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V. C. Foletta, M. J. Prior, N. Stupka, K. Carey, D. H. Segal, S. Jones, C. Swinton, S. Martin, D. Cameron-Smith and K. R. Walder

J. Physiol., April 1, 2009; 587 (7): 1619-1634.

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Effect of physical training on function of chronically painful muscles: a randomized controlled trial

L. L. Andersen, C. H. Andersen, M. K. Zebis, P. K. Nielsen, K. Sogaard and G. Sjogaard

J Appl Physiol, December 1, 2008; 105 (6): 1796-1801.

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Changes in muscle size and MHC composition in response to resistance exercise with heavy and light loading intensity

L. Holm, S. Reitelseder, T. G. Pedersen, S. Doessing, S. G. Petersen, A. Flyvbjerg, J. L.

Andersen, P. Aagaard and M. Kjaer

J Appl Physiol, November 1, 2008; 105 (5): 1454-1461.

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Early skeletal muscle hypertrophy and architectural changes in response to high-intensity resistance training

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Seynnes OR, de Boer M, Narici MV. Early skeletal muscle hypertrophy and architectural changes in response to high-intensity resistance training. *J Appl Physiol* 102: 368–373, 2007. First published October 19, 2006; doi:10.1152/jappphysiol.00789.2006.—The onset of whole muscle hypertrophy in response to overloading is poorly documented. The purpose of this study was to assess the early changes in muscle size and architecture during a 35-day high-intensity resistance training (RT) program. Seven young healthy volunteers performed bilateral leg extension three times per week on a gravity-independent flywheel ergometer. Cross-sectional area (CSA) in the central (C) and distal (D) regions of the quadriceps femoris (QF), muscle architecture, maximal voluntary contraction (MVC), and electromyographic (EMG) activity were measured before and after 10, 20, and 35 days of RT. By the end of the training period, MVC and EMG activity increased by 38.9 ± 5.7 and $34.8\% \pm 4.7\%$, respectively. Significant increase in QF CSA (3.5 and 5.2% in the C and D regions, respectively) was observed after 20 days of training, along with a $2.4 \pm 0.7\%$ increase in fascicle length from the 10th day of training. By the end of the 35-day training period, the total increase in QF CSA for regions C and D was 6.5 ± 1.1 and $7.4 \pm 0.8\%$, respectively, and fascicle length and pennation angle increased by 9.9 ± 1.2 and $7.7 \pm 1.3\%$, respectively. The results show for the first time that changes in muscle size are detectable after only 3 wk of RT and that remodeling of muscle architecture precedes gains in muscle CSA. Muscle hypertrophy seems to contribute to strength gains earlier than previously reported; flywheel training seems particularly effective for inducing these early structural adaptations.

muscle cross-sectional area; weight training; magnetic resonance imaging

RESISTANCE TRAINING INDUCES neural and muscular adaptations (2, 21, 29, 31, 33). It is generally accepted that there is a delay before the onset of muscle hypertrophy and that the initial strength gain is mostly due to the intervention of neural factors (18, 29, 34). Several investigators have in fact reported a rapid increase in neural drive, as judged from an increase in integrated electromyographic (EMG) activity, during a maximal contraction, within few weeks of strength training. For instance, Narici et al. (31) observed a $\sim 8\%$ increase in vastus lateralis (VL) muscle EMG in the initial 3 wk of an 8-wk isokinetic strength training period; likewise, Hakkinen et al. (19) reported a $\sim 23\%$ increase in knee extensors EMG activity following 10 wk of strength training. Instead, muscle hypertrophy assessed with imaging techniques such as ultrasound (41), computerized tomography (11–13, 27), or, more recently, magnetic resonance

