

Skeletal Muscle Satellite Cell Characteristics in Young and Older Men and Women After Heavy Resistance Strength Training

S.M. Roth,¹ G.F. Martel,^{1,2} F.M. Ivey,¹ J.T. Lemmer,¹ B.L. Tracy,¹ E.J. Metter,³
B.F. Hurley,¹ and M.A. Rogers¹

¹Department of Kinesiology, University of Maryland, College Park.

²Department of Physical Therapy, University of Maryland Eastern Shore, Princess Anne.

³Gerontology Research Center, National Institute on Aging, Baltimore, Maryland.

Skeletal muscle satellite cell proportions and morphology were assessed in healthy, sedentary young and older men and women in response to heavy resistance strength training (HRST). Fourteen young (20–30 years) men ($n = 7$) and women ($n = 7$) and 15 older (65–75 years) men ($n = 8$) and women ($n = 7$) completed 9 weeks of unilateral knee extension exercise training 3 days per week. Muscle biopsies were obtained from each vastus lateralis before and after training, with the nondominant leg serving as an untrained control. All four groups demonstrated a significant increase in satellite cell proportion in response to HRST ($2.3 \pm 0.4\%$ vs $3.1 \pm 0.4\%$ for all subjects combined, before and after training, respectively; $p < .05$), with older women demonstrating the greatest increase ($p < .05$). Morphology data indicated a significant increase in the proportion of active satellite cells in after-training muscle samples compared with before-training samples and with control leg samples (31% vs 6% and 7%, respectively; $p < .05$). The present results indicate that the proportion of satellite cells is increased after HRST in young and older men and women, with an exaggerated response in older women. Furthermore, the proportion of satellite cells that appear morphologically active is increased as a result of HRST.

THE loss of muscle mass and strength with age, termed *sarcopenia*, can result in a loss of functional capacity in older individuals (1,2). Although strength training is an important intervention for increasing muscle mass and strength in older individuals (3,4), some evidence suggests that the hypertrophic response of older animals and humans is reduced compared with that of their young counterparts (5–9). Skeletal muscle satellite cells are important for muscle fiber regeneration and hypertrophy (10,11). Given that skeletal muscle regenerative capacity declines with age (12), age-related changes in satellite cell activation in response to muscle injury or overload could have important consequences for older individuals (13,14). Lowe and Alway (6) have suggested that age-related changes in satellite cell activation could contribute to age-related differences in the muscle response to overload.

Although several investigations have demonstrated satellite cell activation following muscle overload stimuli in young and older animals (15–20), only limited research is available regarding the role of strength training in satellite cell activation in humans. Kadi and colleagues (21,22) reported higher satellite cell proportions in male power lifters compared with those in young untrained men. Hikida and colleagues (23,24) have shown maintenance of myonuclear density in young and older men following strength training, an indication of satellite cell activation. The researchers re-

ported no change in satellite cell proportions as a result of training, but they did observe increases in myonuclear number proportional to the increases in muscle fiber area in both the young and the older subjects (23). Satellite cell morphology was not examined in either investigation (23,24). Kadi and coworkers (25) recently reported an increased satellite cell number in young women following 10 weeks of strength training. To our knowledge, no data exist on the satellite cell response of older women to heavy resistance strength training (HRST), nor are data available about the morphology of human satellite cells in response to HRST. Thus, the purpose of the present investigation was to assess satellite cell proportions and morphology, quantified by electron microscopy, in young and older men and women in response to nine weeks of HRST. We hypothesized that satellite cell proportions and activity would be increased similarly in all groups as a result of HRST. A complete analysis of the satellite cell characteristics of these healthy, sedentary subjects before training has been previously published (26).

METHODS

Subject Selection

Twenty-nine healthy, young and older men and women who volunteered for this study had adequate biopsy material

for subsequent analysis. The subjects consisted of seven young (20–30 years) and eight older (65–75 years) men and seven young and seven older women. All subjects were medically screened by a physician who performed a health history, physical examination, and graded maximal treadmill exercise test (GXT). All subjects were nonsmokers and were free of significant cardiovascular, metabolic, or musculoskeletal disorders. Individuals enrolled in the study had not participated in a regular exercise program for at least 6 months before their recruitment. After all methods and procedures were explained to them, the subjects read and signed a written consent form that had been approved by the Institutional Review Boards at the Baltimore Veterans Affairs Medical Center and the University of Maryland, College Park. All subjects were reminded throughout the study not to alter their regular physical activity levels or dietary habits for the duration of the investigation.

Body Composition

Body composition was assessed before and after HRST by using a Lunar DPXL dual-energy x-ray absorptiometer (Lunar software version 1.22, GE Medical Systems, New York, NY) as described previously (27). Subjects were instructed not to eat or drink for at least 8 hours prior to their morning scan. The coefficient of variation for repeated measurements of a calibration standard was less than 1.0%. Body weight was measured weekly during an exercise session by using a medical beam scale, and subjects were encouraged to maintain their before-training body weight.

Strength Testing

Muscle strength was assessed in both quadriceps unilaterally by means of a one-repetition maximum (1RM) test using the Keiser K-300 pneumatic variable-resistance leg extension machine (Keiser, Fresno, CA) as described previously (27). Briefly, three training sessions were conducted by using light resistance prior to the strength testing in order to familiarize the subjects with the equipment, training protocol, and proper exercise technique. For the 1RM test, a resistance was chosen that was thought to be slightly below the 1RM, and the subject performed one repetition. Increases in resistance between 1RM trials were adjusted to minimize the total number of trials (6–8) required before the true 1RM was obtained, and to keep the number of trials similar before and after training. Rest periods of ~60 seconds were allowed between trials. The same investigator administered the 1RM strength tests before and after training, and all testing procedures were standardized based on specific seat and body positions. Following the 1RM test, each subject's five-repetition maximum (5RM) was also determined by using the same procedures to establish the initial resistance for the first regular HRST session.

