

## Bi-modal recovery of quadriceps femoris muscle function after sustained maximum voluntary contraction at different muscle length

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**Key words:** electrical stimulation; posttetanic potentiation; low-frequency fatigue; metabolic fatigue; nonmetabolic fatigue.

**Summary.** The aim of this study was to test the hypothesis that contractility of quadriceps femoris muscle during a 15-min period after a sustained maximum voluntary contraction for 1 min is determined by the interaction of posttetanic potentiation, metabolic fatigue, and non-metabolic fatigue.

Eleven healthy untrained men (age,  $22.9 \pm 1.8$  years; body weight,  $77.5 \pm 5.2$  kg) performed isometric 1-min maximum voluntary contraction at long ( $90^\circ$  in knee joint) and short ( $135^\circ$  in knee joint) muscle length at two different occasions. Contractility of quadriceps femoris muscle was monitored via the evoked contractions at 1, 10, 20, and 50 Hz and maximum voluntary contraction at short and long muscle length on both occasions.

Force generating capacity was reduced immediately after 1-min maximum voluntary contraction at short and long muscle length, and then a bi-modal time-course of recovery was observed which consisted of (1) rapid recovery of all measured indexes at 3 min and (2) divergence in the changes of forces at low and high stimulation frequencies, as well as maximal voluntary contraction force at 7 and 15 min after exercising.

The decline in force immediately after 1-min isometric load was caused by metabolic and nonmetabolic fatigue; however, factors related to the metabolic fatigue were prevalent. As the effect of metabolic fatigue was diminishing and posttetanic potentiation was still present, force generation capacity recovered at 3 minutes after exercising. Further dynamics of contractility can be explained by the fading influence of posttetanic potentiation and dominant effect of nonmetabolic fatigue.

### Introduction

Contractility of skeletal muscle following a bout of exercise is altered and depends on the type, intensity, duration of exercise, and duration of rest may be suppressed or potentiated. Changes in muscle force during and after physical activity depend on metabolic fatigue (1), nonmetabolic fatigue (2), and posttetanic potentiation (3, 4). Most often contractility is determined by the coexistence of these factors; however, it is difficult to discriminate among their influences. For instance, after an intense exercise inducing metabolic fatigue, the effect of posttetanic potentiation is hidden (5), whereas, following exercise that causes nonmetabolic fatigue, expression of low-frequency fatigue (LFF), the best characterized type of nonmetabolic fatigue, can be compensated by posttetanic potentiation (3, 4).

The prevalence of metabolic and nonmetabolic

fatigue or posttetanic potentiation depends on the type, intensity, and duration of exercise and duration of the recovery before contractility is tested. It has been shown that intense and very short (about 5–10 s) isometric contractions induce posttetanic potentiation, i.e. an increase in contractile force evoked by a single twitch and/or low stimulation frequencies, lasting for 5–10 minutes (6). Temporal characteristics of contraction are also affected in a way that force development and relaxation occur at a faster rate (7). Phosphorylation of myosin regulatory light chains has been implicated as the underlying mechanism of posttetanic potentiation in human (6), rat (8), and mouse (9) muscles.

A prolonged duration of intense contraction (10–60 s) induces a substantial disturbance of metabolic profile causing the metabolic fatigue (1). An increase in ADP (10) and Pi (11) occurs with a concomitant decrease in concentration of ATP and PCr (6). The

consequence of these metabolic alterations is a reduction of free  $\text{Ca}^{2+}$  concentration in response to action potential (12) and impaired function at the level of cross-bridges (13), both of which in turn result in a decrease of contraction force (6) and slowing of relaxation (14). Restoration of metabolic homeostasis following exercise occurs in a range of minutes and is concomitant with rapid recovery of contractility (6). Studies on isolated single fibers demonstrated that association between increase in ADP (15) and Pi (16) concentration and impaired contractility is causative.

Various modes of exercise were shown to induce a long-lasting nonmetabolic fatigue. A type of nonmetabolic fatigue that manifests itself by a reduced force ratio at low and high stimulation frequencies is referred to as low-frequency fatigue. A selective reduction of force at low stimulation frequencies might be due to a reduction in  $\text{Ca}^{2+}$  release and a rightward shift of force-frequency relationship (17). Although the underlying mechanism is unknown, an impaired link between T-tubule and sarcoplasmic reticulum was proposed to be the cause for reduced calcium release (18). Another proposed mechanism of nonmetabolic fatigue is related to the damage of sarcomeres (19), which affects maximum contractile force as well as optimal muscle length (20).

