J Appl Physiol 104: 75–81, 2008.
First published November 1, 2007; doi:10.1152/japplphysiol.00335.2007.

Comparison between voluntary and stimulated contractions of the quadriceps femoris for growth hormone response and muscle damage

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Submitted 26 March 2007; accepted in final form 1 November 2007

Jubeau M, Sartorio A, Marinone PG, Agosti F, Van Hoecke J, Nosaka K, Maffiuletti NA. Comparison between voluntary and stimulated contractions of the quadriceps femoris for growth hormone response and muscle damage. *J Appl Physiol* 104: 75–81, 2008. First published November 1, 2007; doi:10.1152/japplphysiol.00335.2007.—This study aimed to compare voluntary and stimulated exercise for changes in muscle strength, growth hormone (GH), blood lactate, and markers of muscle damage. Nine healthy men had two leg press exercise bouts separated by 2 wk. In the first bout, the quadriceps muscles were stimulated by biphasic rectangular pulses (75 Hz, duration 400 μs, on-off ratio 6.25–20 s) with current amplitude being consistently increased throughout 40 contractions at maximal tolerable level. In the second bout, 40 voluntary isometric contractions were performed at the same leg press force output as the first bout. Maximal voluntary isometric strength was measured before and after the bouts, and serum GH and blood lactate concentrations were measured before, during, and after exercise. Serum creatine kinase (CK) activity and muscle soreness were assessed before, immediately after, and 24, 48, and 72 h after exercise. Maximal voluntary strength decreased significantly ($P < 0.05$) after both bouts, but the magnitude of the decrease was significantly ($P < 0.05$) greater for the stimulated contractions (−22%) compared with the voluntary contractions (−9%). Increases in serum GH and lactate concentrations were significantly ($P < 0.05$) larger after the stimulation compared with the voluntary exercise. Increases in serum CK activity and muscle soreness were also significantly ($P < 0.05$) greater for the stimulation than voluntary exercise. It was concluded that a single bout of electrical stimulation exercise resulted in greater GH response and muscle damage than voluntary exercise.

neuromuscular electrical stimulation; isometric strength; blood lactate; creatine kinase; muscle soreness

IN RECENT YEARS, THE ACUTE effects of neuromuscular electrical stimulation (NMES) on neuromuscular and metabolic responses have received attention (16, 28, 33, 37, 39). It has been reported in several studies that electrically evoked contractions result in greater strength loss and greater increases in oxygen consumption and blood lactate compared with voluntary contractions at the same intensity (16, 28, 33, 37, 39). It has been speculated that the specific recruitment pattern of motor units during NMES is mainly attributed to the phenomena (16, 28, 37, 39). Indeed, it is documented that the recruitment of motor units during stimulated contractions is different from voluntary contraction such that fast-twitch fibers could be activated at relatively low force levels (i.e., random/nonselective motor unit recruitment) (10, 17, 20, 30).

It is known that acute voluntary resistance exercise increases growth hormone (GH) secretion (for review see 22); however, limited information is available for acute GH responses to NMES. To the best of our knowledge, only two studies have reported GH responses to NMES. Greisen et al. (11) showed a significant increase (~17-fold) in GH concentration after 30 min of electrical stimulation applied to the abdominal skin. Kjaer et al. (21) showed that plasma GH level was significantly higher during NMES than voluntary cycling exercise at a similar level of oxygen consumption, and they suggested that the decrease in plasma glucose concentration during NMES probably was a feedback stimulus to enhance the GH response. It has been documented that GH release is enhanced by neuromuscular fatigue (15), metabolic fatigue (7), or pain (11). However, no previous studies have investigated the GH response after an acute bout of high-frequency and high-force NMES, which is often used in strength training (14, 26). Considering the greater neuromuscular and metabolic stress, and pain associated with this form of electrical stimulation (14, 16, 25, 28, 37), it was hypothesized that GH release during and following isometric contractions induced by NMES would be greater compared with voluntary isometric contractions.

