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## Skeletal muscle hypertrophy in response to isometric, lengthening, and shortening training bouts of equivalent duration

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**Adams, Gregory R., Daniel C. Cheng, Fadia Haddad, and Kenneth M. Baldwin.** Skeletal muscle hypertrophy in response to isometric, lengthening, and shortening training bouts of equivalent duration. *J Appl Physiol* 96: 1613–1618, 2004; 10.1152/jappphysiol.01162.2003.—Movements generated by muscle contraction generally include periods of muscle shortening and lengthening as well as force development in the absence of external length changes (isometric). However, in the specific case of resistance exercise training, exercises are often intentionally designed to emphasize one of these modes. The purpose of the present study was to objectively evaluate the relative effectiveness of each training mode for inducing compensatory hypertrophy. With the use of a rat model with electrically stimulated (sciatic nerve) contractions, groups of rats completed 10 training sessions in 20 days. Within each training session, the duration of the stimulation was equal across the three modes. Although this protocol provided equivalent durations of duty cycle, the torque integral for the individual contractions varied markedly with training mode such that lengthening > isometric > shortening. The results indicate that the hypertrophy response did not track the torque integral with mass increases of isometric by 14%, shortening by 12%, and lengthening by 11%. All three modes of training resulted in similar increases in total muscle DNA and RNA. Isometric and shortening but not lengthening mode training resulted in increased muscle insulin-like growth factor I mRNA levels. These results indicate that relatively pure movement mode exercises result in similar levels of compensatory hypertrophy that do not necessarily track with the total amount of force generated during each contraction.

resistance exercise; isovelocity actions; insulin-like growth factor I; mechano-growth factor

IN THE ABSENCE OF PATHOLOGICAL conditions, the structural and functional properties of skeletal muscle are generally matched to the current level of demand placed on individual muscles. In response to increased demand, such as might be encountered with changes in occupational or leisure activities, skeletal muscle can adapt via an increase in myofiber size and an alteration in the composition of the metabolic and contractile proteins expressed. Antipodal changes can also occur with significant decreases in loading (26).

The mechanisms that mediate the functional adaptation of skeletal muscle appear to reside, primarily, within the impacted muscle. This circumstance accounts for the specific adaptation of effected muscles.

The skeletal muscle loading experienced as part of occupational and athletic activities often includes periods of loaded muscle shortening and lengthening as well as periods during which muscles are activated but no external length changes occur (isometric loading). The relative contribution of these

three modes of loading to the processes that stimulate muscle adaptation is of great interest in the area of programmed resistance training. It is well known that resistance training paradigms that include sufficient intensity, frequency, and duration can induce skeletal muscle adaptations that include compensatory hypertrophy (22). It has also become common for such programs to emphasize one particular training mode (e.g., lengthening, shortening, or isometric). Training programs that have employed relatively pure shortening, lengthening, or isometric loading have demonstrated that each of these three modes of loading can stimulate muscle adaptations, including hypertrophy and strength gains (11, 13, 15, 18–21, 23, 24, 30, 33). Various studies that have compared modes have reported that one mode appears to be more effective than another in stimulating various measures of adaptation (11, 15–17, 19, 21, 23, 24, 28). For example, Komi and Buskirk (21) reported that training in the lengthening mode resulted in greater increases in strength (testing all 3 modes) than shortening mode exercise. In contrast, Rutherford's group reported that lengthening-mode training (LMT) generally resulted in lesser gains in strength and muscle size than either isometric-mode (IMT) (19, 27, 28) or shortening-mode training (SMT) (19, 27, 28). In addition, studies have shown that combined shortening + lengthening training is superior to training using only the SMT with regard to increases in strength (e.g., Ref. 9). When attempting to understand the various training studies, it is important to note that, depending on the study design, the absolute loading imposed during LMT is often substantially greater than that imposed in SMT or IMT (16, 17, 19, 21). For example, in two such studies, where the lengthening loads could be discerned from the methods, the lengthening exercises involved forces that were 145–166% of that imposed during shortening mode training (19, 21). In a contrasting experimental design, Mayhew et al. (23) compared SMT and LMT at the same relative power and found that SMT resulted in greater hypertrophy (type II fibers) and a greater isometric strength increase.