HRST Protocol

Each training session was preceded by a 3-minute warm-up on a stationary cycle, followed by 5–10 minutes of static stretching of both quadriceps. The training protocol consisted of nine weeks of unilateral HRST of the knee extensors of the dominant leg with the nondominant leg serving as a control, as described previously (27). During the train-

ing sessions, the untrained leg was placed in front of the contralateral leg extension pad to prevent voluntary contraction of that muscle. The training program consisted of five sets of high volume, heavy resistance leg extension exercise performed 3 days per week. The resistance for each set was based on the subject's 5RM. After performing a first set of five repetitions at 50% of the original 1RM for a warm-up, the subject performed a second set of five repetitions at the 5RM resistance following a 30-second rest period. The third set consisted of 10 repetitions, with the first four or five repetitions at the current 5RM value. The resistance was then lowered just enough for the subject to complete one or two additional repetitions before reaching fatigue. The process was repeated until a total of 10, 15, and 20 repetitions were completed for the third, fourth, and fifth sets, respectively. The third, fourth, and fifth sets were preceded by rest periods lasting a minimum of 90, 150, and 180 seconds, respectively. An exercise specialist directly supervised the exercise sessions of every subject at every training session to verify compliance with the training protocol, record resistance values and provide vocal encouragement. As increases in muscle strength occurred throughout the 9-week training program, the 5RM resistance was increased 1–2 kg during the next training session.

Muscle Tissue Sampling, Fixation, and Analysis

Detailed procedures for sampling and fixation procedures are outlined elsewhere (27). Muscle biopsies were taken from each m. vastus lateralis of a subject before and after the HRST program by the same investigator, using the percutaneous needle biopsy technique. The initial sampling site determined for each subject was 14 cm (women) or 16 cm (men) from the proximal border of the patella at the midline of the quadriceps. The biopsy sample taken after training was obtained at a new site 2.5 mm proximal and lateral to the original incision, with the biopsy needle directed into approximately the same location and depth in the muscle as the first biopsy. The before-training biopsy occurred 1 week prior to the familiarization sessions; the after-training biopsy occurred 24–48 hours after the last training session.

Muscle samples were minced for fixation into eight to ten 0.5- to 1.0-mm cubes that were fixed in a 2% solution of glutaraldehyde in 0.12M phosphate buffer (Millonig's buffer) at room temperature for 1 hour and then refrigerated (5–10°C) until postfixation. The before- and after-training tissue samples were postfixated at the same time, using 1% osmium tetroxide, after which samples were stained with 2% uranyl acetate, dehydrated, and embedded longitudinally in epoxy resin (Spurr's). Five sample blocks were obtained from each muscle biopsy sample. Thin sections (60–70 nm) were obtained from each sample block and placed on 75 × 300 copper grids. The sections on each grid were stained with 2% uranyl acetate and 0.1% lead citrate. Prepared grids were viewed on a Zeiss EM 10 CA electron microscope (Zeiss, Thornwood, NY) operated at 80 kV.

Assessment of Satellite Cell Proportions and Morphology

A detailed description of the analysis of satellite cells is presented elsewhere (26). Briefly, each viable muscle fiber

(27,28) was analyzed for total myonuclei and satellite cell proportions by using an electron microscope, with all potential satellite cells photographed (4000-12,500 \times). Each resulting micrograph was then reassessed later to ensure that the mononucleate satellite cell was within the basement membrane yet outside the sarcolemma of the muscle fiber (29). All myonuclei and satellite cells were quantified, and the satellite cell proportion [satellite cells/(myonuclei + satellite cells)] was calculated (29-31). In addition, the number of central myonuclei, those completely surrounded by myofilaments and centered in a muscle fiber, (32) was assessed for each of the four groups.

Satellite cell morphology was assessed to indirectly estimate changes in satellite cell activity as a result of HRST, as well as to determine possible age or gender differences in the response. Each micrograph was developed into a photographic print that was scanned and converted to a graphic computer image file. The following morphological characteristics were examined in each satellite cell (26): satellite cell area, satellite cell nucleus area (nuclear area), and the nuclear area/cell area ratio, nuclear chromatin structure (percent heterochromatin), endoplasmic reticulum (ER) and golgi apparatus, mitochondrial number, ribosomes, pinocytotic vesicles, and the existence of disorganized myofilaments.

Cell and nuclear areas (26,33) were measured by using UTHSCSA ImageTool imaging software (version 1.27, University of Texas Health Science Center at San Antonio, TX) and the nuclear area/cell area ratio was calculated. The percentage of heterochromatin (26,34) was assessed by using histographic-density analysis tools available in the ImageTool software. All area measurements were obtained in duplicate with the investigator blind to age, gender, leg, and training time point. Reliability was assessed by the repeated measuring of multiple cells on separate days (Pearson $r = .99$).