It should be noted that muscle contractions induced by NMES do not generally include lengthening contractions, and when NMES is employed for the purpose of strength training, isometric contractions are mainly performed (14). Although it has been well documented that voluntary isometric contractions induce little or no muscle damage (24, 27), isometric contractions induced by NMES appear to result in muscle damage. For example, Guarascio et al. (12) reported a case of rhabdomyolysis due to excessive use of an electrical stimulator. Maffiuletti et al. (26) showed an increase in neonatal myosin heavy chains after a 4-wk NMES training, which can be viewed as an indicator of regeneration of muscle after muscle damage. Few previous studies have systematically investigated muscle soreness and other markers of muscle damage [i.e., creatine kinase (CK) or CK activity in the blood] after NMES, and no previous study has compared changes in markers of muscle damage between an acute bout of NMES and voluntary isometric contractions. Because NMES is used

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for variety of people, including elderly or athletes (for review see 14, 25), it is important to understand the aspects of muscle damage induced by NMES.

Thus the present study compared between voluntary and stimulated leg press exercise at equivalent force output for changes in serum GH concentration, blood lactate, isometric maximal voluntary contraction (MVC) strength, serum CK activity, and muscle soreness.

METHODS

Study Design

The study was approved by the Ethics Committee of the Italian Institute for Auxology and was conducted in accordance with the principles expressed in the Declaration of Helsinki (last modified in 2000). To compare voluntary and stimulated leg press exercise at equivalent force output for changes in muscle strength, GH, blood lactate, serum CK activity and muscle soreness, nine men had two exercise bouts separated by 2 wk. All subjects had the NMES bout first followed by the voluntary bout. Both bouts were performed in the morning (8–12 AM) to reduce the effects of diurnal variation on GH and muscle strength (13, 18), and each subject performed the two exercise bouts at the same time of day. Figure 1 shows the time course of the measurements for the dependent variables. Changes in the variables over time were compared between NMES and voluntary bouts.

Subjects

Written informed consent was obtained from nine healthy men (mean ± SD; age 28 ± 3 yr, height 178 ± 6 cm, mass 71 ± 7 kg) following detailed explanation of experimental procedures and associated risks. All subjects were habitually active but were not involved in training on a regular basis, and none of them had any signs of musculoskeletal disorders. The subjects were asked not to perform any strenuous exercise for at least 48 h before and during the experimental period, and not to take any medication or nutritional supplements.

Exercise

Subjects were placed in the supine position on a horizontal leg press machine (Technogym, Gambettola, Italy), with the trunk-thigh and thigh-shank angles at 80° (Fig. 2). The force generated during muscle contraction was measured by a strain gauge (Globus Italia, Codognè, Italy) properly mounted on the leg press machine with chains attached to the frame of the machine and the sliding axis of the leg press seat (Fig. 2). The signal from the strain gauge was sampled at 100 Hz and stored on a computer for later analysis with commercially available software (TCS-SUITE 400, Globus Italia). This system recorded and displayed the total force generated by both legs. The exercise protocol consisted of 40 isometric contractions. Each contraction lasted for 6.25 s, and the interval between contractions was 20 s. It is possible that muscles acting about the hip and ankle joints share the load with the knee extensors in the leg press exercise (8); however, it seems that the quadriceps femoris muscles were the prime mover of the exercise, especially at the low force level in the present study, and the force generated by the quadriceps was comparable between the stimulated and voluntary bouts.

NMES. In the first bout, the quadriceps femoris muscles of both legs were simultaneously stimulated by a portable electrical stimulator (Compex Sport-P, Medicompex, Ecublens, Switzerland), which delivered biphasic symmetric rectangular pulses with the following characteristics: frequency 75 Hz, pulse duration 400 μs, on-off ratio 6.25–20 s (rise time 1.5 s and fall time 0.75 s), based on previous studies (26, 37). We used long pulse durations to produce powerful and painless contractions, and we used high-frequency modulation to ensure tetanic contractions (23). Three self-adhesive electrodes (thickness 2-mm) were placed over the anterior aspect of each thigh with two positive electrodes (5 × 5 cm) being positioned over the motor point of the vastus lateralis and vastus medialis muscles and one negative electrode (10 × 5 cm) being placed ~5 cm below the inguinal ligament. Subject were asked to increase the current amplitude (range 37–120 mA) by themselves throughout the 40 electrically evoked contractions at their maximal tolerable level (pain threshold) to maintain the highest possible evoked torque throughout the session. Identical current amplitudes were used for the right and left quadriceps. The mean (± SD) level of isometric force evoked during NMES was 26 ± 19% (range: 12–59%) of the preexercise MVC, and the duration of the plateau phase was 4.5 ± 0.5 s.