imaging (MRI) has been typically found only after 8–12 wk of resistance training (3, 19, 21, 23, 31, 41). Considering, however, that the molecular and cellular responses to strength training (translational: involving mRNA-regulatory mechanisms) occur within hours or even minutes of exercise (8, 35) and that fiber hypertrophy has been found after 4 wk of training (40), it seems likely that the often described delay in the onset of muscle hypertrophy is partly due to the sensitivity of the method used to detect hypertrophy. Proliferation of muscle satellite cells has been found to occur within 4 days following a single bout of resistive exercise, sustained by an increase in myofibrillar protein synthesis of $\sim 60\%$ within 4.5 h of a single bout of combined eccentric-concentric contractions (28). Hence the two fundamental adaptations necessary for muscle hypertrophy (i.e., increased protein synthesis and satellite cells proliferation) are mobilized from the very initial phases of strength training. Based on the early molecular and cellular changes, it is likely that the process of muscle hypertrophy starts from the very early phases of the training period and that not a “sudden” but a progressive increase in muscle mass occurs over the training period. This scenario seems indeed consistent with observations on animal muscle that show a continuous increase in muscle mass in response to overloading (cf. Ref. 16). Of course, the degree of muscle hypertrophy and the speed of its development depend on the mode of training, initial training status, and the muscle group investigated (19, 21, 31, 37, 41). In this respect, it has recently been shown that training with isoinertial contractions against a rotating flywheel (Yo-Yo technology, Stockholm, Sweden) is particularly effective in promoting early gains in muscle mass and strength because of the high torques required to break the rotation of the inertial mass (4, 5, 7, 37). Using this training method, a 6.1% increase in muscle mass has been found after just 5 wk of training in young adults (37). Hence these data suggest that hypertrophy actually starts much earlier than previously described. However, the question is: When does it actually start to become detectable?

Hence, the objective of this study was to examine the time course of early muscular adaptations to high-intensity resistance training. We hypothesized that the frequent assessment of muscle size with highly sensitive scanning methods such as MRI, combined with a high training stimulus, would enable the detection of muscle hypertrophy earlier than previously reported.

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Fig. 1. Picture showing the gravity-independent ergometer used for resistance training.

METHODS

Subjects. Seven recreationally active men ($n = 5$) and women ($n = 2$) volunteered to take part in the training program (age: 20 ± 2 yr; height: 179.3 ± 2.8 cm; weight: 74.6 ± 3.0 kg; means $\pm$ SE), and 6 recreationally active males served as control (age, 22 ± 3 yr; height, 181.8 ± 5.4 cm; weight, 75.1 ± 10.3 kg; means $\pm$ SE). The participants were screened for the following exclusion criteria: history of knee injury, chronic knee inflammation, uncontrolled hypertension, and hernia. All subjects gave written informed consent to the study, which was approved by the Ethics Committee of the Institute for Biophysical and Clinical Research Into Human Movement of the Manchester Metropolitan University.

Experimental design. Subjects were tested four times: at baseline, at 10 and 20 days, and at the end of the 35-day training program.

Resistance training. Bilateral leg extension was performed three times per week on a gravity-independent ergometer (YoYo Technology), based on the flywheel principle (7, 37) (Fig. 1). Briefly, the lever arm of the ergometer is attached to a strap, which is wrapped around a flywheel shaft. During the knee extension, the lever arm pulls the strap, which is unwound from the flywheel shaft against the inertia of the flywheel. Once the pushing phase is completed (the length of the strap is adjusted to match the full knee extension), the kinetic energy of the flywheel keeps the shaft rotating and therefore the strap is rewound, pulling back the lever arm. The subject then performs an eccentric contraction by resisting against force produced by the rotation of the flywheel (for a full description see Ref. 37).

Each session began with three sets of seven submaximal leg extensions as a warm-up, and it consisted of four sets of seven maximal coupled concentric and eccentric contractions, with 2-min rest periods between sets.

Maximal voluntary contraction. Knee extension maximal voluntary contraction (MVC) was assessed using an isokinetic dynamometer (Cybex NORM, New York, NY), at 60° , full extension being set as the anatomic zero. Two 5-s trials were performed, with a 2-min resting period between contractions. To calculate the level of antagonistic coactivation, an additional MVC was performed with the knee flexors muscles acting as agonists (see *EMG activity* below).

