (AE), which can improve fitness and insulin sensitivity; however, AE is not as effective as RE in eliciting strength gains or increasing muscle mass (4). High-intensity interval exercise (HIIT) is a time-efficient alternative to AE but is understudied in the elderly persons; nonetheless, in younger persons, HIIT is a potent stimulus for gains in aerobic fitness, muscle oxidative capacity (5), and improvements in insulin sensitivity (6).

Changes in muscle mass are largely determined by changes in the rates of muscle protein synthesis (MPS). Characterization of the acute MPS responses to RE, AE, and HIIT would be important in determining the potential of these modalities to alleviate declines in muscle mass in older persons. Oftentimes, MPS is measured using intravenous infusion over a 3- to 5-hour period. In contrast, oral ingestion of deuterium oxide (D_2O) can be used to measure MPS over the course of days to weeks, incorporating the influence of habitual diet and physical activity patterns (7–10). The ability of D_2O to measure MPS over this length of time is valuable because it would require multiple infusion trials and yet is too short to detect changes in muscle mass.

Therefore, the aim of this study was to determine how RE, AE, or HIIT affected daily integrated MPS in older men. We hypothesized that RE and HIIT would stimulate an increase in rates of myofibrillar MPS, whereas AE and HIIT would increase rates of sarcoplasmic MPS.

Methods

Participants

The study was approved by the Hamilton Health Sciences Integrated Research Ethics Board. We screened and recruited 22 healthy men aged 60–75 years, all of whom gave their written and informed consent to participate. All participants had a body mass index in the normal–overweight range and resting blood pressure < 140/90 mmHg. No participants reported engaging in structured exercise training in the last 6 months, and all participants demonstrated normal cardiac function during a maximal exercise stress test. Exclusion criteria included smoking, diabetes, regular use of nonsteroidal anti-inflammatory drugs, use of statins, and history of chronic illness that would affect the results of the investigation.

Experimental Design

Approximately 1 week prior to beginning the study protocol, participants underwent a whole body dual-energy x-ray absorptiometry scan (DXA; QDR-4500A Hologic, software version 12.31; Bedford, MA), a peak oxygen consumption ($\dot{V}O_{2peak}$) test to assess cardiovascular fitness, and 10RM testing to assess strength. $\dot{V}O_{2peak}$ tests were conducted on a bicycle ergometer (Ergoline er800s; Ergoline, Bitz, Germany) using the Jones protocol (11) and a breath-by-breath system (SensorMedics, Yorba Linda, CA). Tests lasted 10–12 minutes, and heart rate and function were monitored throughout using a 12-lead electrocardiogram.

Weight machines were used to assess 10RM for leg extension (Atlantis Precision Series Leg Extension C-105; Laval QC) and leg press (HUR 3545 Leg Press Incline; HUR, Northbrook, IL). Following a demonstration of proper technique, participants performed a warm-up of 10 repetitions at a light load (~40%–60% 1RM or 60%–70% 10RM). The weight was then increased, and participants completed up to 10 repetitions. This process was repeated until participants could complete no more than 10 repetitions (ie, 10RM). Participants rested for 3 minutes between attempts, and no more than 3 attempts were required to determine 10RM. If participants were randomized to AE or HIIT, they also completed a familiarization session on a bicycle ergometer to determine the power output necessary to elicit the intensities prescribed (~55%–60% $\dot{V}O_{2peak}$ or ~70% maximal heart rate [HR_{max}] for AE and ~90% $\dot{V}O_{2peak}$ or ~95% HR_{max} for HIIT).

One week following baseline testing and familiarization, participants returned to the laboratory on Days 5, 6, 7, and 8 of the study (Figure 1). The morning of each day, after an overnight fast, participants had a muscle biopsy (~100 mg) from the *vastus lateralis* muscle using a custom-modified 5-mm Bergstrom biopsy needle as described elsewhere (12). Biopsies were taken alternately from the left and right legs, so that each leg received a total of two biopsies that were at least 5 cm apart beginning distally and moving in a proximal direction with successive biopsies. Directly following their second muscle biopsy (on study Day 6), participants completed a single session of either RE, HIIT, or AE (Figure 1).