Voluntary isometric contractions. In the second bout, subjects were asked to match their voluntary force output as accurately as possible to the force recorded during the NMES bout by following the force traces of each NMES contraction displayed on a monitor, and a sound signal was given to indicate the beginning and the end of each contraction. Before the bout, subjects performed three or four familiarization trials to practice matching the force to the force traces including the rise, plateau, and fall phases. This enabled all subjects to closely match the voluntary force output to the force generated in the NMES, and the force level and the duration of the plateau phase in the voluntary bout were 26 ± 18% and 4.5 ± 0.4 s, respectively, without a significant difference from the NMES bout.

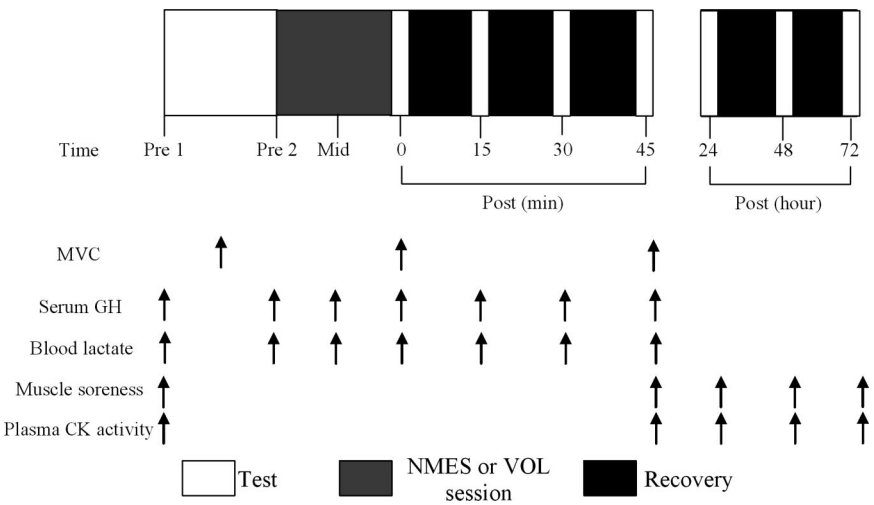

Fig. 1. Time course of the measurements for the dependent variables. Pre 1, before test; Pre 2, before test; Mid, during exercise; Post; after test; MVC, maximal voluntary contraction; GH, growth hormone; NMES, neuromuscular electrical stimulation; VOL, voluntary.

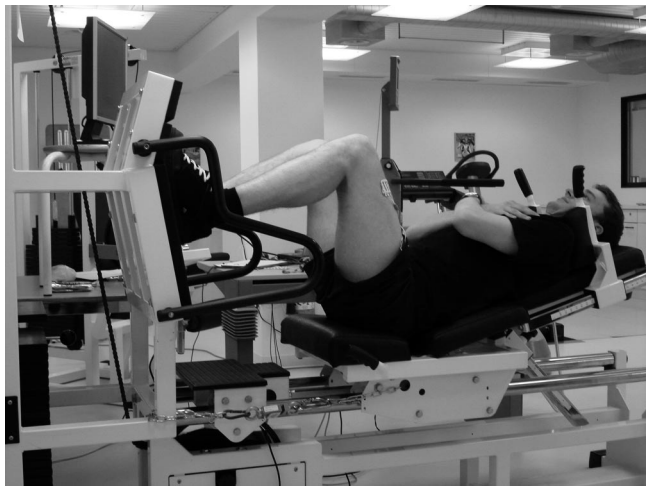

Fig. 2. The horizontal leg press machine equipped with the strain gauge.

Criterion Measures

MVC. After a standardized warm-up protocol, consisting of submaximal NMES (duration: 5 min; frequency 5 Hz; pulse duration 350 μs) and five to six submaximal voluntary isometric contractions, subjects were asked to generate maximal bilateral isometric strength using the modified leg press machine described previously with the same angle setting (trunk-thigh and thigh-shank angles of 80°). The duration of each contraction was 5 s, and the measurement was performed three times with a 90-s rest interspersed between contractions. The peak MVC (combined force from both legs) for each contraction was obtained, and the highest value of the three was used for further analysis. The MVC measurements were performed before, immediately after, and 45 min after exercise (Fig. 1).

