Large energetic adaptations of elderly muscle to resistance and endurance training

SHARON A. JUBRIAS,1 PETER C. ESSELMAN,2 LANCE B. PRICE, M. ELAINE CRESS,3 AND KEVIN E. CONLEY1,4,5

Departments of 1Radiology, 2Rehabilitation Medicine, 3Medicine, 4Physiology and Biophysics, and 5Bioengineering, University of Washington, Seattle, Washington 98195

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Jubrias, Sharon A., Peter C. Esselman, Lance B. Price, M. Elaine Cress, and Kevin E. Conley. Large energetic adaptations of elderly muscle to resistance and endurance training. J Appl Physiol 90: 1663–1670, 2001.—This study determined the cellular energetic and structural adaptations of elderly muscle to exercise training. Forty male and female subjects (69.2 ± 0.6 yr) were assigned to a control group or 6 mo of endurance (ET) or resistance training (RT). We used magnetic resonance spectroscopy and imaging to characterize energetic properties and size of the quadriceps femoris muscle. The phosphocreatine and pH changes during exercise yielded the muscle oxidative properties, glycolytic ATP synthesis, and contractile ATP demand. Muscle biopsies taken from the same site as the magnetic resonance measurements were used to determine myosin heavy chain isoforms, metabolite concentrations, and structural adaptations of elderly muscle to exercise training. RT and ET programs in elderly subjects. We used MR methods to measure muscle size and the ATP supply and demand properties in vivo. The structural correlates of the muscle energetic properties were measured in tissue taken by muscle biopsy from the same site as the MR measurements. These data allow us to describe the changes in muscle energetic function in vivo with exercise training and to see whether altered muscle energetics relate to changes in muscle structures.
METHODS

Subjects

Forty male and female subjects, aged 69.2 ± 0.6 yr (men: n = 17, 174.2 ± 1.5 cm, 82.3 ± 3.5 kg; women: n = 23, 161.3 ± 1.0 cm, 64.8 ± 1.7 kg), participated in this project. Each subject had a physical examination, resting and exercise electrocardiogram, blood testing (complete blood-cell count and mini-panel), and nutritional analysis (3-day food record) to ensure that they were healthy and free from orthopedic or neuromuscular problems. We recruited physically active adults with habitual activities ranging from yard work and occasional walks to tennis or walking a few times per week. None regularly engaged in RT or ET before this study. Control subjects were instructed to continue their normal physical activities and to avoid initiating an RT or ET program during the study. All participants gave informed consent to procedures approved by the University's Human Subjects Research Committee. The pretrained quadriceps cross-sectional area (CSA), oxidative properties, and mitochondrial volume density [Vv(mt,f)] for these subjects have been published previously (30).

Exercise Training

Subjects were randomly assigned to either RT (n = 15), ET (n = 14), or control (n = 11) groups. The training period lasted 24 wk with sessions three times per week. The first 2 wk were spent familiarizing subjects with proper use of the equipment, exercise form, stretching, and warm-up and cooldown routines. The RT group trained with the two-legged leg press (StairMaster Logic Leg Press, StairMaster Sports/Medical Products, Kirkland, WA), an activity in which the quadriceps provide the majority of force (29). They also performed exercises for the arms and shoulders on a StairMaster Gravitron 2000AT conditioning system. We expressed the maximum force production in the leg-press movement as the one repetition maximum (1 RM), defined as the maximum weight that can be pressed one time using proper form. One-RM leg-press strength, assessed initially and then every 2–3 wk throughout the training period, was used to determine and adjust the weight load for each subject during training. We reduced the chance of muscle strain or joint injury during testing by estimating the 1-RM force with a 4-RM test, in which submaximal force is generated. The 4 RM is defined as the maximum weight that can be lifted by the subject four times using proper form. An accurate estimate of the 1-RM weight can then be calculated based on the 4-RM value [1 RM = 4-RM weight x 1.13 (35)] and verified by our own testing. Each subject performed four-repetition sets, beginning with a light load and increasing the weight used in each set until reaching the maximum 4 RM. Two-minute rest periods separated each set, and the maximum 4 RM was generally identified within five sets.