The aim of this study was to test the hypothesis that contractility of quadriceps muscle during a 15-min period after a sustained maximum voluntary contraction (MVC) for 1 min is determined by the interaction of posttetanic potentiation, metabolic fatigue, and nonmetabolic fatigue.

## Materials and methods

### Subjects

Eleven healthy untrained men (age,  $22.9 \pm 1.8$  years; body weight,  $77.5 \pm 5.2$  kg) gave informed consent to participate in this study. The subjects were physically active but did not take part in any formal physical exercise or sport program. Each subject signed written

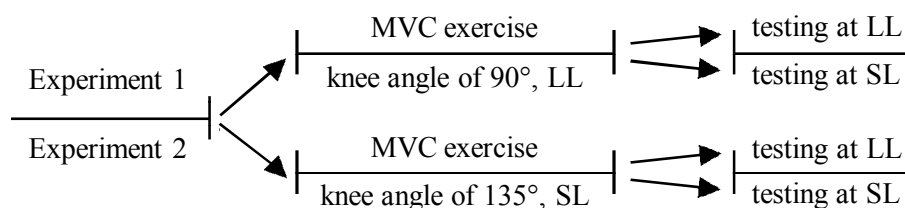
informed consent form consistent with the principles outlined in the Declaration of Helsinki.

### Experimental protocol

The experimental protocol is illustrated in Fig. 1. Two experiments, separated by an interval of 8 weeks, were carried out with the same subjects. The experiments were designed to assess the time-course of recovery of muscle contractile properties after sustained isometric MVC for 1 minute performed at knee angle of  $90^\circ$  ("long" muscle length, LL; Experiment 1) and  $135^\circ$  ("short" muscle length, SL; Experiment 2). The subject was seated in the experimental chair, and after 5 min of resting, muscle initial contractile properties were recorded in the following sequence: force evoked by 1-s train of electrical stimuli at 1 Hz (P1), 10 Hz (P10), 20 Hz (P20), 50 Hz (P50) and MVC (MVC was performed two times with 1-min rest in between) at SL and LL. The contractile properties of skeletal muscle were tested immediately after the exercise (A0) and 3 (A3), 7 (A7), and 15 (A15) min following the exercise. MVC at A0 was the force developed at the end of 1-min MVC. Immediately after the 1-min MVC, testing of stimulation-evoked contractions was carried out at LL and SL. The order of the angle that contractility was tested at was randomized within experiment.

### Force measurements

The equipment and technique used for measuring force have been previously described in detail (3, 5). Briefly, the subject sat upright in the experimental chair with a vertical back support. A strap secured the hips and thighs to minimize uncontrolled movements. The right leg was clamped in a force-measuring device with the knee kept at an angle of  $90^\circ$  or  $135^\circ$ . A 6-cm-wide plastic cuff, placed around the right leg just proximal to the malleoli, was tightly attached to a linear variable differential transducer. The output of the transducer, proportional to isometric knee



**Fig. 1. Experimental design**

MVC – maximum voluntary contraction, LL – long muscle length (knee angle of  $90^\circ$ ), SL – short muscle length (knee angle of  $135^\circ$ ).

extension force, was amplified and digitized at a sampling rate of 1 kHz by a 12-bit analogue-to-digital converter incorporated in a personal computer. The digitized signal was stored on the hard disk for subsequent analysis. The output from the force transducer was also displayed for visual feedback.

### **Electrical stimulation**

A high-voltage stimulator (MG 440, Medcor, Budapest, Hungary) was used to deliver electrical stimuli to the quadriceps muscle through surface electrodes (9×18 cm) padded with cotton cloth and soaked in saline solution. One stimulation electrode was placed just above the patella, while another covered a large portion of the muscle belly in the proximal third of the thigh. The electrical stimulation was always delivered in trains of square-wave pulses of 1-ms duration (voltage of 150 V, which induces approximately 60–85% of MVC). To maximize recruitment of fibers, the highest possible stimulation voltage was employed. The subjects were familiarized with electrical stimulation during the introductory visit before the beginning of experiments.