To standardize dietary conditions, participants were prescribed a weight maintenance diet that provided ~1.1 g protein kg body $mass^{-1}$ d^{-1} (macronutrient distribution: ~55% carbohydrate, ~30% fat, and ~15% protein). Diets began 2 days prior to participants' first muscle biopsy (Figure 1) and were continued throughout the rest of the study. Energy intake was estimated for each participant using the Harris–Benedict equation (13), and meal plans were created using NutriBase11 Pro v11.5 (Cybersoft, Phoenix, AZ). Meals were frozen, prepackaged, and could be reheated and consumed directly (Copper County Foods, Cambridge, Ontario).

Participants wore a pedometer during three nonbiopsy days as well as during 3 days where they received a biopsy to verify that they did not change their habitual activity levels as a result of the muscle biopsies.

Exercise Protocols

Following a warm-up of 10 repetitions at 35% 10RM, participants randomized to RE completed three sets of leg extension and leg press at loads equal to ~95% of their predetermined 10RM. The last set of each exercise was completed to failure.

Participants in the HIIT group completed a single bout of HIIT, which consisted of 10 × 1 minute intervals on a bicycle ergometer cycling at a workload that was determined during familiarization to elicit ~95% HR_{max} (~90% $\dot{V}O_{2peak}$). Participants maintained a cadence of at least 90 rpm during these intervals.

The AE protocol consisted of 30-minute continuous cycling at ~70% HR_{max} (55%–60% $\dot{V}O_{2peak}$). Heart rate was measured throughout each AE and HIIT session.

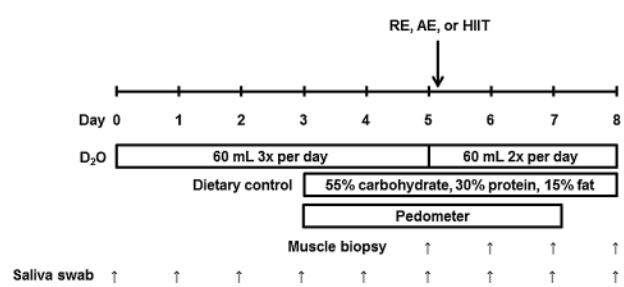

Figure 1. Overview of experimental design. AE = aerobic exercise; HIIT = high-intensity interval exercise; RE = resistance exercise.

The volume and intensity of the RE and AE protocols were based on the physical activity recommendations set out by the American College of Sports Medicine (14). We selected a modified low-volume HIIT model, which we considered preferable to Wingate-based HIIT (5), because it does not require specialized equipment and represents a feasible, time-efficient option for the general population (6).

Isotope Protocol

To increase deuterium (^{2}H) enrichment in total body water to ~1%, participants consumed 3 × 60 mL oral doses of 70% D_2O (Cambridge Isotope Laboratories, Tewksbury, MA) per day during the 5 days prior to their first muscle biopsy (Figure 1). To maintain ~1% enrichment, the dosage was reduced to 2 × 60 mL during the 4 days when participants received muscle biopsies (7,8). All 60 mL doses were consumed at least 3 hours apart. Participants also provided a saliva sample each morning during the days they consumed D_2O to allow for the measurement of ^{2}H enrichment in total body water. Total body water ^{2}H enrichment was used as a surrogate for plasma alanine ^{2}H labeling (7–9).

Muscle Protein Synthesis

Muscle samples (~40–50 mg) were separated into myofibrillar and sarcoplasmic fractions and processed as previously described (12) for analysis by gas chromatography combustion isotope ratio mass spectrometry (Metabolic Solutions, Nashua, NH).

Muscle preparations were analyzed for deuterated-alanine (^{2}H-alanine) with a Thermo Finnigan Delta V isotope ratio mass spectrometry coupled to a Thermo Trace GC Ultra with a gas chromatography combustion interface III and Conflow IV. The *N*-acetyl-*n*-propyl ester of alanine was analyzed using a splitless injection and a Zebron ZB-5 column of 30 m × 0.25 mm × 0.50 µm film thickness (Phenomenex, Torrance, CA). The gas chromatography oven was programmed with an initial column temperature of 80°C with a 2-minute hold, followed by a ramp of 30°C min^{-1} to 330°C. Eluents were directed into the pyrolysis reactor, heated at 1450°C, and converted to hydrogen gas (Metabolic Solutions).