Our RT program was based on the periodization training technique (7). We chose this type of program, which uses cycles of varying lifting intensities, to provide a good training stimulus and help prevent overtraining and injuries during the extended training period. In the first phase, subjects performed moderate work (3 sets of 10–15 repetitions at 60–70% of 1 RM) for 4 wk to allow initial adaptation to the demands of training. In subsequent phases, three to five sets consisting of four to eight repetitions at 70–85% 1 RM were performed. The number of sets, repetitions, and percent of 1 RM lifted varied according to a schedule that included moderate- and heavy-lifting days. Each session started with a warm-up set of 10 repetitions at 65% of the 1 RM.

ET subjects used an alternating one-legged press exercise (StairMaster Crossrobes 1650 LE) and a kayaking-type exercise (StairMaster Crossrobes 2650 UE kayak), beginning with an exercise intensity of 60% calculated with the heart rate reserve method [intensity = HRrest + (% × HRmax – HRrest)], where HRrest is resting heart rate and HRmax is maximum heart rate] for 5–10 min on each exercise, performed consecutively. They progressed as rapidly as possible to 20 min for each exercise and then to an intensity of 80–85% of heart rate reserve. We monitored the exercise intensity during these sessions with heart rate monitors (Polar Pacer, Polar Electro) that had alarms set to signal if subjects exercised below or above their target range (target heart rate ± 5 beats).

MR Determinations

Muscle size. We used MR imaging to determine muscle CSA according to methods described in an earlier paper (30). Using a GE Signa 1.5-T scanner (General Electric Medical Systems, Milwaukee, WI), we collected axial plane T1-weighted, two-dimensional spin-echo images every 2.5 cm from the hip to the thigh (15–20 slices/subject). Our collection parameters were as follows: 600-ms repetition time, 10-ms echo time, 5-mm slice thickness, 20-mm interslice interval, 256 x 192 matrix, and number of excitations = 2. The patient lay supine for imaging. We used standard stereological techniques (56) to determine the largest muscle CSA for the quadriceps, as per Jubrias et al. (30). Quadriceps volume was calculated as \( \sum (CSA_{slice} \times slice\ thickness) \). Subcutaneous and intramuscular fat and other noncontractile tissues were excluded from the calculation of muscle contractile CSA. All MR measurements were made immediately before training and then within 10 days after the training period ended.

\( ^{31}P-MR \). We used the 1.5-T Signa spectrometer for this portion of the study also. We placed a 9-cm-diameter surface coil over the vastus lateralis muscle of the thigh at the level of the biopsy site. After shimming to optimize B0 field homogeneity, we collected a high-resolution \( ^{31}P \) spectrum of the resting muscle, taken with fully relaxed nuclear spins [16 free-induction decays (FID) with a 16-s interpulse delay], a spectral width of ±1,250 Hz, and 2,048 data points. We then used a standard one-pulse experiment with partially saturated nuclear spins (1.5-s interpulse delay) to determine changes in PCr, ATP, P, and pH before, during, and after stimulation of the muscle. Four FIDs were averaged per spectrum, yielding a time resolution of 6 s. We did not gate the signal acquisition to the electrical stimulation but reduced artifacts because of movement by stabilizing the limb during the experiment. The rapidly acquired spectra typically had a 55:1 signal-to-noise ratio for the PCr peak in resting muscle.

Quantitative analyses of spectra. The FIDs were Fourier transformed into spectra and analyzed as described in a previous report (13). The areas of the PCr and P, peaks were expressed relative to the ATP peak, which we calibrated using the ATP concentration measured by HPLC for each subject (see Tissue Analysis). Because adequate tissue was not available to measure [ATP] (where brackets denote concentration) in nine subjects, we used the group’s average value for these subjects. Free [ADP] was calculated from the creatine (Cr) kinase equilibrium (20), and we calculated pH by using the chemical shift of the P, peak relative to the PCr peak (54).
Stimulation and recovery protocol. We activated unloaded contractions in the quadriceps muscles by transcutaneous electrical stimulation of the femoral nerve. A 3 × 4-cm cathode was placed over the femoral nerve distal to the inguinal ligament in the femoral triangle, and a 7.5 × 12.5-cm anode was placed posterolaterally on the hip. We monitored quadriceps activation with an electromyogram using an active electrode over the belly of the vastus lateralis muscle and a reference electrode at the tendon just proximal to the patella. We applied a series of single stimulations (150–350 μs) of increasing intensity that allowed us to determine the intensity that evoked the maximum electromyogram response for each subject. During the experiment, subjects received 2 min of supramaximal stimulations at a rate of 3 Hz. We collected 31P-MR spectroscopy spectra during resting baseline (1 min), stimulation (2 min), and recovery (5 min).