Direct comparisons of the impact of training mode on muscle adaptation have been conducted almost exclusively in humans, most often using voluntary muscle activation. Voluntary resistance training in humans is complicated by factors such as the potential for motor learning and therefore neural adaptation. The purpose of the present study was to compare training paradigms involving muscle shortening, lengthening, or isometric loading in a rat model by using electrical stimulation of the nerve to induce muscle activation. Our working hypothesis was that training modes that produced relatively greater levels of force would result in significantly greater

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hypertrophy. Contrary to this hypothesis, our results indicate that, for a equal period of maximal activation with equivalent stimulation parameters, the hypertrophy response was similar with each of these exercise modes.

## METHODS

**Animals.** This study was conducted in conformity with APS's *Guiding Principles in the Care and USE of Animals*, and the protocol was approved by the University of California IACUC. Young adult female Sprague-Dawley rats weighing  $252 \pm 4$  g were randomly assigned to three groups (minimum 6 per group): IMT, SMT, or LMT. Rats were group housed in standard vivarium cages on a 12:12-h light-dark cycle and were allowed access to food and water ad libitum.

**Muscle activation.** For each training bout, the rats were lightly anesthetized with ketamine (30 mg/kg), xylazine (4 mg/kg), and acepromazine (1 mg/kg). Stimulation electrodes consisting of Teflon-coated stainless steel wire were introduced into the subcutaneous region adjacent to the popliteal fossa via 22-gauge hypodermic needles. The needles were then withdrawn, leaving the wire in place. Before electrode insertion, a small section of Teflon coating was removed to expose the wire. Wire placement was lateral and medial of the location of the sciatic nerve, allowing for field stimulation of the nerve. The stimulation wires were then attached to the output poles of a Grass stimulus isolation unit interfaced with a Grass S8 stimulator. This allowed for the delivery of current to the sciatic nerve, resulting in muscle contraction. The rats were then positioned in a specially built training platform described previously (6). The right leg was positioned in a footplate attached to the shaft of a Cambridge model H ergometer. The voltage and stimulation frequency ( $52 \pm 0.8$  Hz) were adjusted to produce maximal isometric tension. Pilot studies indicated that this approach resulted in reproducible torque production within and between rats over multiple training sessions.

**Training protocols.** For all exercise bouts, the stimulation parameters were 1 s of stimulation with 20 s between stimulations, 5 stimulations per set. Four sets of stimulation were applied with 5 min of recovery between sets. In each case, this protocol resulted in <20% fatigue (first set vs. last set). After each training session, the electrodes were withdrawn.

The training protocols were controlled by computer via a digital-to-analog board (model DDA-06, Keithley Instruments) used to control footplate excursion and to trigger the stimulus. A separate analog-to-digital board (DAS-16) was used to acquire force measurements (100-Hz acquisition). Data acquisition, control of stimulus triggering, and footplate excursion were programmed by using LabTech Notebook (Laboratory Technologies). Data analysis was conducted by using AcqKnowledge software (Biopac Systems). Force output was monitored in real time on the computer screen during each contraction.

Rats were trained at the beginning of their standard light cycle, every other day for 20 days (e.g., 10 training sessions). For the IMT group, rats were positioned with the right foot on the footplate with an angle of  $\sim 44^\circ$  relative to the tibia. During muscle stimulation, there was no change in footplate angle. For the SMT group, the ergometer allowed the footplate to move from  $44$  to  $64^\circ$  after the initial development of maximal isometric tension. For the LMT group, the ergometer allowed the footplate to move from  $44^\circ$  to  $24^\circ$  after the

development of maximal isometric tension. For the SMT and LMT treatments, the 1-s stimulation included 0.3 s of isometric force development and 0.7 s for the movement. The rate of movement in the SMT and LMT treatments was limited to  $29^\circ/\text{s}$  to maintain force development.