We measured the contractile force of the quadriceps muscle evoked by 1-s train of electrical stimuli at 1 Hz, 10 Hz, 20 Hz, 50 Hz, muscle contraction time (T50, time to 50% of P50 contraction), and relaxation time (RTP50, from 100% to 50% of P50). The MVC force was also determined (the peak MVC was reached and maintained for about two seconds before relaxation). The rest interval between sessions of electrical stimulation was 3 s. The ratio of P20/P50 kinetics after exercise was used for the evaluation of LFF (3, 21). The contractile force was tested in a random order at knee-joint angles of 135° (SL) and 90° (LL).

### **Muscle soreness**

Evaluation of muscle soreness 24 h after the exercise was carried out as described previously (5) using a scale from 0 (no pain) to 10 points (very strong pain).

### **Statistical analysis**

Distribution of force and time measurements was tested for normality (SPSS 11.0 statistical package). Distribution of MVC force approximated normality. Evoked contraction forces and T50 did not deviate from normality following square root and logarithmic transformation, respectively. RTP50 approximated normality after reciprocal transformation. A 3-way analysis of variance (ANOVA) was used to determine the effects of exercise (2 levels: 1-min MVC at LL and 1-min MVC at SL), time (5 levels: Ini, A0, A3,

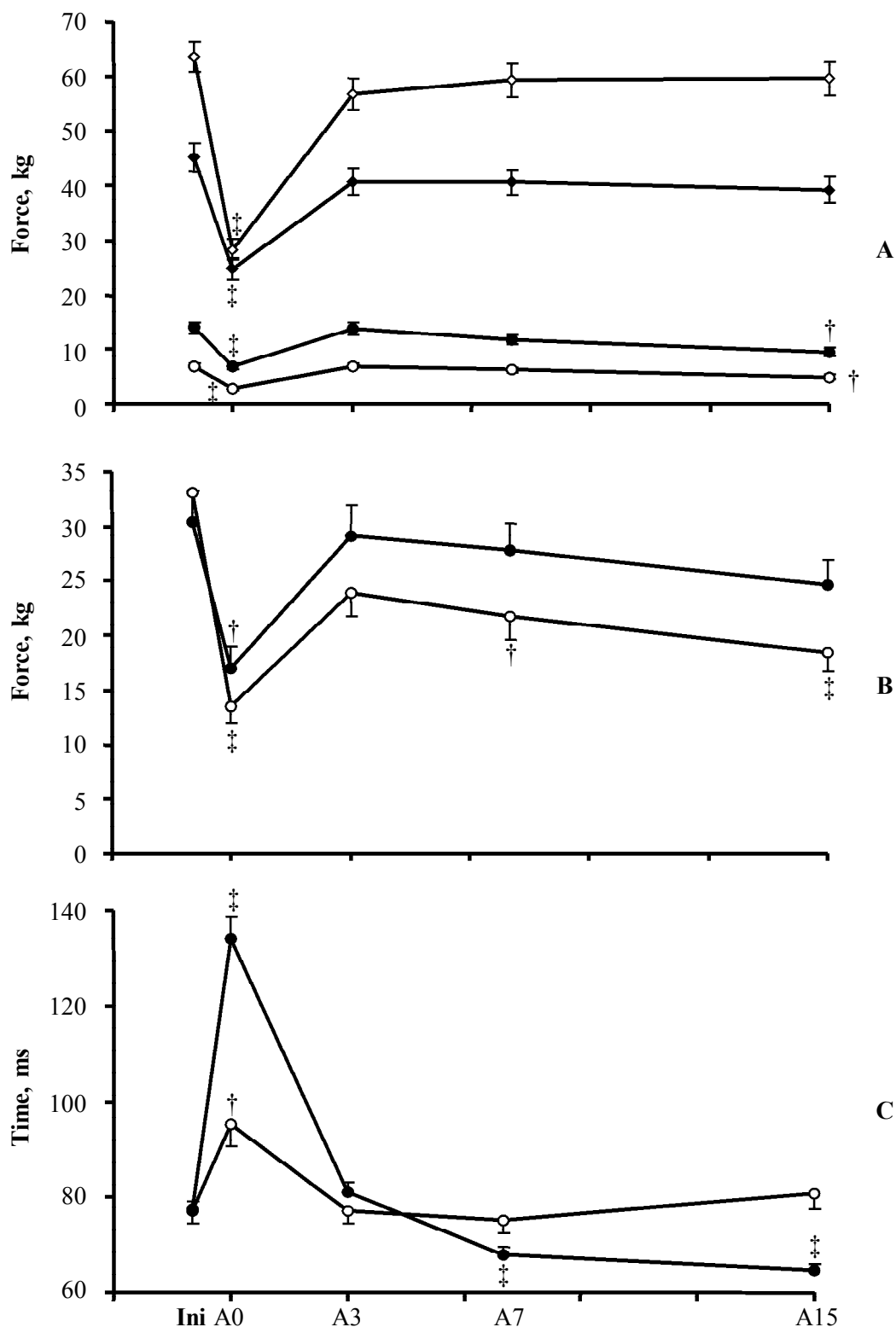
A7, A15), and muscle length (2 levels: LL and SL) on contractile properties of the quadriceps muscle. Where significant main effect was found, *post hoc* test was applied to locate the difference. *P* values of the *post hoc* analyses were adjusted for multiple comparisons and presented at three different levels: <0.05, 0.01, or 0.001. Data are presented as mean ± standard deviation unless otherwise stated.