Blood sampling and measurements of growth hormone and CK. Approximately 30 min before the exercise, an indwelling cannula was inserted into an antecubital vein and maintained in the position until 45 min after exercise with a continuous flow of isotonic saline. Blood samples (5 ml for each time point) were withdrawn immediately before and after the preexercise MVC test, in the middle of the exercise (9 min), and 0, 15, 30, and 45 min after the exercise (Fig. 1). GH concentrations were determined by a commercially available immunometric kit (Immulite 2000, DPC, Los Angeles, CA). Intra- and interassay coefficients of variation for the GH measure were 2.5% and 6%, respectively. All of the samples were run in the same analysis to minimize interassay variability. Integrated GH concentration [area under the curve (AUC)] over 90 min, including all time points, was calculated by using the trapezoidal method (34).

To assess serum CK activity, other venous blood samples were collected using an indwelling cannula inserted into an antecubital vein before and 45 min, 24, 48, and 72 h after the exercise (Fig. 1). All blood samples were allowed to clot, centrifuged for 5 min to obtain serum, and immediately stored at −20°C for the later analysis. Serum CK activity was determined spectrophotometrically by an automatic analyzer using a test kit (Roche/Hitachi 912 Clinical Chemistry System, Roche Diagnostics, Indianapolis, IN).

Blood lactate. A small blood sample (5 μl) was obtained from the earlobe for the determination of blood lactate concentration in the same time course as that for GH (Fig. 1). Blood lactate concentration was measured by a portable analyzer (Lactate Pro, Akray, Japan).

Muscle soreness. Muscle soreness was assessed before and 45 min, 24, 48, and 72 h after exercise (Fig. 1) using a visual analog scale (VAS) with a 50-mm line with "no pain" on one end (0 mm) and "extremely painful" on the other (50 mm). Soreness was quantified during palpation of each quadriceps muscle while the subject was comfortably sitting on a chair (thigh-shank angle of 80°), and the investigator placed his five fingers on vastus lateralis, vastus medialis, and rectus femoris muscle bellies by applying a constant pressure for ~3 s. Muscle soreness during a half-squat exercise, in which the subject was asked to squat slowly (4 s) from a standing position to 80° thigh-shank angle and back to the standing position, was also assessed. Subjects were asked to mark their pain level on the VAS under supervision of the examiner, and the length of the line from 0 to the marked point provided a numeric measure of soreness (range: 0–50). The mean values of the two legs were used for further analysis.

Statistical Analysis

Changes in the criterion measures over time were compared between NMES and voluntary exercise bouts by a two-way repeated measures ANOVA. When significant main effect (exercise or time) or interaction (exercise × time) was found, a least significant difference post hoc test was performed. A paired Student's *t*-test was used to compare the AUC values of GH between NMES and voluntary exercise bouts. Significance was set at $P \leq 0.05$.

RESULTS

No significant differences in the baseline values for any of the criterion measures were evident between NMES and voluntary bouts. All of the criterion measures showed a significant interaction (exercise × time) effect, indicating a significant difference between NMES and voluntary bouts for the changes.

As shown in Fig. 3, MVC decreased significantly immediately after both NMES (−22%) and voluntary (−9%) bouts, and no significant recovery occurred by 45 min after exercise. MVC after NMES was significantly lower than that after the voluntary bout.

Serum GH concentration increased significantly from baseline after both bouts and peaked 15–30 min after exercise; however, the increase after NMES was significantly greater than that after the voluntary bout (Fig. 4). Similarly, the AUC was significantly greater for the NMES (452.2 ± 144.1 $\mu g \cdot ml^{-1} \cdot min$) compared with the voluntary bout (174.7 ± 99.2 $\mu g \cdot ml^{-1} \cdot min$).

As shown in Fig. 5, blood lactate concentration did not change significantly after the voluntary bout, but a significant increase from baseline was evident during (mid) and after the NMES bout (post 0 and 15 min), peaking immediately after