Calculations
Oxidative properties and capacity. We fit the PCr recovery after stimulation to a monoeponential function to estimate the time constant (τ) and rate constant (kPCr, = 1/τ) for PCr recovery. The product of kPCr, and [PCr] in resting muscle provides our measure of the maximum oxidative phosphorylation rate (oxidative capacity, Mox, phos) [PCr]rest

$$M_{\text{ox, phos}} = k_{\text{PCr}}, [\text{PCr}]_{\text{rest}} \quad (1)$$

where [PCr]rest is the PCr concentration at rest. This calculation is based on the linear model of oxidative phosphorylation described by Meyer et al. (17, 43, 45), in which the instantaneous rate for PCr recovery at time (t) = 0 is

$$d[\text{PCr}]/dt = k_{\text{PCr},} \cdot \Delta[\text{PCr}] \quad (2)$$

where Δ[PCr] = [PCr]rest - [PCr]o, and [PCr]o is PCr concentration at time 0. We have demonstrated that kPCr,([PCr]rest provides a good estimate of the muscle’s oxidative capacity (12).

Glycolytic ATP synthesis. A second source of energy in the cell is the ATP supplied directly by glycolysis. We use the dynamics of pH and [PCr] during stimulation to estimate the rate of ATP production resulting from carbon flux through glycolysis. Our laboratory’s calculations for this are presented in detail elsewhere (13), but our approach is as follows. The carbon flux generated by glycolysis is either converted to lactate (or alanine) and H+ or oxidized by respiration. The portion that results in lactate formation is estimated from H+ production. This is done using the measured pH and calculations of the H+ buffering capacity of the individual muscle and H+ consumption (via the Cr kinase reaction) during PCr breakdown. We then estimate ATP production using the stoichiometry of 1.5 ATP produced per H+. The portion of carbon flux through glycolysis that is subsequently oxidized during ATP production. We calculate this ATP production based on 1) the fraction of ATP (3/37) generated by glycolysis during the oxidation of glyco- gen to CO2 and H2O, and 2) the estimated relative contribution of pyruvate (50%) to the substrate supply for oxidative phosphorylation. Thus the total PCr (ATP) synthesis resulting from the carbon flux through glycolysis is the sum of the synthesis resulting from the flux that generates H+ and that which is subsequently oxidized.

Contractile ATP demand. Our estimate of the ATP cost of contraction involves three steps, detailed in a recent paper (13). Briefly, we first calculate the rate of oxidative phosphorylation at given ADP concentrations, determined during PCr recovery after stimulation. We then use this relationship between oxidative phosphorylation and [ADP] to subtract the contribution of oxidative ATP synthesis from the PCr level during exercise. The resulting PCr breakdown provides the measure of contractile ATP demand. This is estimated by linear regression of [PCr] vs. time, starting with the last baseline spectrum and ending before the point of pH acidification (~1 min, 180 stimulations).

Tissue Analysis
Muscle biopsy and tissue preparation procedure. We used the Bergstrom needle biopsy technique (16) to acquire tissue from the right vastus lateralis muscle at midheight immediately before training and then within 10 days after the training period ended. An ~25-mg piece was immersion fixed in glutaraldehyde for morphometric analysis and processed for electron microscopy as previously described (27). The remaining tissue was freeze-clamped immediately after collection and stored at ~80°C until subsequent metabolite and myosin heavy chain (MHC) analysis.

HPLC methods. Methods for the extraction of the frozen tissue and HPLC for analysis of PCR, ATP, and Cr contents have been published (58). We expressed metabolite concentrations per volume of cell water by assuming 0.7 ml intracellular water/g muscle mass, as found for human muscle biopsy samples (51).