EMG activity. EMG activity was recorded on VL and biceps femoris (BF) muscles, by the use of bipolar silver chloride surface electrodes (20-mm interelectrode distance). Skin impedance was reduced below $5 \text{ k}\Omega$ by standard preparation including shaving, gentle abrasion, and cleaning with an alcohol-based tissue pad. Recording electrodes were placed along the sagittal axis over the muscle belly, and the reference electrodes were placed onto the medial and lateral tibial condyles. Raw EMG signals were amplified and filtered with a band-pass filter between 10 and 500 Hz (gain 1,000), and they were stored and integrated online with commercially available software (Acqknowledge, Biopac System). BF integrated EMG was normalized as a percentage of its maximal isometric value when acting as an agonist, and used to calculate the level of antagonist coactivation during knee extension. EMG activity was quantified over a period of 250 ms around the peak torque of each contraction.

Muscle architecture. Fiber length and pennation angle were measured in vivo on the resting VL muscle at 80° of knee flexion, by using real-time B-mode ultrasonography (ATL-HDI 3000, Bothell), with a 40-mm, 7.5-MHz linear-array probe. Scans were taken at 50% of the VL muscle length in the midsagittal plane, at the same location as MRI scanning (see *Muscle cross-sectional area* below). Test-retest measurements (5-wk interval) in control subjects indicated these measurements had a coefficient of variation inferior to 1%.

Muscle cross-sectional area. Axial scans of the quadriceps muscle were taken at 25 and 50% of the femur bone length, from the lateral aspect of the distal diaphysis to the greater trochanter, using a 0.2-T MRI scanner (Esaote Biomedica, Genova, Italy). Scan locations were identified using ultrasound, and they were recorded on acetate paper to ensure identical placement. Regions of interest were identified on the scan images with three reference cod liver oil capsules placed onto the skin, aligned within the plane of the slice of interest.

Each axial scan included 3 slices and was taken using a spin echo 26 half-Fourier with the following parameters: time to echo = 16 ms; time to repetition = 38 ms; field of view = 180×180 mm; matrix, 256×192 ; 7 mm of slice thickness and 0.7 mm of interslice gap. All samples were analyzed three times by the same investigator.

The reliability of this measurement in our laboratory has been assessed over 10 separate measurements of the cross-sectional area (CSA) of three heads of the quadriceps muscle taken distally at 25% of the femur bone length [the rectus femoris (RF) muscle cannot be observed at this location], and over 10 separate measurements of the CSA of the four heads of the quadriceps muscle taken distally at 50%

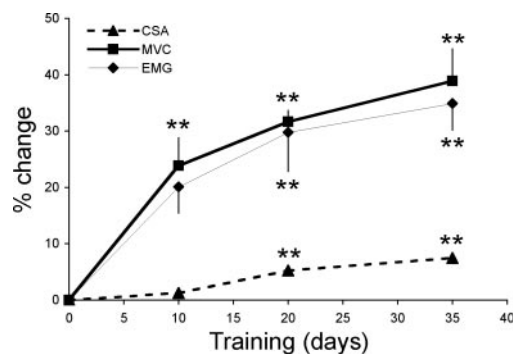


Fig. 2. Time course of changes in proximal quadriceps cross-sectional area (CSA), maximal voluntary contraction (MVC), and EMG activity. Values are means $\pm$ SE. ** $P < 0.01$ vs. baseline.