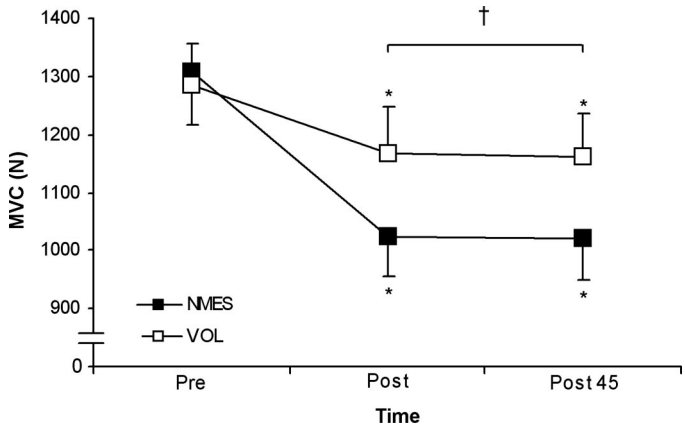

Fig. 3. Changes in isometric leg press MVC before (Pre), immediately after (Post) and 45 min after (Post 45) exercise for the NMES and VOL bouts. Values are means ± SE. *Significantly lower than Pre values, $P < 0.05$. †Significant difference between bouts, $P < 0.05$.

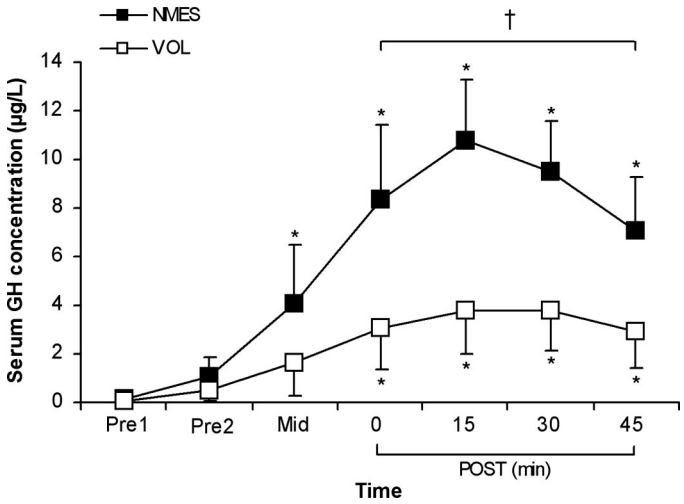

Fig. 4. Changes in serum GH concentration before (Pre 1 and Pre 2), during (Mid), and after (0–45 min) exercise for the NMES and VOL bouts. Values are means ± SE. *Significantly higher than Pre values, $P < 0.05$. †Significant difference between bouts, $P < 0.05$.

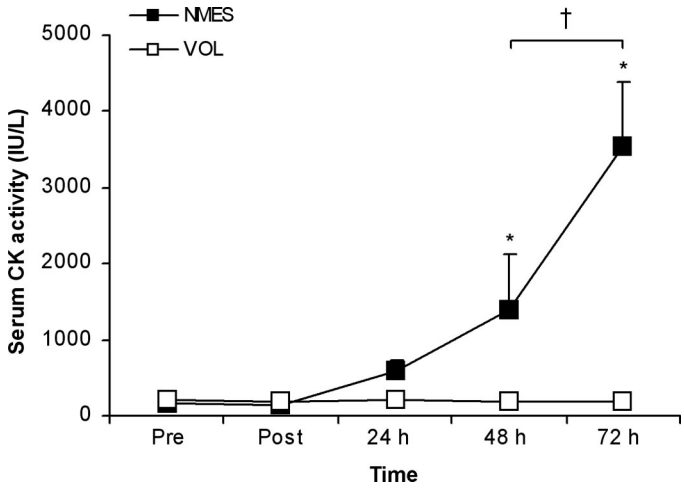

Fig. 6. Changes in serum CK activity before (Pre), immediately after (Post), and 24, 48 and 72 h after exercise for the NMES and VOL bouts. Values are means ± SE. *Significantly higher than Pre values, $P < 0.05$. †Significant difference between bouts, $P < 0.05$.

exercise. Blood lactate concentration during and after (post 0 and post 15 min) NMES was significantly higher compared with the voluntary bout.

A significant increase in serum CK activity was evident only after the NMES bout at 48 and 72 h postexercise, peaking at 72 h post exercise. Serum CK activity was significantly higher for the NMES than voluntary bout at 48 and 72 h after exercise (Fig. 6).

Changes in muscle soreness with half-squat and palpation are shown in Fig. 7. Muscle soreness developed and peaked 2 days after the NMES bout, whereas no significant muscle soreness was evident after the voluntary bout. Muscle soreness was significantly higher after NMES compared with the voluntary bout at all time points after exercise for the half-squat, and it was higher 24–72 h postexercise for the palpation.