Gel procedures. MHC isoforms I, IIa, and IIb (IIx) were separated using the SDS-PAGE technique and subsequent silver staining (32, 53). Rat diaphragm was run on each gel as the standard. Although there are differences in rat diaphragm and human skeletal muscle MHCs, these differences are consistent and well documented (48). We imaged the gels with a charge-coupled device camera interfaced with a framegrabber board and quantified the relative proportion of each isoform using the gel analysis macro in the NIH Image program.

Quantitative morphometry. Ultrathin sections (50–70 nm) were cut transverse or slightly oblique to the fiber axis and counterstained. For each subject’s pre- and posttraining specimen, 25–40 photomicrographs (Philips 420 EM) were sampled on 200-square mesh grids from three or four randomly selected blocks. We determined Vv(mt,f) at a final magnification of ×25,000 using point counting on a B36 grid (144 test points) as described in Hoppeler et al. (27).

Sample sizes. The final number of subjects for the MR data set was less than the number of participants in the training because of computer malfunction (n = 2), subject choice (n = 3), or poor quality (n = 1), leaving 15 RT, 10 ET, and 9 control subjects. Budget limitations resulted in final group sizes for the Vv(mt,f) data set of eight RT, nine ET, and eight control subjects. Insufficient tissue limited HPLC analysis to 13 RT, 10 ET, and 8 control subjects and MHC analysis to 13 RT, 11 ET, and 8 control subjects.

Statistics
We performed planned comparisons using two-way paired Student’s t-tests (pre- vs. posttraining) to determine whether there were changes in the variables after exercise training for each group. Data are reported as means ± SE, and the significance level is P < 0.05.

RESULTS
Our goal was to determine the energetic and structural adaptations of elderly quadriceps muscle to exercise training. In this section, we first consider the effectiveness of the training protocols. Next, using PCr
and pH dynamics during and after exercise, we quantify muscle energetics and describe changes with training. Finally, we report changes in quadriceps size as well as in the cell structures that relate to the energetic measurements.

Effectiveness of Training Protocol

Subject compliance with the training schedule was high (94.2 ± 1.4% attendance), and no significant injuries were incurred. The training programs resulted in functional changes for both exercise groups, evidenced by improvements in performance. We used the force developed in the leg press as the measure of effectiveness of the RT program. Subjects in this group increased their leg-press force by 64%, from 1,244.1 ± 100.2 N pretraining to 2,041.4 ± 215.6 N posttraining \((P < 0.001)\). The ET subjects began their training program with only 5–10 min of light exercise and then advanced to 20 min each of lower and upper body exercise at 60% intensity by 5.2 wk and to 80–85% intensity by 10.0 ± 1.0 wk.

Muscle Metabolites and pH

Metabolite levels at rest before and after training are listed in Table 1. The only change seen in resting muscle was increased \([P_i]\) in the RT group. The changes in \([PCR], [Pi]\), and pH during stimulation are shown for each group before and after training in Fig. 1. The drop in \([PCR]\) during stimulation was smaller after training for the ET group (pretraining: 9.1 ± 1.3 mM PCr vs. posttraining: 5.4 ± 0.5 mM PCr; \(P < 0.05\)).

Muscle Energetics

Oxidative ATP supply. The kinetics of PCr recovery after stimulation reflect the oxidative properties of the muscle and are described by the \(k_{PCR}\). Both exercise groups had a significantly greater \(k_{PCR}\) after training (Table 2). The product of \(k_{PCR}\) and resting [PCR] provides an estimate of the muscle’s capacity for oxidative ATP synthesis (12). Because resting [PCR] was unchanged with training in all groups, the increased \(k_{PCR}\) in the RT and ET groups resulted in a greater oxidative capacity after training (57 and 31%, respectively) (Table 2).

Glycolytic ATP supply. The net change in pH during stimulation in each group documents a small accumulation of \(H^+\) and demonstrates that glycolytic flux exceeded the rate of pyruvate oxidation under all conditions.