Saliva samples were analyzed for ^{2}H enrichment by cavity ring-down spectroscopy by Metabolic Solutions using a Liquid Water Isotope Analyzer with automated injection system (Los Gatos Research, Mountain View, CA). The water phase of the saliva was injected six times, and the average of the last three measurements was used for data analysis. The intrarun precision of this instrument is less than 2.0 δ^2H‰, and the interrun precision is less than 3.5 δ^2H‰. The ^{2}H isotopic enrichments for muscle and saliva initially expressed as δ^2H‰ were converted to atom percent excess using standard equations as previously described (9).

Calculations

The fractional synthetic rate (FSR) of myofibrillar and sarcoplasmic proteins were calculated using the standard precursor-product method as described previously (9). In brief:

$$\mathrm{FSR}\,(\%\,\mathrm{d}^{-1}) = \left[\frac{(E_{\mathrm{Ala2}} - E_{\mathrm{Ala1}})}{E_{\mathrm{BW}} \times t}\right] \times 3.7 \times 100$$

Where $E_{\mathrm{Ala}X}$ is the protein-bound enrichment (in atom percent excess) from muscle biopsies at time *X*. Thus, the difference between times points is the change in protein-bound alanine enrichment between two time points with appropriate correction for ^{2}H incorporation into alanine (9,10). E_{BW} is the mean ^{2}H enrichment (in atom percent excess) in total body water between the time points. Hence, resting FSR (0-hour time point) was calculated using the difference in ^{2}H enrichments between Days 5 and 6; FSR at 24- and 48-hour postexercise was calculated using the difference between Days 6–7 and 7–8, respectively. Lastly, *t* is the tracer incorporation time in days. Multiplication by 3.7 adjusts for the average number of ^{2}H atoms that can become incorporated into alanine, and multiplication by 100 converts the values to percentages.

Statistics

Baseline means and salivary enrichment were compared using a one-way analysis of variance. Other data were compared using a two-way repeated measures analysis of variance with between (exercise type) and within (time) factors. Significant *F* ratios were further scrutinized using Tukey's post hoc test. Statistical significance was accepted at $p < 0.05$. All statistical analysis was completed using Sigma Plot software (Systat Software, San Jose, CA). Data are mean ± *SEM*.

Results

Participants

All measured anthropometric and strength variables were similar between RE, HIIT, and AE groups (Table 1). Participants did not alter their day-to-day activity as a result of the muscle biopsies; participants performed the same number of steps per day on biopsy days as they did on nonbiopsy days (6,227 ± 679 vs 6,774 ± 647, $p = 0.56$). On average, the weight maintenance diets prescribed to participants provided 2,646 ± 51 kcal d^{-1}, consisted of 104 ± 5 g d^{-1} protein, 364 ± 7 g d^{-1} carbohydrate, and 88 ± 2 g d^{-1} fat, and maintained participants' body weights. Diets did not differ between exercise groups (data not shown).

^{2}H Enrichment

Saliva ^{2}H enrichment increased significantly following the initiation of D_2O consumption (Figure 2). The elevation was sustained throughout the remainder of the study and reached ~1%–1.2% by Day 5, an enrichment that was not statistically different from that observed at Day 8 (Figure 2). The responses were similar between exercise groups (data not shown).

Myofibrillar Protein FSR

Prior to exercise, myofibrillar FSR was similar across all groups (Figure 3A). Myofibrillar FSR was significantly increased 24 hours following both HIIT and RE and remained elevated relative to baseline 48-hour postexercise. Although both RE and HIIT resulted in an elevation of myofibrillar FSR, the response was greatest following

Table 1. Physical and Exercise Characteristics of Participants in Each Exercise Group

	RE (n = 7)	HIIT (n = 8)	AE (n = 7)
Age (y)	66 ± 1	67 ± 2	68 ± 1
BMI (kg m^{-2})	26.7 ± 1.3	27.1 ± 1.0	27.3 ± 0.7
% body fat	23.9 ± 1.9	23.9 ± 2.1	25.6 ± 1.6
Lean tissue mass (kg)	60.3 ± 2.5	63.4 ± 2.3	60.1 ± 1.8
$\dot{V}O_{2peak}$ (mL kg^{-1} min^{-1})	27.3 ± 2.4	31.9 ± 2.4	30.7 ± 2.1
Leg press 10RM (kg)	49 ± 7	60 ± 3	61 ± 3
Leg extension 10RM (kg)	52 ± 6	54 ± 5	52 ± 2

Notes: Values are means ± *SEM*. No significant differences exist between groups for any variable. 10RM = 10 repetition maximum; BMI = body mass index; $\dot{V}O_{2peak}$ = peak oxygen consumption.