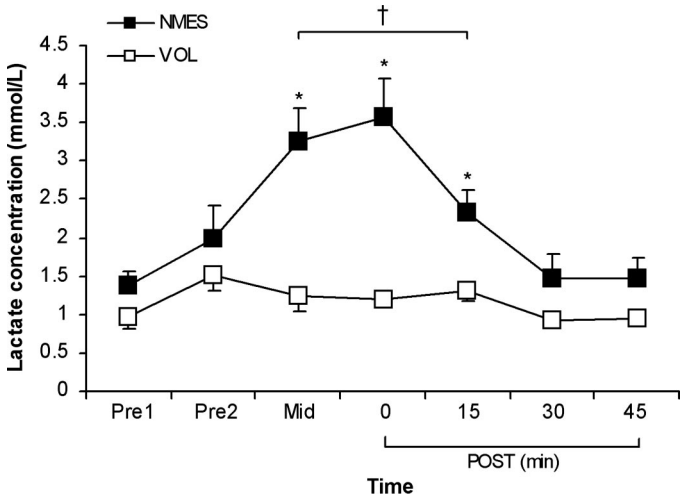

Fig. 5. Changes in blood lactate concentration before (Pre 1 and Pre 2), during (Mid), and after (0–45 min) exercise for the NMES and VOL bouts. Values are means ± SE. *Significantly higher than Pre values, $P < 0.05$. †Significant difference between bouts, $P < 0.05$.

DISCUSSION

The main findings of the present study were that muscle contractions induced by NMES resulted in greater increases of GH release, blood lactate concentration, serum CK activity and muscle soreness, and larger decreases in MVC compared with the voluntary contractions, when the two bouts were performed at the same leg press force output.

To the best of our knowledge, this was the first study to demonstrate that GH release was significantly higher after electrically evoked muscle contractions compared with voluntary contractions of equivalent force output (Fig. 4). This was somewhat surprising because it has been documented that the magnitude of GH release is dependent mainly on the intensity and duration of the exercise (40). In the present study, the intensity and duration of the exercise were similar between the two bouts. Thus it seems reasonable to expect a similar GH response, if exercise intensity was a factor to determine the magnitude of GH response. It is possible that the greater GH release in the NMES compared with the voluntary bout was associated with the level of muscle fatigue, blood lactate concentration, and pain during exercise. Hakkinen and Pakarinen (15) compared two intensive strength training sessions consisting of voluntary contractions and reported that GH release was greater during the more fatiguing session. In the present study, the decrease in MVC was significantly greater after the NMES than the voluntary bout (Fig. 3), suggesting greater neuromuscular fatigue in the NMES bout. Previous studies (16, 28, 37) also showed a greater MVC loss after NMES than voluntary contractions, and it was speculated that this was attributed to the specific recruitment pattern of motor units during electrically stimulated contractions. During voluntary contractions, muscle force output can be maintained by modulating the firing rates of active motor units, but this does not occur during NMES at a fixed (supraphysiological) frequency. During voluntary contractions at a given force level, additional motor units could be recruited when initially recruited units become fatigued, whereas it seems unlikely that such motor units rotation occurs in NMES. The recruitment pattern during NMES has been recently suggested to be spa-