Table 1. Metabolite concentrations in the resting vastus lateralis muscle before and after training

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>ET</th>
<th>RT</th>
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<tbody>
<tr>
<td><strong>ATP</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pre</td>
<td>5.83 ± 0.31(8)</td>
<td>5.86 ± 0.38(10)</td>
<td>6.15 ± 0.24(13)</td>
</tr>
<tr>
<td>Post</td>
<td>5.30 ± 0.26(8)</td>
<td>5.26 ± 0.40(10)</td>
<td>6.07 ± 0.21(13)</td>
</tr>
<tr>
<td><strong>Creatine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>48.61 ± 3.17(8)</td>
<td>46.27 ± 1.49(10)</td>
<td>45.56 ± 1.28(13)</td>
</tr>
<tr>
<td>Post</td>
<td>44.26 ± 1.37(8)</td>
<td>44.48 ± 2.05(10)</td>
<td>46.10 ± 1.94(13)</td>
</tr>
<tr>
<td><strong>PCr</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>26.72 ± 1.64(9)</td>
<td>25.92 ± 1.57(10)</td>
<td>27.32 ± 1.60(15)</td>
</tr>
<tr>
<td>Post</td>
<td>25.79 ± 1.74(9)</td>
<td>23.80 ± 1.82(10)</td>
<td>29.48 ± 1.73(15)</td>
</tr>
<tr>
<td><strong>Pi</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>3.91 ± 0.43(9)</td>
<td>4.07 ± 0.43(10)</td>
<td>3.83 ± 0.38(15)</td>
</tr>
<tr>
<td>Post</td>
<td>4.00 ± 0.34(9)</td>
<td>4.60 ± 0.67(10)</td>
<td>5.11 ± 0.38(15)</td>
</tr>
<tr>
<td><strong>PCr/ATP</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pre</td>
<td>4.58 ± 0.14(9)</td>
<td>4.46 ± 0.21(10)</td>
<td>4.44 ± 0.56(15)</td>
</tr>
<tr>
<td>Post</td>
<td>4.92 ± 0.33(9)</td>
<td>4.56 ± 0.12(10)</td>
<td>4.84 ± 0.60(15)</td>
</tr>
</tbody>
</table>

Values are means ± SE in mM. Nos. in parentheses indicate no. of subjects. C, control; ET, endurance training; RT, resistance training groups; PCr, phosphocreatine; Pre and Post, before and after training, respectively. ATP and creatine values are from HPLC; others are based on magnetic resonance measurements. *\(P < 0.05\), post- vs. pretraining.

Table 2. Energetic properties of the vastus lateralis muscle before and after training

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>ET</th>
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<tbody>
<tr>
<td><strong>Recovery rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>constant, s⁻¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>0.021 ± 0.002</td>
<td>0.021 ± 0.002</td>
<td>0.023 ± 0.002</td>
</tr>
<tr>
<td>Post</td>
<td>0.021 ± 0.001</td>
<td>0.030 ± 0.002*</td>
<td>0.034 ± 0.004*</td>
</tr>
<tr>
<td><strong>Oxidative capacity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mM PCr/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>0.573 ± 0.07</td>
<td>0.535 ± 0.04</td>
<td>0.627 ± 0.06</td>
</tr>
<tr>
<td>Post</td>
<td>0.535 ± 0.05</td>
<td>0.700 ± 0.07*</td>
<td>0.985 ± 0.12*</td>
</tr>
<tr>
<td><strong>Glycolytic ATP synthesis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mM PCr/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>0.034 ± 0.004</td>
<td>0.050 ± 0.011</td>
<td>0.029 ± 0.004</td>
</tr>
<tr>
<td>Post</td>
<td>0.029 ± 0.005</td>
<td>0.022 ± 0.005*</td>
<td>0.004 ± 0.004</td>
</tr>
<tr>
<td><strong>Contractile ATP demand</strong></td>
<td></td>
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<td></td>
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<tr>
<td>mM PCr/s</td>
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<td></td>
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</tr>
<tr>
<td>Pre</td>
<td>0.219 ± 0.021</td>
<td>0.246 ± 0.027</td>
<td>0.231 ± 0.033</td>
</tr>
<tr>
<td>Post</td>
<td>0.183 ± 0.018</td>
<td>0.195 ± 0.027*</td>
<td>0.240 ± 0.024</td>
</tr>
</tbody>
</table>

Values are means ± SE in mM; \(n = 9, 10, \) and 15 subjects for C, ET, and RT, respectively. *\(P < 0.05\), post- vs. pretraining.
ditions (Fig. 1). The onset of glycolysis is delayed after stimulation begins, as shown by the alkalization of pH. The plateau and subsequent acidification of pH reflect the onset of glycolysis, and this change in pH along with the drop in PCr during exercise is the basis of our estimate of glycolytic flux. Only the ET group showed a change in glycolytic ATP supply, which decreased by about one-half (Table 2).