The organelle morphological characteristics (e.g., ER, golgi, and mitochondria) were assessed by using the photographic prints based on semiquantitative procedures outlined in previous research (26,33,34). Organelles were ranked according to the frequency and extent of their appearance, such that each organelle was described as follows: not observed (–), and rarely (+), seldom (++) , occasionally (+++), or frequently (++++) observed. Changes in cell morphology as a result of HRST were assessed within and among groups. An increased frequency or abundance of these organelle structures has been used previously to indicate satellite cell activation indirectly (33). As such, a rating of “Active” or “Inactive” was assigned to each cell following the morphological analysis. For this categorization, the investigator was similarly blind to condition and the rating assignment was based on the general pattern of scores for each of the morphological characteristics. All satellite cells assigned as Active exhibited at least four organelle categories with scores of +++ or greater. All cells were measured in duplicate, and a reliability analysis was performed as described above (Pearson $r = .96$).

Statistical Analysis

Changes in satellite cell proportions as well as cell and nuclear areas, the nuclear area/cell area ratio, and hetero-

chromatin percentage as a result of HRST were analyzed by using a three-factor (Experimental Condition \times Age \times Gender) repeated-measures analysis of variance (ANOVA). Each subject's mean value for each variable was used in those analyses. The morphological characteristics of satellite cells were analyzed by chi-square analysis, with Fisher's Exact Test used when the number of cases fell below five. Statistical significance for all analyses was accepted at $p \leq .05$. All data are reported as means \pm SE.

RESULTS

Physical Characteristics

Subject characteristics are presented in Table 1. All subjects completed at least 27 HRST sessions over approximately 9 weeks. Both before and after HRST, the 1RM strength values of the older men (73.7 ± 2.9 kg and 94.6 ± 3.6 kg, respectively) and young men (79.4 ± 8.0 kg and 99.8 ± 8.6 kg, respectively) were significantly higher than those of the older women (42.7 ± 2.1 kg and 52.1 ± 3.0 kg, respectively; $p < .05$). The strength of the young women (61.9 ± 6.6 kg and 85.1 ± 7.1 kg, respectively) was significantly greater than that of the older women before and after HRST ($p < .05$). HRST resulted in a significant increase in percent muscle strength in all groups ($p < .05$) with no significant differences among groups.

Satellite Cell Proportions

In the trained leg, a total of 2500 myonuclei (33 central myonuclei) were observed in 564 fibers in before-HRST samples compared with a total of 2661 total myonuclei (36 central myonuclei) observed in 618 fibers in after-HRST samples, with an average of ~ 90 myonuclei per subject per time point. Including samples obtained from the control limb, 7922 total myonuclei were observed in 1863 fibers, including 183 satellite cells; these numbers are similar to those found in previous work (29,35,36). The number of muscle fibers analyzed before and after HRST did not differ significantly. Within the trained leg, a total of 58 satellite cells were evident in before-HRST samples compared with a total of 86 satellite cells in after-HRST samples ($p < .05$). The increase in satellite cell number after HRST resulted from a significant increase observed in the older women (22 cells observed before HRST, and 44 cells after HRST; $p < .05$).

Figure 1 is a representative micrograph of a skeletal muscle satellite cell in relation to a myonucleus. The satellite

Table 1. Subject Characteristics

Parameter	Older Men	Older Women	Young Men	Young Women
<i>n</i>	8	7	7	7
Age (y)	69 ± 3	67 ± 3	25 ± 3	26 ± 1
Height (cm)	173.3 ± 4.3	157.0 ± 6.1	180.4 ± 10.7	168.5 ± 5.8
Weight (kg)	83.6 ± 10.5	71.1 ± 8.8	93.0 ± 18.3	69.2 ± 6.4
% Body fat				
Before HRST	30 ± 6	$41 \pm 6^*$	26 ± 8	31 ± 5
After HRST	30 ± 5	$39 \pm 7^*$	26 ± 8	32 ± 3

Notes: Data are means \pm SE. HRST = heavy resistance strength training.

*Significantly greater than all other groups ($p < .05$).

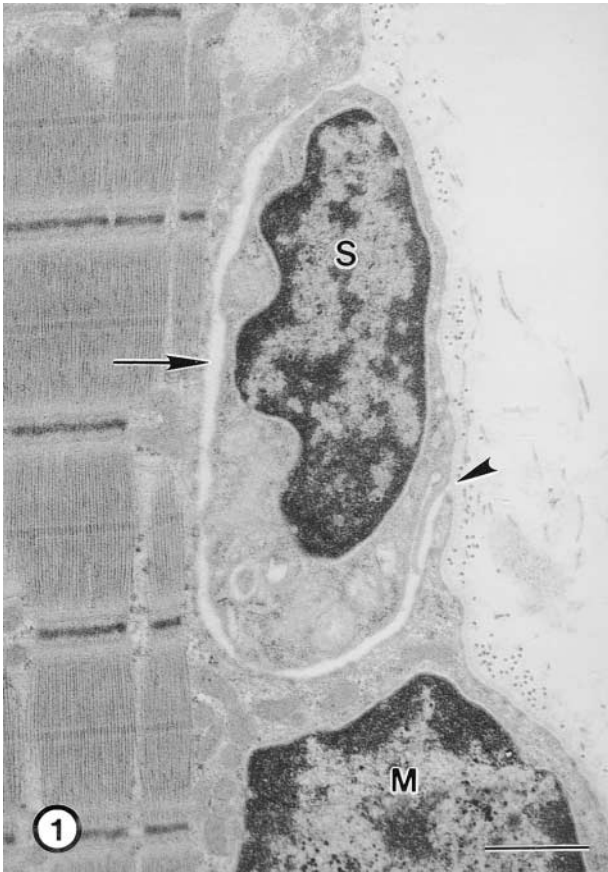


Figure 1. Electron micrograph representative of a human skeletal muscle satellite cell (S) compared with a myonucleus (M; bar = 1 μ m). Note the presence of the basement membrane surrounding both nuclei (arrowhead), while the satellite cell is located outside of the muscle fiber's sarcolemma (separation indicated by arrow).