**Force and torque measurement.** The ergometer system used in these studies allows for rotation of a central shaft that is also instrumented for the detection of torque. The degrees of movement are known for the lengthening and shortening modes of exercise, and thus work can be calculated. However, isometric exercise does not include external work (i.e., length change), and therefore work cannot be calculated. Because the moment arm was essentially the same for each animal, the data for each exercise mode represent a measure of force generation. To allow direct comparisons between modes, the data are reported as a torque-time integral.

**Tissue collection.** Twenty-four hours after the last training bout (day 20), the rats were killed via an injection of Pentosol euthanasia solution (Med-Pharmex) at a dose of 0.4 ml/kg ( $\sim 160$  mg/kg pentobarbital sodium ip) (14). At the cessation of heart beat, a skin incision was made, and the leg muscles of interest (tibialis anterior, plantaris, soleus, and medial gastrocnemius) were dissected free, weighed, and snap-frozen for later analysis.

**Biochemical and molecular analyses.** Tissue samples were analyzed for total protein content as described previously (1). Myofibrillar protein content was determined via a modification of the method described previously (29).

**Total RNA isolation.** Total RNA was extracted from preweighed frozen muscle samples using the TRI Reagent (Molecular Research Center, Cincinnati, OH) according to the company's protocol, which is based on the method described by Chomczynski and Sacchi (7). Extracted RNA was precipitated from the aqueous phase with isopropanol and after, being washed with ethanol, was dried and suspended in a known volume of nuclease-free water. The RNA concentration was determined by optical density at 260 nm (using an optical density 260-nm unit equivalent to  $40 \mu\text{g}/\text{ml}$ ). The muscle total RNA concentration is calculated on the basis of total RNA yield and the weight of the analyzed sample. The RNA samples were stored frozen at  $-80^\circ\text{C}$  to be used subsequently in relative RT-PCR procedures.

**RT.** One microgram of total RNA was reverse transcribed for each muscle sample by using the SuperScript II RT from GIBCO BRL and a mix of oligo(dT) (100 ng/reaction) and random primers (200 ng/reaction) in a  $20 \mu\text{l}$  total reaction volume at  $45^\circ\text{C}$  for 50 min, according to the provided protocol. At the end of the RT reaction, the tubes were heated at  $90^\circ\text{C}$  for 5 min to stop the reaction and then were stored at  $-80^\circ\text{C}$  until used in the PCR reactions for specific mRNA analyses (see below).

**PCR.** A relative RT-PCR method using 18S as an internal standard (Ambion, Austin, TX) was applied to study the expression of specific mRNAs for insulin-like growth factor I (IGF-I) and mechano-growth factor (MGF). The sequence for the primers used for the specific target mRNAs is shown in Table 1. These primers were purchased from Life Technology, GIBCO. In each PCR reaction, 18S ribosomal RNA was coamplified with the target cDNA (mRNA) to serve as an internal standard and to allow correction for any differences in starting amounts of total RNA.

Table 1. Sequence of the specific sets of primers that were used in RT-PCR mRNA analyses

Target mRNA	PCR Primer Sequence 5' → 3'	Product Size, bp	GenBank Accession No.
IGF-I (all)	5' sense: GCATGTGGATGAGTGTTC	202 all 254 MGF	X06043
	3' antisense: GGCTCCTCCTACATTCTGTA		
MGF	5' sense: GCATGTGGATGAGTGTTC	163	X06108
Load-sensitive IGF-I	3' antisense: CTTTTCTTGTGTGTCGATAGG		

IGF-I, insulin-like growth factor I; MGF, mechano-growth factor.