### **Results**

The initial MVC force was 65.4±9.4 kg and 62.2±12.1 kg at the SL and LL, respectively. The initial force of the evoked contractions at the highest stimulation frequency, P50, was 82% and 61% of the MVC at the corresponding muscle length (SL and LL).

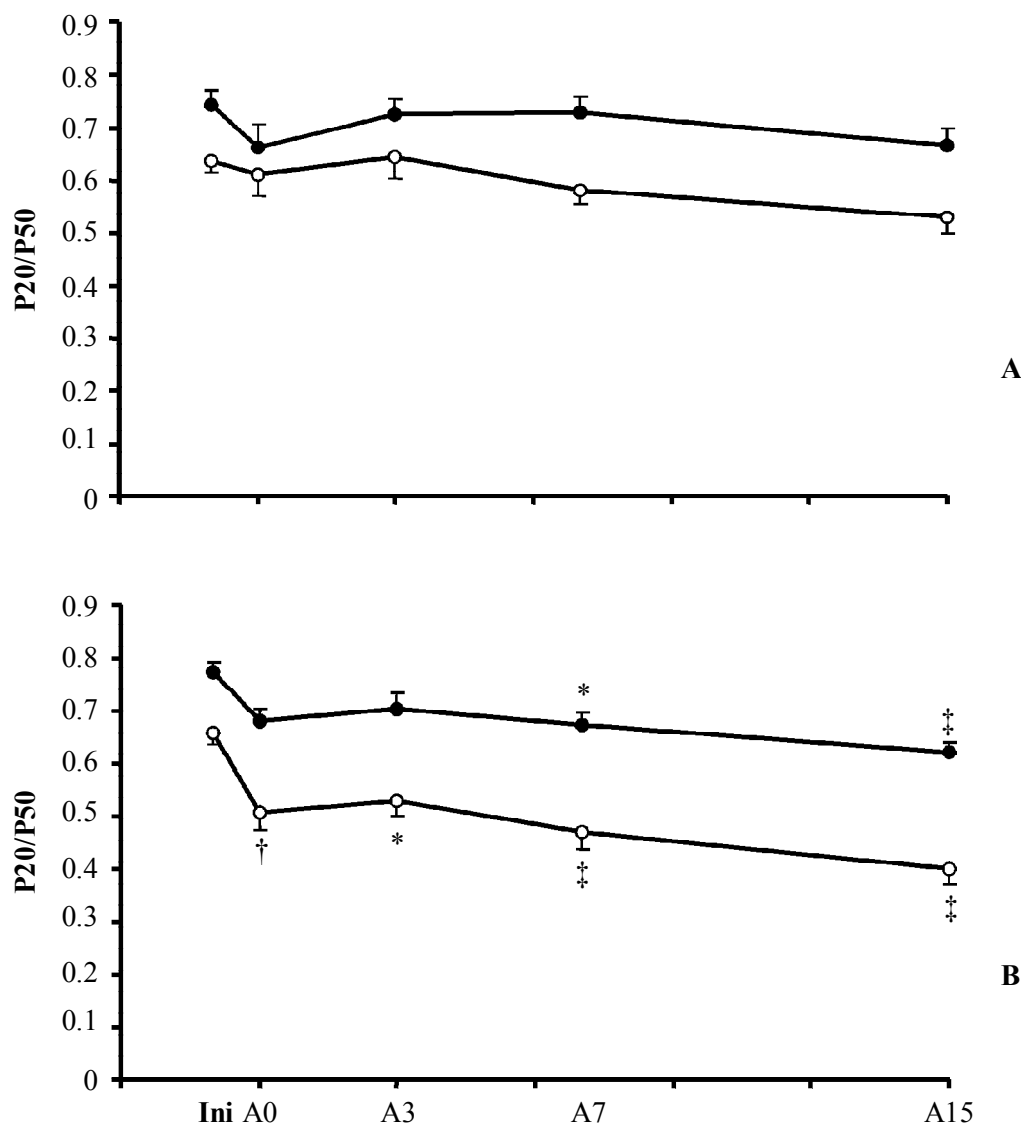
Analysis of variance showed that the MVC force generated at SL was about 12% greater than that at LL (collapsed measurements at all time points, *P*<0.01). The force of evoked contractions varied depending on the muscle length and stimulation frequency: P1, LL>SL by 8% (*P*<0.05); no significant influence on P10 and then an inverse between the LL and SL for P20, LL<SL by 9% (*P*<0.01) and P50, LL<SL by 18% (*P*<0.001). Temporal characteristics of P50 were also dependent on muscle length; T50 was 24% shorter at LL than SL (*P*<0.001), whereas difference of 4% (*P*<0.05) of opposite direction, i.e. SL shorter than LL, was observed for RTP50.