**Contractile ATP demand.** To determine contractile demand during stimulation, we calculated and subtracted oxidative PCr resynthesis from the net PCr breakdown before the onset of significant glycolytic ATP synthesis. This calculation revealed a 21% drop in contractile ATP demand in the ET group after training (Table 2).

**Muscle Structure**

Two cellular structural correlates of the energetics measured by MR were determined from muscle biopsies to evaluate the structural adaptation to exercise. An ultrastructural representative of oxidative capacity, Vv(mt,f), was 31% greater in the RT group after training (Table 3). No other group showed a significant change. We also calculated one measure of mitochondrial function, oxidative capacity per Vv(mt,f), for subjects with both values available (control: n = 7; ET: n = 7; RT: n = 8). The increased oxidative capacity without change in Vv(mt,f) seen for the ET group resulted in a significantly elevated oxidative capacity per Vv(mt,f) (pretraining: 0.17 ± 0.01 vs. posttraining: 0.21 ± 0.02 mM ATP·s⁻¹·%⁻¹, *P < 0.05). There was no change in oxidative capacity per Vv(mt,f) for the other two groups.

Our second structural measure, the MHC composition of the muscle (Table 3), represents the key protein determining the contractile ATPase rate. No change in MHC composition is apparent in any group after training, despite the significant reduction in contractile ATP demand in the ET group.

### Table 3. Mitochondrial volume density and myosin heavy chain isoforms in the vastus lateralis muscle before and after training

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>ET</th>
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<tbody>
<tr>
<td>Vv(mt, f)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.69 ± 0.22</td>
<td>3.11 ± 0.29</td>
<td>2.69 ± 0.22</td>
</tr>
<tr>
<td>Post</td>
<td>2.91 ± 0.36</td>
<td>3.41 ± 0.22</td>
<td>3.53 ± 0.19*</td>
</tr>
<tr>
<td>MHC I</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pre</td>
<td>0.42 ± 0.05</td>
<td>0.42 ± 0.05</td>
<td>0.42 ± 0.02</td>
</tr>
<tr>
<td>Post</td>
<td>0.41 ± 0.04</td>
<td>0.39 ± 0.04</td>
<td>0.41 ± 0.04</td>
</tr>
<tr>
<td>MHC IIa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>0.42 ± 0.03</td>
<td>0.38 ± 0.03</td>
<td>0.41 ± 0.02</td>
</tr>
<tr>
<td>Post</td>
<td>0.40 ± 0.03</td>
<td>0.43 ± 0.04</td>
<td>0.45 ± 0.03</td>
</tr>
<tr>
<td>MHC IIb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>0.18 ± 0.04</td>
<td>0.20 ± 0.04</td>
<td>0.17 ± 0.03</td>
</tr>
<tr>
<td>Post</td>
<td>0.19 ± 0.03</td>
<td>0.18 ± 0.02</td>
<td>0.14 ± 0.03</td>
</tr>
</tbody>
</table>

Values are means ± SE; Nos. in parentheses indicate no. of subjects. Mitochondrial volume density [Vv(mt, f)] is expressed as % muscle cell volume; myosin heavy chain (MHC) data are expressed as fraction of total MHC content. *P < 0.05, post- vs. pretraining.

**Muscle area and volume.** Muscle CSA and volume increased in the RT group by ~10% after training (Table 4). There was no change for the ET or control groups.

### Table 4. Quadriceps muscle cross-sectional area and volume before and after training

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>ET</th>
<th>RT</th>
</tr>
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<tbody>
<tr>
<td>CSA, cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>45.8 ± 5.1</td>
<td>51.2 ± 5.6</td>
<td>48.0 ± 3.1</td>
</tr>
<tr>
<td>Post</td>
<td>45.0 ± 4.1</td>
<td>52.0 ± 5.5</td>
<td>52.7 ± 3.5*</td>
</tr>
<tr>
<td>Volume, ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1,191.5 ± 147.1</td>
<td>1,301.5 ± 158.7</td>
<td>1,175.2 ± 85.8</td>
</tr>
<tr>
<td>Post</td>
<td>1,147.3 ± 121.6</td>
<td>1,324.2 ± 156.4</td>
<td>1,277.2 ± 97.7*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 9, 10, and 15 subjects for C, ET, and RT, respectively. CSA, cross-sectional area. *P < 0.05, post- vs. pretraining.