RE compared with HIIT. Myofibrillar FSR was not different compared with baseline at any time point following AE.

Sarcoplasmic Protein FSR

Sarcoplasmic protein FSR increased by ~25% following the performance of HIIT (Figure 3B) but returned to baseline by 48-hour postexercise. Neither AE nor RE stimulated a significant increase in sarcoplasmic protein FSR.

Discussion

The main finding from this study was that performing RE or HIIT resulted in an increase in myofibrillar protein FSR in older men, 24- and 48-hour postexercise. The magnitude of this increase was greater following RE compared with HIIT at both time points. Interestingly, only the performance of HIIT stimulated an increase in sarcoplasmic protein FSR at 24-hour postexercise. Considering these results represent changes in protein synthetic rates that are integrated over a 24-hour period, we propose they may be of greater relevance from an application standpoint compared with the results of acute infusion trials. Specifically, integrated FSR responses may better reflect the potential of these exercise modes to induce phenotypic adaptations (ie, muscle mass changes) over longer-term interventions.

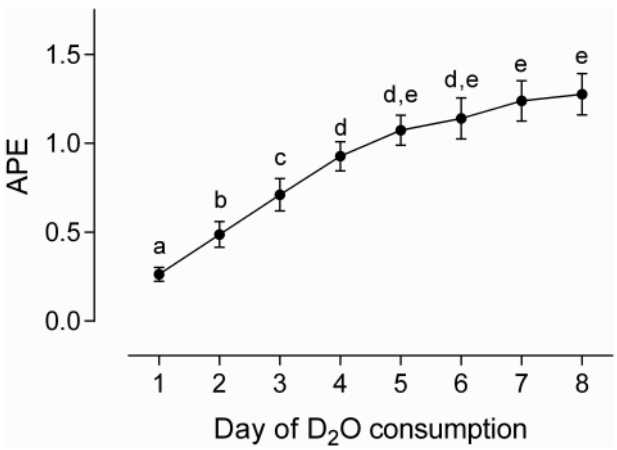

Figure 2. Saliva ^2H enrichment during Days 1–8 of the study. Means with different letters are significantly different ($p < 0.05$). Data are means ± *SEM*. APE = atom percent excess.

There are no previous data comparing acute RE, HIIT, and AE using an integrated measure of FSR in older men. In fact, few studies have used D_2O to measure FSR in response to acute exercise in any population, so it is difficult to make comparisons of our data. Under fasted conditions at rest, traditional tracer infusion trials have reported sarcoplasmic FSR as exceeding myofibrillar FSR by approximately twofold (~0.050% h^{-1} vs ~0.025% h^{-1}) in both younger and older individuals. A multitude of infusion trials have observed increases in mixed-muscle FSR with acute bouts of both RE and AE although these appear to be driven primarily by myofibrillar FSR in the case of RE (12) and by mitochondrial FSR in the case of AE (15). To our knowledge, the synthetic rate of the larger sarcoplasmic subfraction has not yet been fully characterized using stable isotope infusions following acute AE. Nonetheless, based on the stimulation of mitochondrial FSR with AE, we hypothesized that sarcoplasmic FSR would also be elevated in response to AE.