A 1-min MVC significantly (*P*<0.001) affected contractile force of quadriceps muscle (Fig. 2). The P1, P10, and P50 were not influenced statistically significantly by the length of muscle that 1-min MVC was performed at, whereas the P20 was lower (*P*<0.05) in the LL than that in the SL exercise. Force generating capacity at all stimulation frequencies was reduced, whereas contraction time, T50, and relaxation time RTP50 increased right after the 1-min MVC (*post hoc* test Ini vs A0, *P*<0.001, *P*<0.01, and *P*<0.001, respectively). The P50 comprised only ~50% and ~60% of the initial following the 1-min MVC at LL and SL, respectively. The ability to generate maximum force voluntarily was also reduced (*P*<0.001) at A0 to 38% of the initial force at LL and to 51% at SL. The time course of recovery of contractile properties during a 15-min rest exhibited a bimodal pattern, consisting of (1) rapid recovery of all measured indexes by the A3 (Ini vs A3, NS), and (2) divergence in the changes of P50, T50, MVC force and P1, P10, P20, RTP50 at A7 and A15. There were no significant differences between P50, T50 and MVC force between Ini and A7 or A15, whereas a significant reduction was observed for P1 (*P*<0.01), P10 (*P*<0.01), P20



**Fig. 2.** Contractile force (A, B), contraction time and relaxation time (C) of quadriceps muscle (mean  $\pm$  SE) before 1-min MVC (Ini), right after (A0) and following 3, 7, and 15 minutes of recovery (A3, A7, and A15, respectively)

A – force at a stimulation rate of 1 Hz (○), 10 Hz (●), 50 Hz (■) and MVC (□) across long and short muscle length (effect of muscle length during 1-min MVC, NS). B – force of P20 at LL (○) and SL (●) protocol of 1-min MVC (effect of muscle length during 1-min MVC,  $P < 0.05$ ). C – contraction time T50 (○), and half relaxation time RTP50 (●) across long and short muscle length. Statistically significant differences from Ini determined via *post hoc* test (Bonferroni) are indicated as: \* $P < 0.05$ , † $P < 0.01$ , ‡ $P < 0.001$ .



**Fig. 3. Low-frequency fatigue (LFF) following 1-min MVC at short muscle length (A; knee angle of 135°, SL) and long muscle length (B; knee angle of 90°, LL)**

Mean  $\pm$  SE. Contractility was tested at LL (●) and SL (○). Statistically significant effects under different conditions were determined by 1-way ANOVA with time as a factor. Difference compared to Ini is indicated as: \* $P < 0.05$ , † $P < 0.01$ , ‡ $P < 0.001$ .

( $P < 0.001$ ) and RTP50 ( $P < 0.001$ ) at A15 and for P20 ( $P < 0.05$ ) and RTP50 ( $P < 0.001$ ) already at A7. There were no statistically significant interactions observed between the main effects (muscle length during 1-min MVC, muscle length during testing, time) in any of the tested characters.