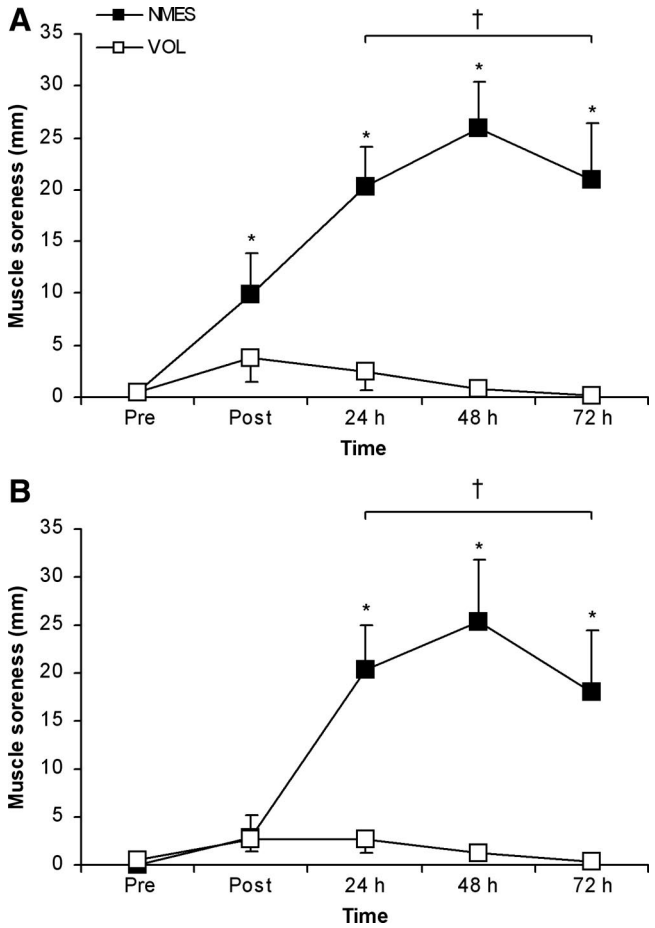

Fig. 7. Changes in muscle soreness during half-squat (*A*) and with palpation (*B*) before (Pre), immediately after (Post), and 24, 48, and 72 h after exercise for the NMES and VOL bouts. Values are means ± SE. *Significantly higher than Pre values, $P < 0.05$. †Significant difference between bouts, $P < 0.05$.

tially fixed, temporally synchronous, and random/nonselective (10, 20), whereas selective activation of fast motor units (inverse size principle) in NMES has been also documented (17, 30). It seems possible that the greater muscle fatigue induced by NMES was associated with the specific activation pattern, and this might have played a role in the greater GH release in the NMES compared with the voluntary bout.

As shown in Fig. 5, a significant increase in blood lactate concentration was seen in the NMES bout, whereas no significant changes occurred for the voluntary bout. Hakkinen and Pakarinen (15) suggested that blood lactate concentration could be one of the factors responsible for GH liberation during voluntary contractions. The results of the present study appear to support this notion that there is a link between blood lactate accumulation and GH release. Indeed, high concentrations of lactate within the muscle are reported to stimulate sympathetic nerve activity through chemoreceptive reflex, which plays a role in the regulation of pituitary secretion of GH (7, 35).

It is also well documented that opioids regulate GH secretion (9). Greisen et al. (11) observed that a significant GH release occurred when acute pain was experimentally induced by electrical stimulation. It should be noted that subject discomfort/pain is often the limiting factor during NMES (14, 25). The subjects of the present study received 40 electrically evoked contractions at individual pain threshold throughout the NMES session. On the other hand, they reported that the voluntary exercise was painless. It would appear that the higher levels of pain induced by surface NMES contributed to the greater GH release compared with the voluntary bout.

Giustina and Veldhuis (9) proposed that the final common pathway mediating GH release likely involves either increases in GH-releasing hormone and/or decreases in somatostatin release. Although no hormones other than GH were measured in the present study, it seems reasonable to assume that the NMES bout resulted in significant modifications of GH releasing hormone and/or somatostatin concentrations. Further study is necessary to examine changes in other hormones during and after NMES. Considering the greater GH release in the NMES bout, it would appear that NMES is useful in sport training and postimmobilization rehabilitation, because acute hormonal response to exercise represents one of the primary stimuli for subsequent tissue remodeling, including muscle hypertrophy (7).

Another important finding of the present study was the occurrence of muscle damage in the NMES bout. It should be noted that no symptoms of muscle damage were observed after the voluntary bout (Figs. 6 and 7). It has been well known that voluntary isometric contractions induce little or no muscle damage (24, 27). Several studies have reported that muscle contractions induced by NMES result in muscle damage (6, 12, 26, 29, 31); however, this was the first study to report serum CK activity and muscle soreness after NMES compared with voluntary isometric contractions of equivalent force output. It is interesting that the magnitude of the increase in CK after the NMES bout was large and similar to that observed after a single bout of voluntary eccentric contractions of the quadriceps muscle (32, 36).