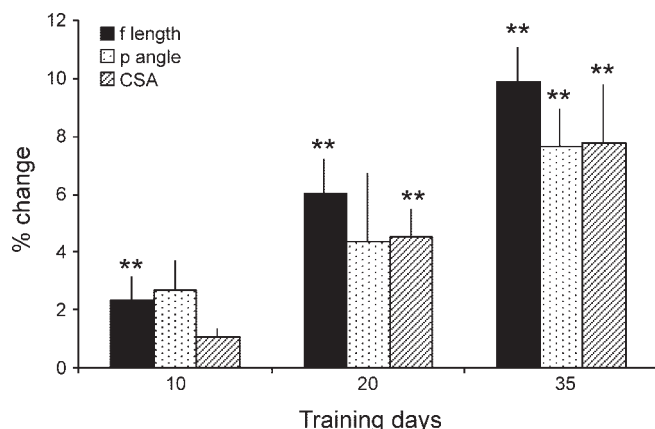


Fig. 3. Time course of structural changes in the vastus lateralis (VL) muscle. f length, Fascicle length; p angle, pennation angle. ** $P < 0.01$ vs. baseline.

of the femur bone length. Investigators were trained to analyze scan images until a satisfactory coefficient of variation ($<1\%$) was obtained. In addition, test-retest measurements in control subjects showed that observed changes in muscle CSA after 5 wk were inferior to 1% (with the exception of the distal VI CSA: 2.34%; data not shown).

Statistical analysis. Differences between training and control group at baseline were tested using an unpaired Student's *t*-test. Because the time course of training-induced changes was only assessed for the training group, a one-way repeated-measures ANOVA was used to look for differences in both training and control group over time. A post hoc Scheffé's test was used when appropriate. Differences between changes in muscle CSA at different locations were tested by using paired *t*-tests. Correlations between variables of interest were calculated using Pearson's correlation coefficient. Data are presented as means $\pm$ SE. Level of significance was set at $P < 0.05$.

RESULTS

There was no significant difference between groups at baseline, and data from the control group did not show any significant change throughout the training program, in any of the measured variables.

MVC. The time course of changes in MVC is presented in Fig. 2. A significant increase was observed after only 10 days of resistance training ($P < 0.01$). At the end of the training program, MVC of the trained group increased by $38.9 \pm 5.7\%$ ($P < 0.001$).

EMG activity. In the training group, there was a progressive increase in EMG activity throughout the training period: $20.1 \pm 4.7\%$ (not significant) after 10 days, $29.8 \pm 7.0\%$ ($P < 0.01$) after 20 days, and $34.8 \pm 4.7\%$ ($P < 0.01$) after 30 days of training (Fig. 2). Antagonist EMG activity did not change significantly over the training period.

Muscle architecture. Fascicle length of the VL muscle increased by $2.4 \pm 0.7\%$ after 10 days of training ($P < 0.01$), and it increased by $9.9 \pm 1.2\%$ at the end of the training period ($P < 0.001$). Although a similar trend was observed with the angle of pennation of the fascicles, these changes were only significant ($7.7 \pm 1.3\%$; $P < 0.01$) after 35 days of resistance training (Fig. 3).

Muscle CSA. The increase in cross-sectional area of the whole quadriceps in the trained group became significant after 20 days of resistance training, both distally ($P < 0.01$) and proximally ($P < 0.001$) (Table 1, Fig. 4). The total increase in quadriceps CSA following training was $6.5 \pm 1.1\%$ ($P < 0.001$) and $7.4 \pm 0.8\%$ ($P < 0.001$) distally and proximally, respectively. There was no correlation between the magnitude of muscle CSA changes and baseline CSA. There was no significant difference between changes in CSA of the quadriceps distally and at midhigh. The time course of these changes is presented in Fig. 5.

Individual muscles CSA. Scans from the distal part of the thigh showed a significant hypertrophy of the VL muscle of $9.0 \pm 3.7\%$ ($P < 0.05$) after 20 days, and of $13.8 \pm 3.1\%$ ($P < 0.01$) at the end of the training program. Significant increases of the CSA of the vastus intermedius (VI) and vastus medialis (VM) muscles were only observed after 35 days of training ($6.0 \pm 1.9\%$, $P < 0.001$; and $5.5 \pm 1.9\%$, $P < 0.01$, respectively).