cell proportion [satellite cells/(myonuclei + satellite cells)] increased significantly as a result of HRST in the trained leg [omnibus $F(1,25) = 5.60$; $p < .05$; Figure 2], with a significant Age \times Gender interaction resulting from a significantly greater increase in proportion in the older women compared with the other groups [$F(3,25) = 3.05$; $p < .05$; Figure 2]. When the data for all subjects were pooled, HRST elicited a significant increase in satellite cell proportion in the trained leg ($2.3 \pm 0.4\%$ vs $3.1 \pm 0.4\%$, respectively; $p < .05$). No changes in satellite cell proportion occurred in the untrained (control) limb following HRST in any of the four groups. A histochemical analysis of fiber type and area indicated no significant differences among the groups for fiber-type before or after HRST, no significant change in fiber type proportions after HRST, and significant increases in fiber area for all fiber types in all groups (unpublished observations).

The proportion of myonuclei that were central (i.e., located within the myofibrils) was significantly higher in the older men compared with that in all other groups before HRST (3.3% compared with 0.5–1.0%, respectively; $p < .05$). This significant difference remained after HRST, as the proportion of central myonuclei did not change as a result of HRST.

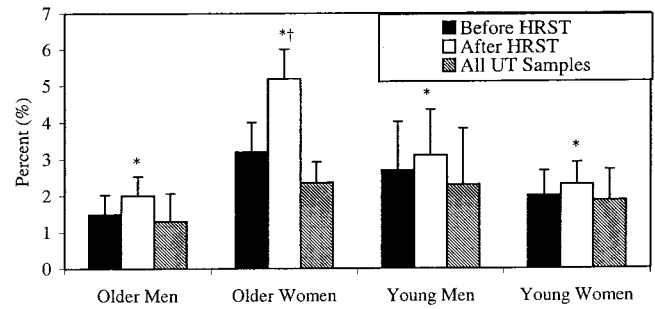


Figure 2. Satellite cell proportions [satellite cells/(myonuclei + satellite cells)] from the vastus lateralis muscle for healthy young and older men and women before and after heavy resistance strength training (HRST). Before HRST = data from dominant leg before HRST; after HRST = data from dominant leg after HRST. All untrained (UT) samples = pooled data for the untrained leg only. *Significantly different from before HRST, omnibus $F(1,25) = 5.60$; $p < .05$. †Significant Age \times Sex interaction, $F(3,25) = 3.05$; $p < .05$. Data are means (%) \pm SE.

Satellite Cell Morphology

Young women had significantly greater satellite cell areas compared with those of young and older men, both before and after HRST ($p < .05$), although no significant differences were noted for nuclear area or nuclear area/cell area ratio among the groups either before or after HRST. Because both control leg samples (before and after HRST) did not receive the HRST stimulus and no significant changes in satellite cell proportion or morphology were seen between the samples, the data from all untrained samples were combined (before-training sample of the trained leg + both control leg samples) and compared with data from the after-HRST sample. In this analysis, a significant increase in satellite cell area and nuclear area was noted in the after-HRST samples ($p < .05$; Table 2). No differences were noted for nuclear area/cell area ratio or heterochromatin percentage between the pooled untrained samples and the after-training samples (Table 2).

Satellite cell morphology was assessed for each time point and a global assignment of Active or Inactive was assigned based on this analysis. The number and proportion of satellite cells scored as Active increased as a result of HRST (Figure 3). Chi-square analysis revealed a significant difference between the proportion of active cells in after-

Table 2. Satellite Cell Morphological Characteristics in Trained Leg Samples vs All Untrained Samples

Parameters	All Untrained Samples	After HRST
<i>n</i>	94	72
Cell area (μ^2)	12.4 ± 0.7	$15.3 \pm 1.2^*$
Nuclear area (μ^2)	7.4 ± 0.4	$9.1 \pm 0.7^*$
Nucleus/cell area ratio (%)	59.1 ± 1.3	60.4 ± 1.4
Heterochromatin (%)	39.5 ± 1.6	39.0 ± 1.0

Notes: Data are means \pm SE. HRST = heavy resistance strength training. "All untrained samples" are defined as any muscle sample not subjected to the HRST stimulus (before-training samples pooled with both control leg samples).

*Significantly greater than all untrained samples ($p < .05$). No other significant differences.