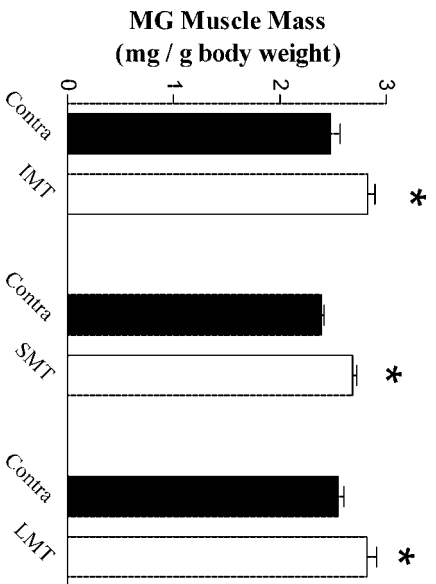


Fig. 1. Increased muscle mass resulting from resistance training. IMT, isometric mode training; SMT shortening mode training; LMT, lengthening mode training; Contra, contralateral untrained muscle; MG, medial gastrocnemius. Values are means  $\pm$  SE. \* $P < 0.05$  vs. Contra.

For the 18S amplification, we used the Alternate 18S Internal Standards (Ambion), which yields a 324-bp product. The 18S primers were mixed with competitors at an optimized ratio that could range from 1:4 to 1:10, depending on the abundance of the target mRNA. Inclusion of 18S competitors was necessary to bring down the 18S signal, which allows its linear amplification to the same range as the coamplified target mRNA (Relative RT-PCR kit protocol, Ambion).

For each target mRNA, the RT and PCR reactions were carried out under identical conditions by using the same reagents premix for all the samples to be compared in the study. To validate the consistency of the analysis procedures, at least one representative from each group was included in each RT-PCR run.

One microliter of each RT reaction (0- to 10-fold dilution depending on target mRNA abundance) was used for the PCR amplification. The PCR reactions were carried out in the presence of 2 mM  $MgCl_2$  by using standard PCR buffer (GIBCO), 0.2 mM dNTP, 1  $\mu$ M specific primer set, 0.5  $\mu$ M 18S primer-competitor mix, and 0.75 unit of DNA *Taq* polymerase (GIBCO) in 25  $\mu$ l total volume. Amplifications were carried out in a Stratagene Robocycler with an initial denaturing step of 3 min at 96°C, followed by 25 cycles of 1 min at 96°C, 1 min at 55°C (55–60°C depending on primers), 1 min at 72°C, and a final step of 3 min at 72°C. PCR products were separated on a 2–2.5% agarose gel by electrophoresis and stained with ethidium bromide, and signal quantification was conducted by laser scanning densitometry, as reported previously (31). In this approach, each specific mRNA signal is normalized to its corresponding 18S. For each primer set, PCR conditions (cDNA dilutions, 18S competitor-primer mix,  $MgCl_2$  concentration, and annealing temperature) were set to optimal conditions so that both the target mRNA and 18S product yields were in the linear range of the semilog plot when the yield is expressed as a function of the number of cycles (5).

**Statistical analysis.** All values are reported as means  $\pm$  SE. For each time point, treatment effects were determined by one-way ANOVA with post hoc testing by using the Prism software package (Graphpad). Pearson's correlation analysis was used to assess the relationship between torque-time integrals and changes in muscle mass by using the Prism package. Analysis of nonparametric data, such as percents, was conducted by using Kruskal-Wallis testing with Dunn's post hoc analysis (Prism, Graphpad). For all statistical tests the 0.05 level of confidence was accepted for statistical significance.

## RESULTS

All three resistance training paradigms resulted in muscle hypertrophy. Relative to the contralateral muscles, the mass of

the trained medial gastrocnemius muscles increased by 14, 12, and 11%, for the IMT, SMT, and LMT groups, respectively (Fig. 1). For each group, the total and myofibrillar protein concentrations of the treatment and contralateral medial gastrocnemius muscles were not different, indicating that the differential changes in mass were related to the hypertrophy response and not some other factor such as edema (data not shown).