The time-course of the P20/P50 is shown in Fig. 3. A 3-way ANOVA indicated that the length of the muscle at which that force was tested, the length of the muscle during 1-min MVC, and time were significant factors affecting P20/P50 (all  $P < 0.001$ ). The P20/P50 was always greater when tested at LL than SL, and the difference increased to a greater extent

following the 1-min MVC at LL than that at SL (exercise-by-muscle length,  $P < 0.01$ ). A 1-min MVC at LL induced greater overall reduction in P20/P50 than that at SL ( $P < 0.001$ ); therefore, the difference of P20/P50 between the two 1-min MVC occasions, although absent at Ini (collapsed P20/P50 across 90 and 135 degrees were  $0.72 \pm 0.02$  vs  $0.69 \pm 0.02$  after 1-min MVC at SL and LL, respectively) became significant (exercise-by-time,  $P < 0.05$ ) during recovery ( $0.51 \pm 0.03$  vs  $0.60 \pm 0.03$  at A15).

Perceived muscle soreness, assessed 24 hours after the exercise, was greater ( $P < 0.05$ ) following the 1-min MVC at LL ( $3.8 \pm 1.1$ ) than that at SL ( $1.1 \pm 0.7$ ).

Differential effects of 1-min MVC on various contractile indexes evidence the interaction of diverse intracellular mechanisms in determination of muscle contractility.

### Discussion and conclusions

Several studies have demonstrated that contractility of skeletal muscle following short exercise of maximum intensity is modified by coexistence of potentiating and suppressing mechanisms (3, 4). However, to the best of our knowledge, this is the first study reporting existence of a bimodal pattern of recovery and exploring its underlying mechanisms in human muscle. The present results extend our knowledge about the complex coexistence of metabolic fatigue, nonmetabolic fatigue and posttetanic potentiation in determining contractility during a short period of recovery following a maximum isometric contraction in humans.

The main finding of the study is a bi-modal recovery of muscle force within 15 min after 60-s MVC: 1) in early, fast-recovery phase, muscle function was restored after performing exercise at both short and long length; 2) in the second phase (from 3 min to 15 min), P50 and MVC force did not differ from the initial; however, low frequency stimulation forces gradually decreased and were suppressed at 15 min following the exercise.

**Metabolic fatigue.** The isometric exercise used in the present study (1-min MVC) was analogous to the one employed by Houston and Grange (6). They demonstrated that after such exercise, there was a significant decrease in ATP and phosphocreatine concentration. Breakdown of ATP and phosphocreatine in turn increases concentration of ADP and Pi. The latter metabolites have a profound effect on temporal characteristics of contraction and generated force of single fibers (15, 16). The voluntary force in the present study decreased by more than 50%. This was accompanied by a similar depression of the P50 and prolonged contraction and relaxation time of the evoked contractions (Fig. 2), indicating the peripheral localization of fatigue. The reduction of force of similar magnitude in a single-fiber model was an outcome of both reduced release of  $\text{Ca}^{2+}$  and alterations at the cross-bridge level (12). Thus, the acute changes of contractile properties following the 1-min MVC are consistent with the characteristics of metabolic fatigue. These metabolic changes, however, are transient and recover within 1–3 min following protocols similar to the one used in the present study (6). Consistently with this time frame, the recovery of force and temporal characteristics of contraction was observed by

the third minute following the 1-min MVC, further supporting the importance of metabolic fatigue (Fig. 2). A prolonged intense exercise increases the concentration of hydrogen ions (22) suggesting their possible association with muscular fatigue. A number of studies supported the suppressive influence of hydrogen ions on muscle contractility (23, 24). Doubts regarding their importance were stimulated by the fact the influence on contractility diminished as temperature of experimental conditions approached physiological temperatures (25). The most recent findings indicated that in fact intracellular acidosis preserves excitability of muscle fibers, thus acting as a fatigue-resisting factor rather than one that contributes to it (26).

**Posttetanic potentiation.** A prominent feature of the posttetanic potentiation phenomenon is an increased twitch and low frequency force accompanied by a shortening of contraction and relaxation time (4, 6). It has been suggested that posttetanic potentiation is caused by phosphorylation of myosin regulatory light chains (27). Metzger and coauthors (28) proposed that phosphorylation of myosin regulatory light chains induces retraction of myosin head from the backbone of thick filament and thus shortens the distance to the actin filament, which in turn could enhance cross-bridge attachment rate. The importance of spatial proximity between actin and myosin is supported by the observation that posttetanic potentiation is more pronounced at a short muscle length when the distance between filaments is plausibly greater. No significant increase in twitch force was observed in the present study (Fig. 2), although similar protocols have been shown to increase twitch force (6). Yet we hypothesize that mechanisms underlying posttetanic potentiation were engaged causing slightly greater low-frequency forces and the P20/P50 at 3 min than at 15 min after exercising, but complete expression of the posttetanic potentiation was counteracted by the metabolic fatigue and nonmetabolic fatigue.