Recently, Wilkinson and coworkers (9) used bolus D_2O ingestion to assess the effect of RE on MPS in young men. Myofibrillar and sarcoplasmic FSR measurements by our group and by Wilkinson and coworkers were similar, both at baseline and following acute RE. In comparison to tracer infusion trials, our FSR measurements are slightly higher, even on a daily basis, although this difference may be explained by integrative nature of D_2O. In the present study, we observed a mean baseline myofibrillar FSR of 1.59 ± 0.03% d^{-1} for all participants combined (fasted state), which translates to ~0.07% h^{-1}. For men of a similar age, tracer infusion trials have reported baseline myofibrillar FSR values of ~0.03–0.05% h^{-1} in the postabsorptive state and ~0.06–0.09% h^{-1} in the postprandial state (16,17). In the present study, we observed an increase in myofibrillar FSR to 3.10 ± 0.25% d^{-1} (~0.13% h^{-1}) 24-hour post-RE, whereas tracer infusion studies have reported values of ~0.07–0.10% h^{-1} for older men following acute RE (16,18). It may be that the exercise in the present study resulted in an increased sensitivity to meal feeding, which we have observed previously (19), thus allowing for a greater net FSR to be observed in the fed state over the course of a day. Even in the fasted state, an acute bout of RE has been shown to stimulate FSR for up to 48 hours (20). Thus, a daily rate of 0.1% h^{-1} at 24-hour post-RE is not unrealistic. The discrepancies in FSR between our study and infusion trials are more likely due to the fact that D_2O allows for the measurement of an integrated MPS response. Therefore, direct comparisons of FSR determined using tracer infusions and in a free-living environment are not possible. It is also likely that our exercise naive participants would show

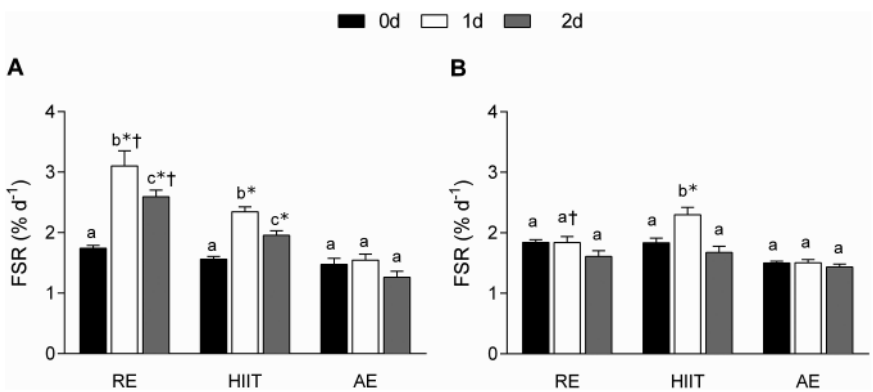

Figure 3. Myofibrillar (A) and sarcoplasmic (B) protein fractional synthesis rate (FSR) at baseline and postexercise. Data are means ± *SEM*. Bars bearing different letters are significantly different within each exercise group. *Significantly different ($p < 0.05$) from AE within that time point; †significantly different ($p < 0.05$) from HIIT within that time point. AE = aerobic exercise; HIIT = high-intensity interval exercise; RE = resistance exercise.

an uncharacteristically high FSR response to acute RE that would undoubtedly be attenuated with training (21,22).

To our knowledge, we are the first to report an increase in myofibrillar and sarcoplasmic FSR following acute HIIT in older men. Our results are supported by Scalzo and coworkers (7), who observed an increase in sarcoplasmic FSR using D_2O following 4 weeks of Wingate-based HIIT in young adults. In that study, mixed-muscle and mitochondrial FSR were also elevated post-training (7). Similar to traditional AE, participants who have undergone HIIT typically demonstrate an increased muscle oxidative capacity (5,6). Mixed-muscle FSR has been shown to be elevated following acute AE, and evidence suggests that this is driven by increases in mitochondrial FSR (15). Following the separation of specific muscle subfractions for isotope ratio mass spectrometry, the majority of skeletal muscle mitochondria are located in the sarcoplasmic (cytosolic) fraction. Hence, it follows that increases in mitochondrial FSR may be partially responsible for the observed increase in sarcoplasmic FSR 24-hour post-HIIT in the present study. However, because we did not directly measure mitochondrial FSR, we can only speculate that increases in sarcoplasmic FSR with HIIT are driven by increased synthesis of mitochondrial proteins. The lack of mitochondrial FSR measurement is a result of tissue constraints during data collection and is a limitation of our study; nonetheless, we believe the sarcoplasmic FSR data offer novel insight into the MPS response to HIIT in older adults.