It has been documented that isometric contractions do not usually result in large increases in serum CK activity and muscle soreness. For example, previous studies (3, 5, 19) reported little or no increases in CK, muscle soreness, and decrease in MVC after maximal voluntary isometric contractions of the knee extensors, reflecting little or no muscle damage after maximal voluntary isometric contractions. It is important to note that the voluntary isometric contractions performed in the present study were submaximal. The possibility that a protective effect was conferred by the NMES bout cannot be excluded because Triffletti et al. (38) reported that 40 maximal voluntary isometric contractions induced a protective effect against the same exercise performed 3 wk later. Chen et al. (4) reported that the magnitude of the protective effect conferred was dependent on the exercise intensity of the initial bout, and the higher the intensity, the greater the protective effect. Considering the fact that the isometric contractions evoked by the NMES were submaximal in the present study, it seems unlikely that the NMES bout conferred a protection for the subsequent voluntary bout. Thus it seems reasonable to assume that the submaximal voluntary isometric contractions (~25% MVC) used in the present study did not induce any muscle damage, even if the voluntary bout had been performed before the NMES bout. However, further research is necessary to evaluate the magnitude and the duration of the protective effect associated to one NMES bout.

The mechanism underlying muscle damage induced by NMES is not clear from the present study, but it is possible to

make some speculations. As previously discussed, the recruitment pattern of motor units during NMES is spatially fixed; thus it seems likely that fewer motor units were activated in the NMES bout compared with the voluntary bout (1, 20), and the same muscle fibers were continuously activated by NMES (10). It is possible that higher mechanical stress was placed on the activated muscle fibers in the NMES bout, which could cause muscle damage. This is supported by the fact that our subjects described the localization of their muscle soreness induced by NMES in the superficial areas of the quadriceps (i.e., in the proximity of the stimulating electrode). It appears that NMES preferentially recruits muscle fibers located near the electrodes (39), and this could explain the location of the muscle soreness. It should be noted that the same force output between the NMES and voluntary bouts does not necessarily mean that the muscles were used identically between the bouts. It may be that NMES induced greater mechanical stress to the knee extensors compared with the voluntary bout. Nevertheless, it is necessary to confirm the results of the present study by including MVC measurements in the recovery days, histological changes in the muscle receiving NMES, and visualization of muscle damage by magnetic resonance or ultrasound images.

The use of the horizontal leg press machine (Fig. 2) in the present study could be viewed as a methodological limitation to compare between the stimulated and voluntary isometric contractions. It is possible that the intensity of the stimulated exercise for the quadriceps muscle was greater compared with the voluntary exercise, because muscles other than the knee extensors (e.g., hip extensors, plantar flexors, knee flexors) might have contributed to the voluntary exercise, whereas only the knee extensors were used in the NMES bout. However, it seems likely that the contribution of hip, ankle, or knee flexor muscles in the voluntary exercise was minimal, if any, especially at these low force levels (~25% MVC), and the mechanical stress to the knee extensors was similar between the NMES and voluntary bouts. We have demonstrated that the magnitude of decrease in MVC after NMES is similar (20–22%) between a knee extension exercise in a sitting position and on the horizontal leg press exercise used in the present study (37). Moreover, Alkner et al. (2) demonstrated similarities in quadriceps muscle activation between the multijoint leg press and the single-joint knee extension actions, at least in isometric contractions. Therefore, it is unlikely that the greater GH response and muscle damage in the NMES bout compared with the voluntary isometric exercise bout were due to the exercise setting. Further research is necessary to confirm the results of the present study using a different exercise model, such as knee extension in a sitting position, and by a different study design, such as comparing one leg (NMES) with another (voluntary).

In conclusion, the present study showed greater increases in GH release, blood lactate concentration, serum CK activity and muscle soreness, and larger decreases in muscle function after stimulated than voluntary isometric exercise at the same force output. It seems possible that the greater increase in GH and induction of muscle damage is attributable to the different recruitment of motor units during NMES compared with voluntary contractions. The present findings may have significant implications for the use of NMES as a training modality for both healthy individuals and patients with GH deficiency. It should be also considered the fact that NMES resulted in delayed-onset muscle soreness and muscle damage. Further study is necessary to investigate the mechanisms underlying the present findings.

ACKNOWLEDGMENTS

The authors express their gratitude to Dr. Monica Resnik for clinical monitoring for the experiment. We also acknowledge Dr. Gianlugi Train, Marco Proietti, Saverio Ottolini, Franca Pera (head nurse), and other nursing staff of the Italian Institute for Auxology (Piancavallo, Italy) for technical assistance, and all the volunteers who participated in the present study.

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