**DISCUSSION**

The major results of this study are the large energetic changes in elderly muscle after training that exceeded changes in the corresponding muscle structures. All energetic pathways adapted in the ET group with a >30% increase in oxidative properties of the quadriceps and declines in both glycolytic ATP supply (~56%) and contractile ATP demand (~21%). These changes are consistent with those seen in the activities of marker enzymes measured in young muscle after ET (24). However, in contrast to young muscle after ET (26, 28), our ET subjects showed no change in muscle mitochondrial volume. The large increase in oxidative properties in our RT group also contrasts with the response of young muscle to RT (36). Thus our MR and structural measurements indicate some unique adaptations to exercise training in elderly muscle.

**Muscle Energetics**

**Oxidative properties.** The greatest functional change was apparent in the faster PCr recovery kinetics (higher kPCr) after training for both the ET and RT groups. Many studies indicate that kPCr reflects the oxidative properties of muscle. In humans, kPCr is proportional to oxidative enzyme activity (41) and correlates with muscle O2 uptake and whole body pulmonary O2 uptake for the quadriceps (46) and plantar flexors (40). In addition, the estimate of muscle oxidative capacity for young adults based on kPCr agrees closely with that determined from mitochondrial volume and the maximum respiration rate of isolated mitochondria (12). These studies confirm that the higher kPCr seen in our trained subjects represents a greater muscle oxidative capacity.

**ET and oxidative properties.** The increase in kPCr and muscle oxidative capacity for our ET subjects is consistent with elevations in oxidative enzymes and muscle O2 consumption in elderly muscle (10, 42, 44) and greater muscle oxidative capacity in young muscle after ET (24). Despite this increased function, the ET...
group did not show an increase in Vv(mt,f). A similar discrepancy was found in the elderly by Orlander and Aniansson (44), who reported that Vv(mt,f) was unchanged with ET even though the activity of marker oxidative enzymes increased significantly. We have reported that untrained elderly muscle has a reduced oxidative capacity per mitochondrial volume (12). In the present study, the mismatch of changes in muscle oxidative capacity and mitochondrial volume resulted in a significant elevation of oxidative capacity per mitochondrial volume with ET. Nonetheless, the post-training oxidative capacity per mitochondrial volume (0.21 mM ATP·s⁻¹·%⁻¹) remained well below the value we found in younger adult muscle (0.32 mM ATP·s⁻¹·%⁻¹) (12). Thus, although mitochondrial function can be improved in elderly muscle by training, the ET program used in this study was insufficient to raise this value to that found in younger muscle.

**RT and oxidative properties.** The increase in kPCr and oxidative capacity in the RT group was unexpected. RT in young subjects typically results in lower oxidative enzyme activity and Vv(mt,f), reflecting the dilution of mitochondrial structure with the increase in muscle size (9, 36, 37). Our RT subjects had greater muscle size after training, but this did not lead to a reduction in Vv(mt,f) or oxidative properties. Instead, we found an increased oxidative capacity, and this increase (50%) was greater than that found for the ET group. In addition, Vv(mt,f) increased after RT, in contrast to the lack of change after ET. These improvements in oxidative properties for the RT group are supported by previous reports of increased oxidative enzyme activity and capillary-to-fiber ratio after RT in the elderly (18, 22, 23). Our results indicate that elderly muscle shows adaptations in muscle size and strength in common with young muscle after RT, but the increase in oxidative properties is an unexpected response of elderly muscle to this training.

**Glycolytic properties.** ET resulted in a significant decline in glycolytic ATP supply (~56%). The drop in ATP production from glycolysis is consistent with the reduction of whole body carbohydrate oxidation seen during exercise after ET in elderly subjects (50). On the other hand, the decreased glycolytic flux is in contrast to assays of glycolytic enzymes from biopsies that show either a rise or no change in phosphofructokinase activity after ET in elderly muscle (10, 44).