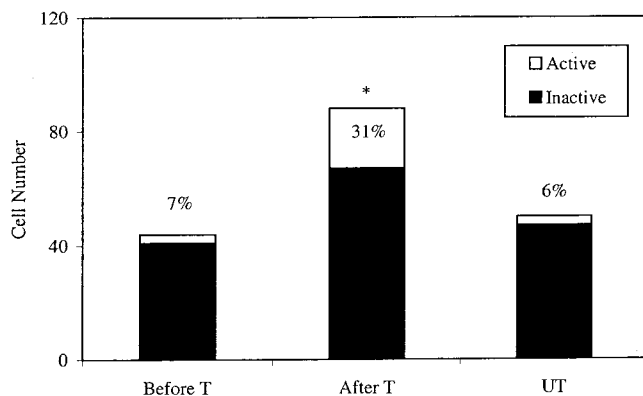


Figure 3. Number of satellite cells labeled "Active" and "Inactive" in before T, after T, and both UT leg samples (combined) for all subjects combined. Before T = before-training samples; After T = after-training samples; UT = untrained pooled control leg samples. *Significantly different from Before T and UT samples. Data are presented as total cell number, with the percentage of active cells presented for the corresponding column.

training muscle samples compared with all untrained muscle samples (21 of 67 satellite cells in after-HRST samples compared with 6 of 88 satellite cells from before-HRST + control leg samples; $p < .05$). Although not significantly different ($p = .14$), a higher proportion of active satellite cells was found in older women than in other groups after HRST (36% compared with 17–25%, respectively).

Active satellite cells were generally scored higher for all morphological traits assessed, especially for ER, pinocytotic vesicles, and mitochondrial number. Figures 4A–4F depict cells representative of active satellite cells or morphological traits representative of active satellite cells. Older women had more satellite cells scored with high values for lipofuscin granules, but no other significant group, age, or gender differences were noted in cell morphology. Lipofuscin granule content did not change as a result of HRST. A complete analysis of the satellite cell populations in the before-training and untrained (control leg) muscle samples is presented elsewhere in the context of aging skeletal muscle (26). Cilia were noted in several satellite cells in muscle samples from all time points, most of which were categorized as Active (Figures 4E and 4F).

DISCUSSION

In the present investigation, satellite cell proportion in young and older men and women was significantly increased as a result of 9 weeks of HRST. Additionally, an assessment of satellite cell morphology after HRST indicated a significant increase in the proportion of active satellite cells, cells with higher levels of mitochondria, ER, and pinocytotic vesicles. Interestingly, older women demonstrated a significantly greater increase in satellite cell proportion (significant interaction, $p < .05$) and the largest increase in the number of active satellite cells in response to HRST ($p = .14$) compared to the other groups.

Substantial previous work in young and older animals has demonstrated increases in satellite cell proportion in response to various muscle overload stimuli (15–20), although

some reports have found no change in satellite cell activation with an overload stimulus (6,37). Umnova and Seene (16) reported an increase in satellite cell proportion from 3.4% to 9.6% in rats following 6 weeks of treadmill exercise training, and Hanzlikova and colleagues (15) reported an increase from 5.8% to 16.6% in rats following synergist ablation. Although the increase in satellite cell proportion noted in the present investigation is modest (from 2.3% to 3.1%), a direct comparison with animal studies is difficult as a result of species differences and the variable nature of the various overload stimuli used. The HRST program used in the present study resulted in three relatively short periods of stimulation each week, whereas many animal studies allow for a constant 24-hour stimulus over days or weeks (15,17,38). Furthermore, increases in satellite cell proportion are seen most dramatically early in an intervention, presumably during the height of cell proliferation (17,30,38). Given that the present study investigated satellite cell characteristics at the end of a 9-week HRST program, we speculate that peak satellite cell activation likely occurred earlier in the training period and that substantial differentiation of cells had occurred by 9 weeks. This observation would correspond well with the data of Hikida and colleagues, (23) who demonstrated no change in satellite cell proportion after 8–16 weeks of strength training in young and older men, and Kadi and colleagues, (25) who reported an increase in satellite cell proportion from 3.7% to 5.4% after 10 weeks of strength training in young women. In addition to the significant increase in satellite cell proportion, the present data indicated no change in the satellite cell proportions of the untrained leg and provided morphological evidence for increased cellular activity. Thus, these results provide substantial evidence for satellite cell activation and proliferation in the muscle response to HRST in young and older men and women.

Additional evidence for satellite cell activation in humans in response to strength training exists, although data are limited. Kadi and coworkers (21,22) recently reported satellite cell proportions of ~7% in the trapezius muscle of elite male power lifters compared with values of ~4% in untrained controls. Although the data were cross sectional, satellite cell activation resulting from long-term strength training was indicated indirectly by the maintenance of myonuclear density despite substantial increases in muscle fiber size in the power lifters (21,22). Recently, Hikida and coworkers (23) assessed satellite cell proportions in muscle fiber cross sections in young and older (65 years) men following lower body strength training. The researchers reported no differences in satellite cell proportions with age or with strength training (~2.4% in both groups before and after training), although differences in the duration of the strength training stimulus for young versus older men (8 vs 16 weeks) limits comparison between the groups. Hikida and colleagues (23,24) have also observed that myonuclear number increased proportionately to muscle fiber area in response to strength training in both young and older men, indirectly indicating satellite cell activation in both age groups (39). Using an electron microscopic analysis of longitudinally oriented muscle fibers, the current investigation indicated both an increased proportion of satellite cells and