The CSA of the RF muscle could not be observed distally because of its anatomic location; however, a significant hypertrophy of $7.4 \pm 2.7\%$ ($P < 0.001$) was observed on this muscle at midhigh following 20 days of resistance training. This increase reached $11.4 \pm 5.0\%$ ($P < 0.001$) by the end of the training program. At the same anatomic location, CSA of VL and VM muscles increased by $4.5 \pm 1.0\%$ ($P < 0.05$) and $6.3 \pm 2.8\%$ ($P < 0.05$), respectively, after 20 days of training, and it increased up to $7.8 \pm 2.0\%$ ($P < 0.01$) and $8.6 \pm 3.0\%$ ($P < 0.01$), respectively by the end of the training period. The $5.9 \pm 2.9\%$ change in VI muscle CSA was not significant (Fig. 6).

Paired *t*-tests did not reveal any anatomic site-dependent differences between changes observed distally and at midhigh in the VL, VI, and VM muscles. Similarly there were no significant differences between changes in CSA of different muscles when compared at the distal end of the quadriceps or at midhigh.

DISCUSSION

Along with increased muscle strength, this study reports for the first time significant quadriceps muscle hypertrophy (3.5 – 5.2%) after only 20 days of a 5-wk training period in young

Table 1. Muscle- and region-specific quadriceps CSA following 20 days and 35 days of resistance training

Training Days	Midhigh CSA					Distal CSA				
	VL	VI	VM	RF	Quadriceps	VL	VI	VM	Quadriceps	
0	22.36 $\pm$ 1.36	20.85 $\pm$ 0.82	16.89 $\pm$ 1.66	5.71 $\pm$ 0.28	65.81 $\pm$ 3.19	5.21 $\pm$ 0.72	14.12 $\pm$ 1.22	20.85 $\pm$ 1.56	40.19 $\pm$ 2.89	
20	23.33 $\pm$ 1.34*	21.77 $\pm$ 0.64	17.84 $\pm$ 1.62*	6.21 $\pm$ 0.36†	69.16 $\pm$ 3.09†	5.70 $\pm$ 0.82*	14.51 $\pm$ 1.10	21.35 $\pm$ 1.55	41.57 $\pm$ 2.96†	
35	24.08 $\pm$ 1.48†	22.01 $\pm$ 0.78	18.20 $\pm$ 1.61†	6.35 $\pm$ 0.34†	70.65 $\pm$ 3.07†	5.96 $\pm$ 0.86†	14.86 $\pm$ 1.09†	21.99 $\pm$ 1.67†	42.81 $\pm$ 3.10†	

Values are means $\pm$ SE given in cm². CSA, cross-sectional area; VL, vastus lateralis; VI, vastus intermedius; VM, vastus medialis; RF, rectus femoris. *Significantly greater than baseline, $P < 0.05$. †Significantly greater than baseline, $P < 0.01$.

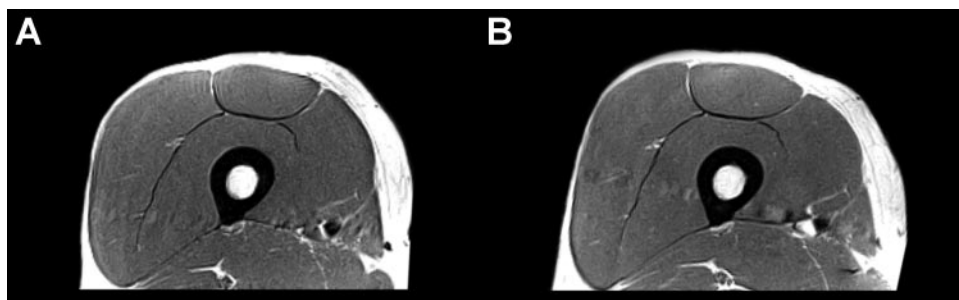


Fig. 4. Magnetic resonance imaging scans of the quadriceps muscles before (A) and after (B) 20 days of resistance training. In B, hypertrophy of the knee extensors is clearly visible.

adults. This finding not only represents the earliest onset of muscle hypertrophy so far documented but also shows a striking rate of increase in muscle size of $\sim 0.2\%$ per day over the first 20 days of training.