The hypertrophy response in the trained muscles was accompanied by a significant increase in muscle DNA and total RNA content that was similar for all three treatment modes (Fig. 2, A and B).

We have previously reported that IGF-1 and the loading-sensitive IGF-1 isoform, MGF, respond to changes in loading state (1, 2, 14). We have used IGF-1 and MGF mRNA as markers of molecular level responses generated by the resistance training protocols. IMT and SMT training resulted in significant increases in the expression and/or accumulation of the mRNAs for IGF-1 and MGF, the loading-sensitive IGF-1 isoform (32) (Fig. 3). IGF-1 and MGF mRNAs were not significantly increased in response to LMT training (Fig. 3).

As an index of the relative torque produced during each training paradigm, the integral of the torque curves for the third stimulation from each set was calculated. For the 10 training sessions, the mean value for these integrals was significantly different for all three modes of training (Fig. 4). LMT training resulted in a torque integral that was 1.9- and 3-fold greater than that of the IMT and SMT treatments, respectively (Fig. 4). The mean torque integral of the IMT group was 1.6-fold greater than that of the SMT group (Fig. 4). Similar responses were noted if the accumulated torque values were analyzed (data not shown).

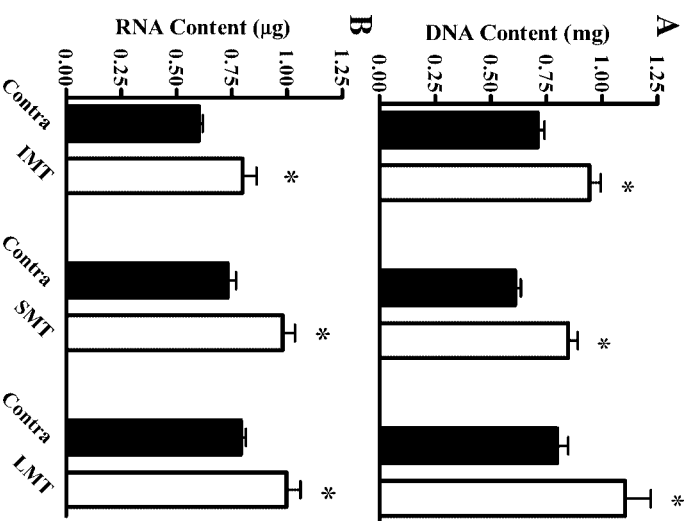


Fig. 2. Increased content of DNA (A) and RNA (B) resulting from resistance training. Values are means  $\pm$  SE. \* $P < 0.05$  vs. Contra.

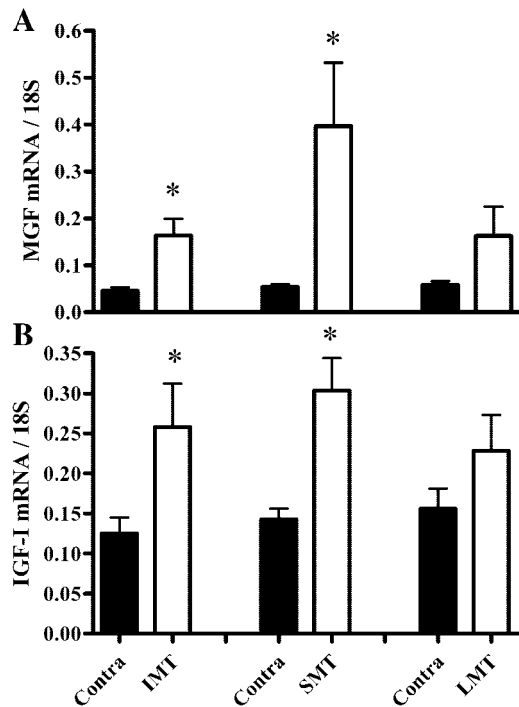


Fig. 3. Changes in the expression and/or accumulation of mRNA for mechano-growth factor (MGF; A) or insulin-like growth factor I (IGF-I; B). \* $P < 0.05$  vs. Contra.