**Contractile ATP demand.** There are no direct measurements of contractile ATP demand in young muscle after training to compare with the 21% reduction in contractile cost seen in our ET subjects. However, the shift in fiber types from IIb(x) to IIA reported for young muscle after ET (1, 3) is consistent with lower contractile costs because IIA fibers have a lower ATP demand (52). We found no change in MHC isoform composition in our ET or RT subjects. Thus, with training programs similar to those evoking interconversions in the young, our elderly trained subjects showed reduced contractile ATP demand but no isoform interconversions.

**Muscle Adaptation**

Several results of this study suggest that the adaptation of elderly muscle to exercise training is distinct from that of the young. The most striking difference is the increased oxidative capacity in elderly muscle with RT compared with the reduction typically seen in the young. The third dissimilar response of elderly muscle is the large change in energetic properties with ET that was not accompanied by similar changes in the underlying structural properties. No change was found in Vv(mt,f), despite an increase in oxidative capacity that, if seen in young muscle, would be accompanied by a >30% increase in mitochondria (26). Similarly, the shift in MHC composition that is typically seen in young muscle after ET did not accompany the drop in contractile cost as would be expected.

The disparity between structure and function exists in elderly muscle even before training. We have reported that elderly subjects have a reduced oxidative capacity per mitochondrial volume compared with younger (40-yr-old) subjects (12). This observation, made in vivo, supports the findings in vitro of reduced mitochondrial function in elderly muscle (5, 14, 55). Our ET group's significant increase in oxidative capacity without a change in mitochondrial volume resulted in an increased oxidative capacity per mitochondrial volume. Orlander and Aniansson (44) reported a similar finding, with elderly subjects showing elevated citrate synthase activity without a change in Vv(mt,f) after ET. This suggests that the lower mitochondrial function seen with age may be reversible with ET. Indeed, well-trained elderly subjects have been reported to show no deficit in mitochondrial function compared with similar younger subjects (6). Thus it is possible that both mitochondrial content and function can change with exercise training in the elderly.

Another disparity between structure and function is apparent in the change in contractile ATP demand (Table 2) without alteration in MHC composition (Table 3) after ET in the elderly. This disparity is unlikely to stem from differences in the training response of the muscle tissue examined by biopsy (a smaller, more superficial sample) and by MR (a larger, deeper sample). Analysis of fiber-type distribution in whole cross sections of elderly human vastus lateralis muscle demonstrates no systematic difference between superficial and deep regions (34). Thus, in the elderly, fiber recruitment and training effects are unlikely to be confined to or concentrated in one part of the muscle. The lack of change in MHC composition does not appear to be due to the low contractile protein synthesis rate reported for elderly muscle (2, 57) for two reasons. First, exercise training increases protein synthesis rates in elderly muscle to the level found in young muscle (21, 59). Second, the increase in muscle size in this study with RT demonstrates the adaptability of the contractile proteins in elderly muscle. A plausible alternative explanation is that aging results in damage to the myosin isoforms and that exercise training induces a replacement of damaged myosin with undam-
aged protein. Brooks and Faulkner (8) proposed that an impaired capacity for regeneration coupled with contraction-related injury leads to reduced contractile function in old muscle. Isolated fibers from elderly muscle have a lower maximum shortening velocity than do fibers from young muscle (25, 33). Hook et al. (25) suggested that glycosylation of myosin occurs with age and showed that artificial glycosylation of myosin isolated from young muscle reduces the maximum shortening velocity by 13%. A training-induced replacement of defective isoforms may also explain the change in contractile ATP demand without change in MHC.

In conclusion, we found large changes in muscle energetic properties after exercise training in elderly muscle. The increase in oxidative capacity and decrease in both glycolytic ATP synthesis and contractile ATP demand are consistent with the pattern of changes in muscle properties measured on biopsied tissue taken from the young after ET. However, the increase in oxidative capacity after RT is in striking contrast to the decrease in oxidative marker enzyme activity usually seen in the young. In addition, the structures related to these altered energetic fluxes showed either no adaptation (ET group) or relatively less adaptation than the corresponding energetic changes (RT group). These results suggest that the nature of the adaptive process is quite different in the elderly compared with that found in young muscle. Nonetheless, our data demonstrate a significant adaptation of muscle energetics to exercise training in elderly muscle.

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