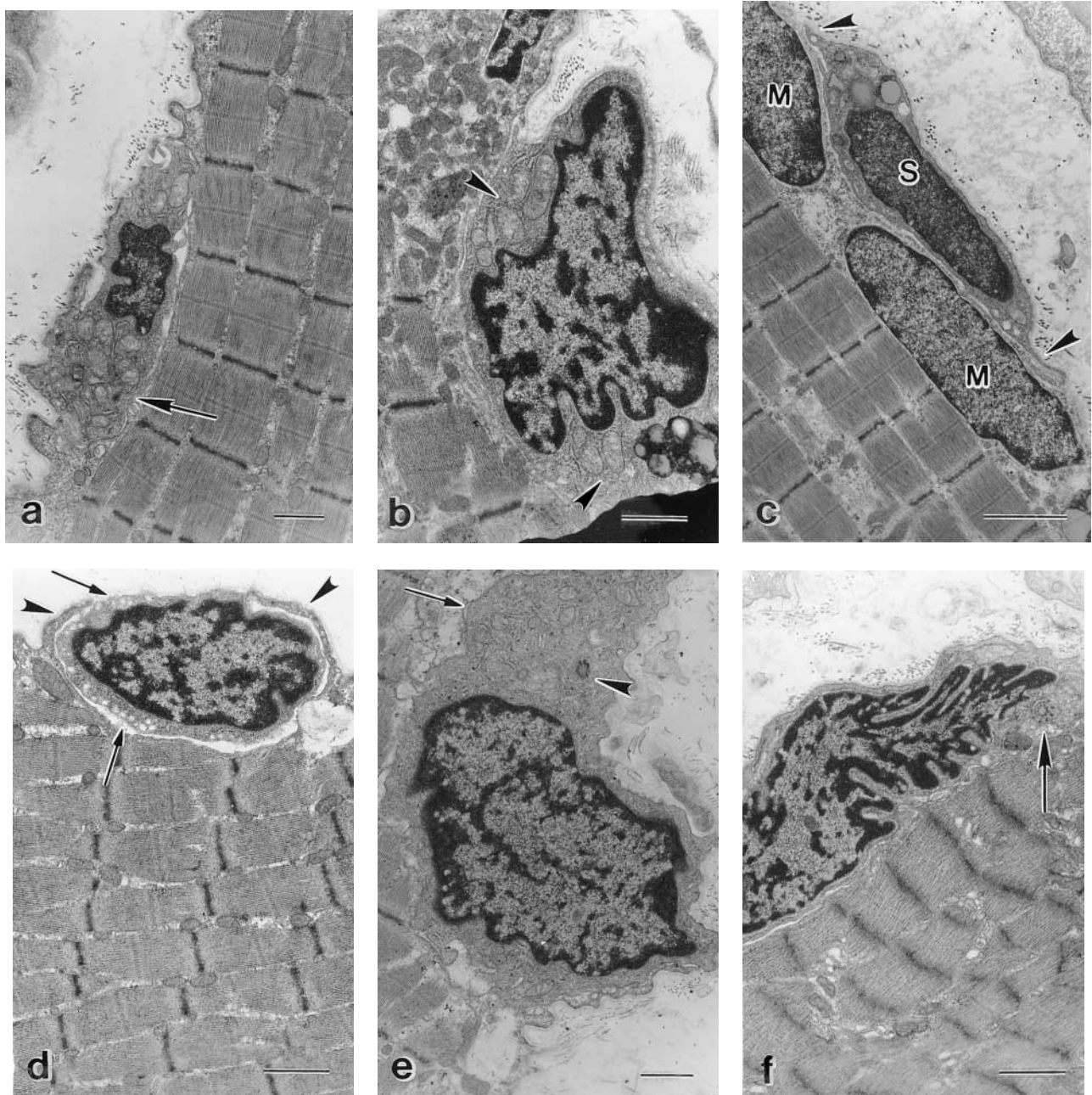


Figure 4. Representative micrographs of satellite cells obtained from after-training muscle samples labeled as “Active” based on morphological criteria. For reference, Fig. 1 is representative of an inactive satellite cell. **A**, Satellite cell exhibiting expanded cytoplasm and endoplasmic reticulum (ER), and numerous mitochondria (arrow; bar = 1 μ m). **B**, Active satellite cell showing numerous mitochondria (arrowheads) and pinocytotic vesicles (bar = 1 μ m). **C**, Satellite cell (S) demonstrating expanded cytoplasm in the form of a lamellapodia (arrowheads), as well as euchromatic chromatin appearance (bar = 2 μ m). This cell appears to be traveling along the muscle fiber, over the top of myonuclei (M). **D**, Satellite cell exhibiting numerous pinocytotic vesicles (arrows; bar = 1 μ m). Note also the wrapping of the muscle cell’s cytoplasm (arrowheads) around the periphery of the satellite cell. **E**, Satellite cell exhibiting expanded cytoplasm and ER, and numerous mitochondria (arrow), along with euchromatic chromatin appearance (bar = 1 μ m). A cilium (arrowhead) also appears to be present in the cytoplasm of the cell. **F**, Active satellite cell exhibiting a cilium (arrow; bar = 1 μ m). Note also the substantial festooning of the nucleus in this cell, also demonstrated in **A** and **B**. This nuclear structure was seen regularly throughout active and inactive satellite cells.

an increased number of active satellite cells following 9 weeks of HRST, providing evidence for satellite cell proliferation in both young and older men and women. In the present investigation, increases in satellite cell proportions and activity accompanied increases in both muscle strength

and mass (outlined in detail elsewhere; see Ref. 40) following 9 weeks of HRST. Substantial evidence indicates that the number of myonuclei increases in proportion to increases in muscle fiber volume such that myonuclear density is maintained (24,39), and that the increase in myonu-

clear number is a result of satellite cell proliferation and differentiation (41). The present results provide further evidence for satellite cell proliferation in response to HRST, and the first evidence for a possible gender difference in the satellite cell proliferative response. These data provide indirect evidence for a role for satellite cells in the muscle mass response to HRST.