**Nonmetabolic fatigue.** The concentration of metabolites, i.e., ATP, Pi, PCr, recovers within 10–15 min after the 1-min MVC (6) or even longer exercise; therefore, decrease in force at 15 min after exercising has to be attributed to nonmetabolic fatigue. There were two different mechanisms proposed to explain long-lasting nonmetabolic fatigue: 1) reduced  $\text{Ca}^{2+}$  release from sarcoplasmic reticulum due to impaired excitation-contraction coupling (17), and 2) damage of weak sarcomeres in the fibers (29). In support to the theory of impaired excitation-contraction coupling, the *in vivo* experiments indicated that ingestion of caffeine ameliorated symptoms of LFF in humans

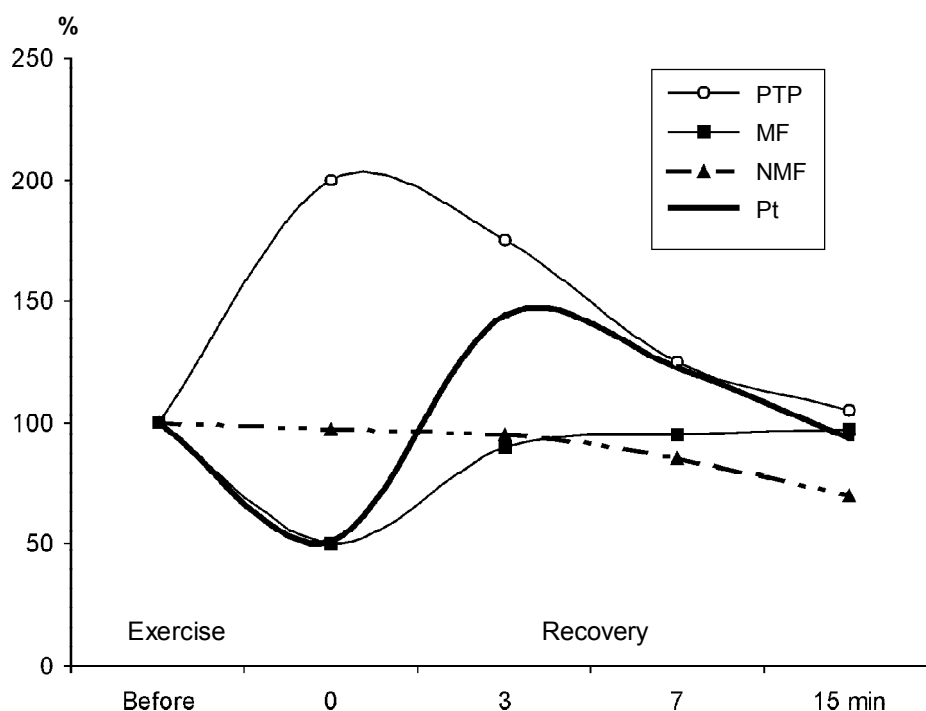
(30). The studies in single fibers also showed that fatigue caused by reduced free  $\text{Ca}^{2+}$  concentration can be overcome by application of caffeine (31), which facilitates release of  $\text{Ca}^{2+}$  from sarcoplasmic reticulum. In support of the damage hypothesis, a decrease in maximum force accompanied by an increase in optimal length and over-stretched sarcomeres were observed after a series of eccentric contractions in toad muscle (20). In the present study, however, MVC force and P50 did not differ significantly from the initial by 3 min or later following 1-min MVC at either LL or SL (Fig. 2). The latter suggests that even though some muscle damage, indicated by muscle soreness, might have occurred, particularly in the LL protocol, integrity of sarcomere structure was not the major cause of the nonmetabolic fatigue. The decrease in P20/P50 was an indication of the LFF following the 1-min MVC (Fig. 3); in addition, the RTP50 was also reduced at 15 min after exercising. It has been shown that relaxation time depends on the duration of  $\text{Ca}^{2+}$  transient in myoplasm (13) further suggesting that LFF was an outcome of a decreased  $\text{Ca}^{2+}$  transient during stimulation at low frequencies. Although effect of nonmetabolic fatigue became obvious only later in recovery, a decrease in P20/P50 at the short muscle length following the 1-min MVC at LL indicates that

the onset of it is immediately after exercise.