It remains unclear whether HIIT can induce hypertrophy, but lower intensity aerobic training can induce hypertrophy in older men (23). Thus, it seems reasonable to speculate that HIIT would, with training, induce some degree of hypertrophy in older participants. The increase in myofibrillar FSR following acute HIIT in the present study lends strong credence to this hypothesis. It is thought that damage to the contractile apparatus with RE contributes to the stimulation of myofibrillar protein synthesis and subsequent muscle hypertrophy (24). The relatively high-intensity muscle contractions inherent to HIIT may induce muscle damage in a manner similar to RE, increase the need for the repair of actin, myosin, and associated contractile proteins and, therefore, stimulate myofibrillar protein synthesis. Thus, as an exercise modality that can induce improvements in aerobic fitness, mitochondrial content, insulin sensitivity, and potentially hypertrophy, we view HIIT for older persons as an interesting avenue for further study.

The American College of Sports Medicine recommends that older adults accumulate 30–60 minutes of moderate intensity AE per day (150–300 minutes per week) or 20–30 minutes of vigorous AE per day (75–150 minutes per week), as well as moderate to vigorous RE of each major muscle group at least 2 days per week (14). We selected our AE and RE exercise protocols based on these recommendations. We view HIIT as being somewhere between RE and AE on the "exercise spectrum" because it stimulates aerobic adaptations; however, it involves higher intensity muscle contractions compared with AE. Further, a single session of HIIT demands a greater volume of exercise, in terms of number of muscle contractions, compared with a session of RE, but other studies have shown that the HIIT model we employed in the present study demands a considerably lower exercise volume than a session of traditional continuous AE (5). We appreciate that it is not possible to "equate" the exercise bouts in the present study because they require differing patterns of muscle activation, different forces, different muscle fiber recruitment, and involve different energy expenditures. Our choice to compare these three modes of exercise was based on current guidelines for older persons to engage in both RE and AE, but with HIIT being less well understood but effective alternative mode of exercise.

Contrary to our hypothesis, we did not observe an increase in sarcoplasmic FSR with AE. Sarcoplasmic FSR was possibly increased transiently in the hours immediately following exercise. This increase may have been washed out over 48 hours in the D_2O protocol we used, whereas a short-term stable isotope infusion trial may have picked it up. This should be noted as a potential limitation of the D_2O method for assessing MPS and rationale for the continued use of infusion trials to answer specific questions. Another possibility is that our AE protocol was not vigorous enough to stimulate sarcoplasmic protein synthesis. Previous work demonstrating an increase in mitochondrial FSR with AE employed exercise protocols that were more intense (>65% $\dot{V}O_{2peak}$) (25) or longer (~45 minutes) (15). Given that our AE protocol was based on current exercise recommendations, these recommendations may need to be revised to encourage participation in higher intensity aerobic activity that is capable of stimulating MPS.

The novel findings we observed were that although RE induced the greatest increases in myofibrillar protein FSR at both 24- and 48-hour postexercise, HIIT was also able to induce significant increases in myofibrillar protein FSR albeit not to the same degree. Despite this, HIIT was the only mode of exercise that resulted in a stimulation of sarcoplasmic protein FSR 24-hour postexercise. An important limitation of this study was the exclusion of women. The study was restricted to men to reduce variability in the strength and body composition measurements and to improve the homogeneity of our sample, but we acknowledge that the exclusion of one sex may limit the generalizability of our findings. Considering that HIIT is also a potent stimulator of aerobic fitness, muscle oxidative capacity, and insulin sensitivity, it may be beneficial to incorporate HIIT into exercise recommendations for older adults. Future research should examine the effect of a training program combining HIIT and RE on changes in muscle mass and metabolic and functional improvements as well as the effect of a single bout of RE, AE, or HIIT on mitochondrial protein synthesis in older men using the D_2O method.

Funding

This work was supported by funding from the Labarge Optimal Aging Initiative from McMaster University (to G.P.) and a Canadian Institutes of Health Research (CIHR) grant (MOP-123296) to S.M.P. K.E.B. was supported by a CIHR Canada Graduate Scholarship (PGS-D).

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