There was no correlation between training-induced changes in muscle mass (e.g., trained minus contralateral mass) and the mean torque integral value for all treatment muscles (Fig. 5).

#### DISCUSSION

The relative effectiveness of LMT, SMT, or IMT has been a matter of interest for quite some time (e.g., Ref. 8). Clearly,

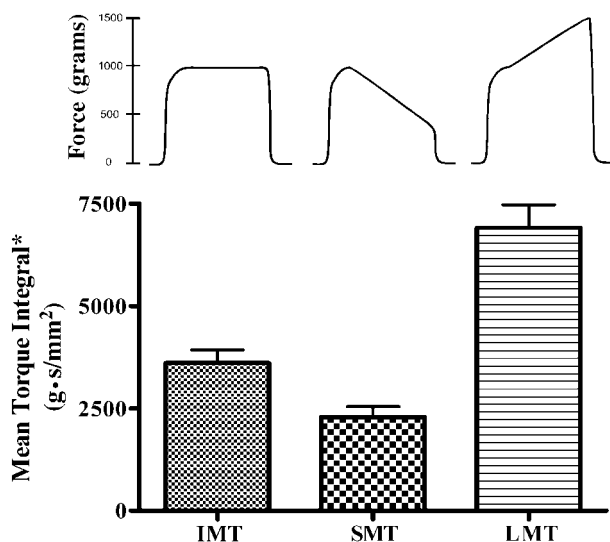


Fig. 4. Torque production during functional electrical stimulation-induced resistance exercise training. *Top*: typical 1-s torque tracings from data sets collected during resistance exercise training. For SMT, foot position moved from 44° to 64° and from 44° to 24° for LMT. *Bottom*: mean torque integral calculated from all of the training sessions for all rats presented by training mode. Values are means  $\pm$  SE. \*Each mean torque integral value is significantly different from the other,  $P < 0.05$ .

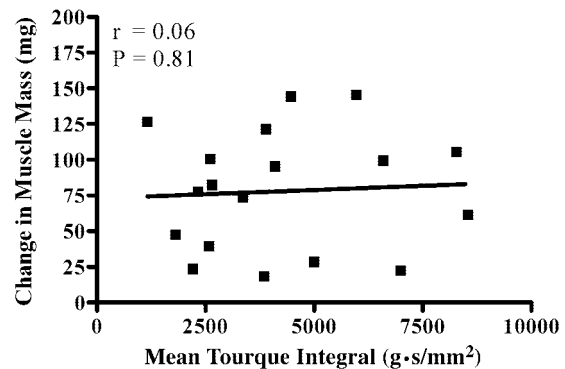


Fig. 5. Across modes, there was no apparent relationship between the change in muscle mass and the mean torque integral after resistance exercise training.

each training mode can contribute to muscle adaptation. However, the results from numerous studies conducted in humans have often led to some confusion as to the relative effectiveness of IST, SMT, or LMT. This is particularly true with regard to changes in strength. In this context, some of this confusion is related to the types of testing involved, in that the impact of the individual training mode appears to have some specificity for testing in the same mode.

Muscle mass is arguably the most important determinant of functional capabilities and as such is an important consideration in a number of occupational and clinical settings. Load-bearing or resistance-type exercise is the primary method for the maintenance, increase, or recovery of muscle mass. This can be particularly important in settings where muscle atrophy is a risk such as bed rest or spaceflight. The focus of the present study was the relative effectiveness of IMT, SMT, and LMT in stimulating a hypertrophy response. Although there have been a number of human resistance training studies that included reliable measurements of changes in muscle- or muscle fiber-size, few of these studies have also included systematic comparisons of the relative impacts of training mode on the compensatory hypertrophy response. As a result, we know that IST, SMT, or LMT can stimulate muscle hypertrophy but little is known about the relative effectiveness of each mode in stimulating this response.