*Coexistence of metabolic fatigue, posttetanic potentiation, and nonmetabolic fatigue.* We hypothesized that time-course of muscle recovery within 15 min after 1-min MVC depends on metabolic fatigue, nonmetabolic fatigue, and posttetanic potentiation. The coexistence of these three factors might explain the bi-modal recovery of muscle function in the present study (Fig. 4). Depression of force after the 1-min MVC is caused by metabolic and nonmetabolic fatigue, the former being the major factor. Rapid recovery of contractile properties during the first 3 min is brought about by fading metabolic fatigue and still presents traces of the posttetanic potentiation, which compensated for the effect of nonmetabolic fatigue. The subsequent (3 to 15 min) decline in low-frequency stimulation force is an outcome of diminishing influence of posttetanic potentiation on the background of still persistent nonmetabolic fatigue. The main cause of nonmetabolic fatigue is reduced release of  $\text{Ca}^{2+}$  from sarcoplasmic reticulum, whereas influence of structural damage is smaller.

### Conclusion

Time course of recovery of contractility of the quadriceps femoris muscle following 1-min maximal



**Fig. 4. Hypothetical model of factors determining contractile force of skeletal muscle during and 15 min after the sustained maximal voluntary contraction for 1 min**

PTP – posttetanic potentiation; MF – metabolic fatigue; NMF – nonmetabolic fatigue; Pt – twitch force. Time-course of muscle twitch force depends on coexistence of PTP, MF, and NMF.

voluntary contraction is determined by the concomitant and complex interaction of mechanisms enhancing (posttetanic potentiation) and suppressing (metabolic and nonmetabolic fatigue) the contractile potential of the muscle. The interaction was not influenced

significantly by the length of muscle that 1-min maximal voluntary contraction was performed. This has to be taken into account when the function of skeletal muscle is being assessed after isometric contraction of maximum intensity.

### **Keturgalvio šlaunies raumens jėgos bimodalinis atsigavimas po nepertraukiamo maksimalios valingos jėgos krūvio esant skirtingam raumens ilgiui**

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**Raktažodžiai:** elektrostimuliacija, potetaninė potenciacija, mažų dažnių nuovargis, metabolinis nuovargis, nemetabolinis nuovargis.

**Santrauka.** Tyrimo tikslas. Patikrinti hipotezę, kad keturgalvio šlaunies raumens susitraukimo savybės, praėjus 15 min. po 1 min. maksimalios valingos jėgos krūvio, yra sąlygotos potetaninės potenciacijos, metabolinio bei nemetabolinio nuovargio sąveikos.

Vienuolika nesportuojančių sveikų vyrų ( $22,9 \pm 1,8$  m.,  $77,5 \pm 5,2$  kg) atliko izometrinį 1 min. maksimalios valingosios jėgos krūvį esant ilgam ( $90^\circ$  kampas per kelio sąnarį) ir trumpam ( $135^\circ$  kampas per kelio sąnarį) raumens ilgiui. Po krūvio buvo registruojama keturgalvio šlaunies raumens susitraukimo jėga, sukelta elektros stimulais (1, 10, 20 ir 50 Hz dažniu) bei maksimali valinga jėga esant ilgam ir trumpam raumens ilgiui, raumens susitraukimo ir atsipalaidavimo trukmė.

Raumens susitraukimo jėga sumažėjo iškart po 1 min. krūvio esant ilgam ir trumpam raumens ilgiui. Po krūvio nustatytas bimodalinis raumens jėgos atsigavimas: 1) visi matuoti rodikliai atsigavo per 3 min. po krūvio; 2) mažais dažniais sukelta jėga, 3–15 min. trukmės po krūvio mažėjo, o dideliais dažniais sukelta ir maksimali valinga jėga išliko tokia pati.

Jėgos sumažėjimą iškart po 1 min. maksimalios valingos jėgos krūvio sukėlė metabolinis ir nemetabolinis nuovargis. Tačiau veiksniai, lemiantys metabolinį nuovargį, buvo vyraujantys. Greitas raumens susitraukimo savybių atsigavimas per pirmąsias 3 min. aiškinamas mažėjančiu metaboliniu nuovargiu ir vis dar esančiais potetaninės potenciacijos pėdsakais. Vėlesnė raumenų susitraukimo savybių kaita gali būti aiškinama mažėjančios potetaninės potenciacijos ir vis dar esančio nemetabolinio nuovargio sąveika.

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