Although the percentage is not significantly different ($p = .14$), older women in the present study tended to have a higher proportion of active satellite cells than other groups (36% compared with 17–25%, respectively), and they demonstrated the largest increase in satellite cell proportion at the end of 9 weeks of HRST ($p < .05$). Alternatively, given that satellite cell proliferation peaks early following an overload stimulus (17,30,38), this difference might indicate delayed satellite cell activation in the older women, if we assume that similar increases in cell proliferation had occurred earlier in the other groups. Except that the increases in muscle fiber area as a result of HRST were not significantly different among the groups, we have no additional data to support or refute this alternative explanation. In previous work from our laboratory (27,42), these same older female subjects demonstrated a significantly greater number of muscle fibers exhibiting ultrastructural muscle damage (17%) as a result of HRST compared with the other groups (3–7% of fibers exhibiting damage). Muscle activity and other possible mediators of satellite cell proliferation and activation independent of muscle damage cannot be ruled out as stimuli in the present study.

In summary, the data from the present investigation are the first to indicate that HRST elicits increases in satellite cell proportion in young and older men and women, with a possible Age \times Gender interaction in the response. Furthermore, the present data provide the only known evidence for an increased proportion of morphologically active satellite cells following HRST in these groups.

ACKNOWLEDGMENTS

This work was supported by NIH Research Contract AG-42148 (to B.F. Hurley and M.A. Rogers). S.M. Roth was supported by NIA Grants AG-00268 and AG-05893.

We thank Tim Mangel, Director of the Laboratory for Biological Ultrastructure, and Dr. Stephen Wolniak for their expert insight and technical assistance. This work is Contribution 88 from the Laboratory for Biological Ultrastructure, University of Maryland, College Park (UMCP). We thank Dr. Colleen Farmer and the staff of the Wellness Research Laboratory at UMCP for the use of their facilities. We also extend our appreciation to Dorothy O'Donnell, Diane Hurlbut, Dr. Mary Lott, and Nancy Roth for their assistance with the project; Dr. Jerome Fleg for manuscript review; and to the subjects who participated in this investigation. A preliminary report of these results was presented at the 2000 American College of Sports Medicine Annual Meeting (43).

Address correspondence to Stephen M. Roth, A300 Crabtree Hall, Department of Human Genetics, University of Pittsburgh, Pittsburgh, PA 15261. E-mail: sroth@helix.hgen.pitt.edu

REFERENCES

- Evans WJ, Campbell WW. Sarcopenia and age-related changes in body composition and functional capacity. *J Nutr.* 1993;123:465–468.
- Rantanen T, Guralnik JM, Ferrucci L, Leveille S, Fried LP. Coincidence: strength and balance as predictors of severe walking disability. *J Gerontol Med Sci.* 1999;54A:M172–M176.
- Fiatarone MA, Marks EC, Ryan ND, Meredith CN, Lipsitz LA, Evans WJ. High-intensity strength training in nonagenarians. *JAMA.* 1990; 263:3029–3034.
- Hurley BF, Hagberg JM. Optimizing health in older persons: aerobic or strength training? In: Holloszy JO, ed. *Exercise and Sport Sciences Reviews.* Baltimore: Williams and Wilkins; 1998:61–90.
- Blough ER, Linderman JK. Lack of skeletal muscle hypertrophy in very aged male Fischer 344 X Brown Norway rats. *J Appl Physiol.* 2000;88:1265–1270.
- Lowe DA, Alway SE. Stretch-induced myogenin, MyoD, and MRF4 expression and acute hypertrophy in quail slow-tonic muscle are not dependent upon satellite cell proliferation. *Cell Tissue Res.* 1999;296: 531–539.
- Carson JA, Alway SE. Stretch overload-induced satellite cell activation in slow tonic muscle from adult and aged Japanese quail. *Am J Physiol.* 1996;270:C578–C584.
- Häkkinen K, Kallinen M, Izquierdo M, et al. Changes in agonist-antagonist EMG, muscle CSA, and force during strength training in middle-aged and older people. *J Appl Physiol.* 1998;84:1341–1349.
- Welle S, Totterman S, Thornton C. Effect of age on muscle hypertrophy induced by resistance training. *J Gerontol Med Sci.* 1996;51A: M270–M275.
- Rosenblatt JD, Yong D, Parry DJ. Satellite cell activity is required for hypertrophy of overloaded adult rat muscle. *Muscle Nerve.* 1994;17: 608–613.
- Phelan JN, Gonyea WJ. Effect of radiation on satellite cell activity and protein expression in overloaded mammalian skeletal muscle. *Anat Rec.* 1997;247:179–188.
- Sadeh M. Effects of aging on skeletal muscle regeneration. *J Neurol Sci.* 1988;87:67–74.
- Carlson BM. Factors influencing the repair and adaptation of muscles in aged individuals: satellite cells and innervation. *J Gerontol Biol Sci.* 1995;50A:B96–B100.
- Chakravarthy MV, Davis BS, Booth FW. IGF-I restores satellite cell proliferative potential in immobilized old skeletal muscle. *J Appl Physiol.* 2000;89:1365–1379.
- Hanzlikova V, Mackova EV, Hnik P. Satellite cells of the rat soleus muscle in the process of compensatory hypertrophy combined with denervation. *Cell Tissue Res.* 1975;160:411–421.
- Umnova MM, Seene TP. The effect of increased functional load on the activation of satellite cells in the skeletal muscle of adult rats. *Int J Sports Med.* 1991;12:501–504.
- Snow MH. Satellite cell response in rat soleus muscle undergoing hypertrophy due to surgical ablation of synergists. *Anat Rec.* 1990;227: 437–446.
- Darr KC, Schultz E. Exercise-induced satellite cell activation in growing and mature skeletal muscle. *J Appl Physiol.* 1987;63:1816–1821.
- Jacobs SCJM, Wokke JHJ, Bar PR, Bootsma AL. Satellite cell activation after muscle damage in young and adult rats. *Anat Rec.* 1995;242: 329–336.
- McCormick KM, Thomas DP. Exercise-induced satellite cell activation in senescent soleus muscle. *J Appl Physiol.* 1992;72:888–893.
- Kadi F, Eriksson A, Holmner S, Butler-Browne GS, Thornell LE. Cellular adaptation of the trapezius muscle in strength-trained athletes. *Histochem Cell Biol.* 1999;111:189–195.
- Kadi F, Eriksson A, Holmner S, Thornell LE. Effects of anabolic steroids on the muscle cells of strength-trained athletes. *Med Sci Sports Exerc.* 1999;31:1528–1534.
- Hikida RS, Walsh S, Barylski N, Campos G, Hagerman FC, Staron RS. Is hypertrophy limited in elderly muscle fibers? A comparison of elderly and young strength-trained men. *Basic Appl Myol.* 1998;8: 419–427.
- Hikida RS, Staron RS, Hagerman FC, et al. Effects of high-intensity resistance training on untrained older men. II. Muscle fiber characteristics and nucleo-cytoplasmic relationships. *J Gerontol Biol Sci.* 2000; 55A:B347–B354.
- Kadi F, Thornell L-E. Concomitant increases in myonuclear and satellite cell content in female trapezius muscle following strength training. *Histochem Cell Biol.* 2000;113:99–103.
- Roth SM, Martel GF, Ivey FM, et al. Skeletal muscle satellite cell populations in young and older men and women. *Anat Rec.* 2000;260: 351–358.
- Roth SM, Martel GF, Ivey FM, et al. Ultrastructural muscle damage in