With regard to animal studies and resistance exercise, the results found in the literature generally involve models in which the loading and/or contraction mode of muscles or muscle groups cannot be quantified (e.g., Refs. 2, 3, 10). The methods used in the present study represent an attempt to overcome this shortcoming. One shortcoming of the present study is that the force output recorded was the net result of activation of all the muscles downstream from the point of stimulation on the nerve. For each training mode, the 10 training sessions imposed in this study had no measurable effect on the mass of the soleus and tibialis anterior muscles and minimal impacts on the plantaris (data not shown). Therefore, we have assumed that the majority of the force measured during stimulation is being generated by the gastrocnemius muscle. In the rat, the gastrocnemius muscle makes up 75–80% of the mass in the posterior leg muscles (e.g., triceps surae plus the plantaris), whereas the medial head of the gastrocnemius accounts for ~40% of that total muscle mass. Thus we believe that the changes seen in the medial gastrocnemius muscles are reflective of the impact of this resistance training protocol.

In light of the significant differential in torque integrals for the three training modes (Fig. 4), it may seem somewhat surprising that the majority of the anabolic impacts were remarkably similar. For example, the relative changes seen in DNA and RNA were not different for the three modes (Fig. 2 and data not shown). However, at the molecular level, there was some divergence in the responses measured in the medial gastrocnemius muscle. For example, the mRNA for the two IGF-I isoforms was significantly increased after IMT and SMT, but these changes did not reach significance in the LMT muscles (Fig. 3). In an acute study (e.g., single bout), Bamman et al. (4) found that lengthening but not shortening exercise resulted in a significant increase in IGF-I mRNA in muscle (4). However, it is not clear whether there is a conflict between the findings of Bamman et al. and the present study because our data were collected after 10 training sessions. Our present findings indicate that the stimuli driving adaptation in skeletal muscles using this model are probably not stoichiometrically related to the accumulated work or the integrated force generated in the course of the training. This conclusion can also be drawn from the data presented by a number of investigators, including Smith and Rutherford, who reported that the amount of muscle force generated during training was not quantitatively linked to the magnitude of the adaptations hypertrophy in humans (16, 23, 28). In a set of companion papers, Rutherford and colleagues (27, 28) speculated that adaptation may be a function of the metabolic load imposed by the training activities. The results of the present study do not adhere to the tenants of this metabolic hypothesis (greater metabolic load with SMT vs. LMT) in that the LMT and SMT resulted in equivalent changes in measures of muscle hypertrophy in rats. A number of additional studies with human subjects have also indicated that the relationship between metabolic load and muscle adaptation does not appear to be a primary determinant of adaptation (e.g., Refs. 12, 30).

One notable aspect of the design of our rat training protocol was that we allowed a period of isometric force development before movement in both the SMT and LMT modes (see METHODS and Fig. 4, top). It is possible that there was a significant contribution of this isometric force development to the adaptation process in these otherwise dynamic treatments. It is difficult to discern whether a similar isometric component was present in the majority of the published studies comparing training modes in human subjects. However, although it is not explicitly stated, it is reasonable to speculate that, depending on the training modality (e.g., isokinetic vs. constant external resistance), isometric components exist in some protocols designed to test dynamic movements. For example, in an eccentric training study by Housh et al. (18), the authors mention that subjects indicated that they had "control of the load" before full release and movement. This suggests that subjects were holding some portion of the load isometrically before the initiation of the eccentric action. It seems quite likely that mechanical constraints (e.g., the inability to instantaneously begin movement when muscles are activated and/or the requirement to overcome inertia) of most systems would require subjects to develop significant, if transient, levels of isometric force in most training situations.

In summary, using a model that should not include any motor learning, we found that resistance training with the same activation parameters in isometric, shortening, or lengthening

modes led to essentially equivalent levels of muscle hypertrophy. Within these training bouts, the integrated torque varied significantly such that LMT > IMT > SMT. These findings support previous studies that have reported that measures of work production during resistance training do not directly scale with the adaptation responses seen in skeletal muscle.

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