Maximal muscle strength increased by 38% at the end of the training period, and given that quadriceps CSA increased by 7%, this suggests that neural factors accounted for a major portion of the observed strength gain, in line with previous observations of our laboratory and others (2, 29, 31, 33). Whereas the neural factors (increased recruitment) have been typically found to account for the early strength gains occurring within the first 4–5 wk of training, the hypertrophic factors have been claimed to have a later onset (34). In the present study, we observed a significant gain in MVC after 10 days of training, about fivefold greater than the increase in muscle CSA (Fig. 2). The fact that a gain in MVC occurred before any sizeable increase in CSA could be detected is likely due to an increase, yet nonsignificant, in EMG activity (20%) after 10 days of training. This is in agreement with previous observations of early changes in neural drive accounting for the early gains in muscle strength (29).

It is noteworthy that the summation of the increases in agonist EMG activity (35%) and in CSA (7%) exceeds the increase in MVC (39%). Indeed, because there is a direct proportionality between muscle size and force (10), one would expect the summed increased contributions of neural and muscular factors to match more or less the strength gains. The slight discrepancy between the strength gains and the improvement in muscle activation and muscle CSA could be due to the site of recording of the EMG activity. Indeed, the EMG activity acquired from the sole VL muscle may not be representative of the overall increase in the quadriceps femoris, because adaptations to resistance training in this muscle group are heterogeneous (32). Another possible explanation could lie in the

nonlinearity of the relationship between MVC and EMG activity. This relationship has been reported to depend on muscle fiber composition (25, 39). Being the quadriceps muscle of mixed composition, it can be hypothesized that an increase in strength within the curvilinear portion of the relationship would result in a bigger relative increase in EMG activity.

It was not the aim of this study to measure the cellular and molecular responses that promote muscle growth, e.g., gene transcription factors, translational mechanisms, local production of insulin-like growth factor I (IGF-I), or protein synthesis rate. However, previous research has shown that these adaptive processes occur within hours following one single bout of resistance training (8, 17). In addition, muscle overload is known to result in the expression of IGF-I which in turn stimulates protein synthesis by activation of the phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) pathway (see Ref. 15 for review). In transgenic mice, Lai et al. (26) recently showed that an acute activation of Akt for 2–3 wk elicited a twofold increase of muscle fiber CSA. Although the experimental setting and model used by Lai et al. and in the present work are completely different, future investigations should examine whether the dramatic increase in protein synthesis rate by the activation of Akt coincides with the observation of muscle growth at the macroscopic level. Regardless of the mechanisms underlying the present findings, early structural changes at the macroscopic level seem related to both the training stimulus and the method of measurement of the hypertrophic response. However, considering the similar hypertrophy (6% increase in muscle volume) observed in a 35-day strength training study using the same equipment and protocol (37), it is likely that the early onset time of hypertrophy detected in the present study is mostly attributable to the

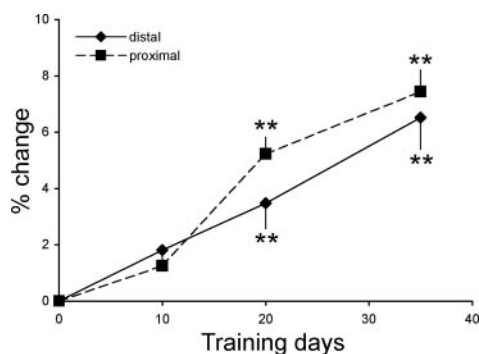


Fig. 5. Time course of changes in quadriceps CSA. Values are means $\pm$ SE. ** $P < 0.01$ vs. baseline.