- young vs. older men following heavy resistance strength training. *J Appl Physiol.* 1999;86:1833–1840.
28. Roth SM, Martel GF, Rogers MA. Muscle biopsy and muscle fiber hypercontraction: a brief review. *Eur J Appl Physiol.* 2000;83:239–245.
 29. Snow MH. The effects of aging on satellite cells in skeletal muscles of mice and rats. *Cell Tissue Res.* 1977;185:399–408.
 30. Winchester PK, Gonyea WJ. A quantitative study of satellite cells and myonuclei in stretched avian slow tonic muscle. *Anat Rec.* 1992;232:369–377.
 31. Ishimoto S, Goto I, Ohta M, Kuroiwa Y. A quantitative study of the muscle satellite cells in various neuromuscular disorders. *J Neurol Sci.* 1983;62:303–314.
 32. Snow MH. A quantitative ultrastructural analysis of satellite cells in denervated fast and slow muscles of the mouse. *Anat Rec.* 1983;207:593–604.
 33. Campion DR, McCusker RH, Richardson RL. Ultrastructure of muscle satellite cells in hypersomatotropic rats. *Acta Anat.* 1987;128:67–70.
 34. Wakayama Y, Schotland DL. Muscle satellite cell populations in Duchenne dystrophy. In: Mauro A, et al., ed. *Muscle Regeneration*. New York: Raven Press; 1979:121–129.
 35. Schmalbruch H, Hellhammer U. The number of satellite cells in normal human muscle. *Anat Rec.* 1976;185:279–288.
 36. Schultz E. Fine structure of satellite cells in growing skeletal muscle. *Am J Anat.* 1976;147:49–70.
 37. Lee J, Alway SE. Adaptations of myonuclei to hypertrophy in patagialis muscle fibers from aged quail. *Mech Ageing Devel.* 1996;88:185–197.
 38. Putman CT, Dusterhoft S, Pette D. Satellite cell proliferation in low frequency-stimulated fast muscle of hypothyroid rat. *Am J Physiol Cell Physiol.* 2000;279:C682–C690.
 39. Roy RR, Monke SR, Allen DL, Edgerton VR. Modulation of myonuclear number in functionally overloaded and exercised rat plantaris fibers. *J Appl Physiol.* 1999;87:634–642.
 40. Ivey FM, Roth SM, Ferrell RE, et al. Effects of age, gender and myostatin genotype on muscle volume response to heavy resistance strength training. *J Gerontol Med Sci.* 2000;55A:M641–M648.
 41. Moss FP, Leblond CP. Satellite cells as the source of nuclei in muscles of growing rats. *Anat Rec.* 1971;170:421–436.
 42. Roth SM, Martel GF, Ivey FM, et al. High volume, heavy resistance strength training and muscle damage in young and older women. *J Appl Physiol.* 2000;88:1112–1118.
 43. Roth SM, Martel GF, Ivey FM, et al. Satellite cell response to nine weeks of strength training in young and older men and women. *Med Sci Sports Exerc.* 2000;32:S294.

Received September 21, 2000

Accepted December 12, 2000

Decision Editor: John A. Faulkner, PhD

GSA's 54th Annual Scientific Meeting

Chicago, November 15-18, 2001



Preliminary Program
Coming in July

Early Bird Registration
Deadline is October 19, 2001

Visit the Web Site for More
Information!

<http://www.geron.org>