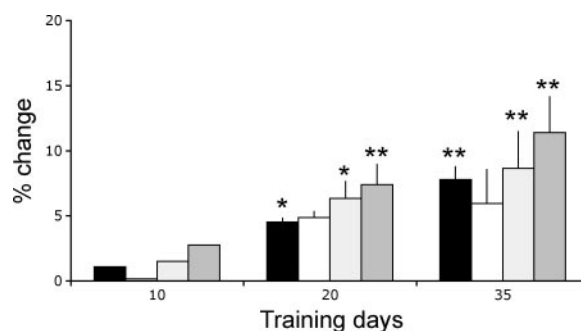


Fig. 6. Time course of changes in CSA of VL, vastus intermedius (VI), vastus medialis (VM), and rectus femoris (RF) muscles at the proximal part of the thigh. Values are means $\pm$ SE. * $P < 0.05$ vs. baseline. ** $P < 0.01$ vs. baseline.

particularly effective mechanical loading provided by the isoinertial flywheel.

By means of rotating flywheels, this inertia-based system not only sets the exercise independent from gravity but also allows maximal voluntary exertion both concentrically and eccentrically. This specificity is of critical importance in the enhancement of the training stimulus for eccentric contraction produces more myofibrillar disruption (14), increased local production of IGF-I (6) and therefore a greater hypertrophic response (20, 21). Thus the near maximal effort throughout the whole range of motion during both concentric and eccentric contractions probably provided a greater stimulus than that obtained with conventional high-intensity resistance training.

The greater significant change in muscle CSA was observed on the RF, at midthigh, corresponding to the distal portion of this muscle. This region-specific muscle hypertrophy is in line with previous training studies (22, 30, 31, 37). Our findings show that, distally, VL CSA increased earlier (20 days) and to a greater extent than VM and VI, and a similar trend was observed at midthigh on RF CSA. All together, these results extend previous literature on muscle and region specificity of the hypertrophic response, and they point out the importance of the scan location in training studies. The physiological mechanisms underlying these differences have not, to our knowledge, been clearly demonstrated. However, mechanical stimuli being a determinant factor for muscle growth (16), the discrepancies in hypertrophic response could be due to regional differences in the amount of stimuli transmitted along the muscle length. Muscle fiber forces are not only transmitted longitudinally to the tendinous structures but are also transmitted laterally (36) through the connective tissue matrix. Therefore, any intermuscle differences in architecture will lead to differences in the transmission of force to tendinous structures along the sarcomeres and thus to intermuscular differences in the amount of protein disruption. Similarly, lateral transmission of fiber forces leads to differences in the amount of force generated along the muscle proximally and distally (24), which could also explain regional differences in hypertrophic response.

In the present study, muscle hypertrophy was associated with significant changes in muscle architecture. This finding is in line with previous reports of an increase in fascicle length and pennation angle with strength training (1, 9). An increase in fascicle length and pennation angle suggests the addition of sarcomeres both in series and in parallel (38). In the present study, a significant increase in fascicle length (2%) was observed before any significant increase in angle of pennation and anatomic CSA. This finding suggests that remodelling of muscle architecture by addition of sarcomeres in series preceded the development of hypertrophy at the macroscopic level. It is known that stretch combined with overloading is the most effective stimulus for promoting muscle growth through the addition of sarcomeres in parallel and in series (16). The present findings suggest that the stronger eccentric component of the flywheel ergometer induces greater stretch of muscle fibers than conventional weight-lifting machines, and it promotes a faster addition of sarcomeres in series (as inferred from the increase in fascicle length) than of sarcomeres in parallel (as inferred from the increase in anatomic CSA and pennation angle). As a matter of fact, an increased in fascicle length was detected after only 10 days of training, whereas increases in

CSA and pennation angle were found after 20 and 35 days, respectively.

In conclusion, the present study shows for the first time that changes in muscle size can be observed at a macroscopic level after only 3 wk of resistance training, providing that the training stimulus is sufficient. These results do not challenge previous findings on the contribution of neural factors to the early strength gains; instead, they suggest that the contribution of hypertrophy to strength gains during training occurs earlier than previously reported.

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