

Gender Differences in the Fatigability of Human Skeletal Muscle

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Semmler, John G., Devin V. Kutzscher, and Roger M. Enoka. Gender differences in the fatigability of human skeletal muscle. *J. Neurophysiol.* 82: 3590–3593, 1999. After participating in a 4-wk intervention that reduced normal usage of the elbow flexor muscles, all six women, but only one of six men, experienced a marked increase in the endurance time during a low-force fatiguing contraction. The increase in endurance time was associated with an altered pattern of muscle activation that did not involve the commonly observed progressive increase in muscle activity. Rather, the muscle activity comprised intermittent motor unit activity. In those individuals who exhibited this behavior, the novel pattern of muscle activity was only present immediately after 4 wk of limb immobilization and not before the intervention or after 4 wk of recovery. These findings suggest possible differences between women and men in the adaptations of the neuromuscular system.

INTRODUCTION

Muscle fatigue is often defined as an exercise-induced decline in the capacity of muscle to exert its maximum force (Gandevia et al. 1995). At the level of the whole organism, the particular physiological mechanism that is most responsible for fatigue depends on the characteristics of the task that is being performed (Enoka and Stuart 1992). This assertion appears to be most secure for high-force contractions when the decline in force appears to be caused largely by processes that are located distal to the neuromuscular junction (Gandevia 1998; Westerland et al. 1998). In contrast, it has proven difficult to ascribe specific roles to the various physiological mechanisms during low-force muscle contractions. The principal reason for this difficulty is that several mechanisms appear to contribute concurrently to the fatigue exhibited by the muscle. These include mechanisms that are distal to the neuromuscular junction, such as excitation-contraction coupling, and some that are located within the CNS, such as a decline in cortical output and an increase in the inhibitory effects of sensory feedback (Fuglevand et al. 1993; Garland 1991; McKenzie et al. 1992; Miller et al. 1993).

In an attempt to distinguish among these mechanisms during low-force contractions, we have compared the performance of subjects before and after their participation in an intervention that disturbed the normal balance among physiological processes. The intervention was limb immobilization. Most studies find that limb immobilization has a minimal effect on the capacity of muscle to sustain a force (Davies et al. 1987; Duchateau and Hainaut 1991; Fuglevand et al. 1995; Robinson et al. 1991). In contrast, we found that immobilization had no

effect on the ability of the elbow flexors to sustain a force that was 65% of maximum, but the endurance time for a fatiguing contraction at a force of 20% of maximum was increased by an average of 59% of the preimmobilization value (Yue et al. 1997).

The purpose of this study was to identify the mechanisms responsible for the intensity-dependent effect of immobilization on the endurance time of a fatiguing contraction. We found that the effect of limb immobilization on the endurance time of a low-force contraction largely depended on the gender of the individual. Furthermore, postimmobilization increases in endurance times were accompanied by novel patterns of muscle activation.

METHODS

The experiments were performed on 16 healthy volunteers (age 18–45) after they had given informed consent. Twelve of these individuals (6 women and 6 men) performed a 4-wk immobilization intervention whereas the other 4 subjects (1 woman and 3 men) comprised the control group. The project was approved by the Institutional Review Board at the University of Colorado at Boulder. The subjects who performed the immobilization had the nondominant (left) arm immobilized in a fiberglass cast that extended from the middle of the upper arm down across the wrist, leaving the thumb and fingers free to move. Subjects were encouraged to place the cast in a sling during the intervention to provide support for the added mass. In all subjects, experiments were performed before and immediately after immobilization (within 1 h of cast removal) and after 4 wk of recovery.

Subjects sat in a chair with the left elbow on a padded support, the elbow joint at a right angle, and the wrist connected to a force transducer (JR3 Universal Force-Moment Sensor System; JR3, Woodland, CA). The task was to exert an upward-directed force with the wrist by using the elbow flexor muscles, principally involving the biceps brachii, brachialis, and brachioradialis muscles. Both the target force and the force exerted by the subject were displayed on an oscilloscope. To determine the maximum voluntary contraction (MVC) force, subjects were instructed to increase the force from zero to maximum at a constant rate over ~3-s period and to hold the maximum for ~3 s. Muscle fatigue was assessed as the duration that individuals could sustain an isometric contraction with the elbow flexor muscles at a force that was 15% of the value achieved during a MVC. The fatiguing contraction was terminated when the subject could no longer maintain the required force for ≥ 3 s.

Muscle activity during the fatiguing contraction was measured with surface (biceps brachii, brachioradialis, and triceps brachii) and intramuscular (brachialis) electrodes. The surface electrodes were 8 mm in diameter and attached to the skin with a distance of ~2 cm between the centers of the two electrodes. The intramuscular electrode comprised insulated stainless steel wires that had a diameter of 100 μm (California Fine Wire, Grover Beach, CA). Reference electrodes were attached over bony processes around the left elbow. The electromyography

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graphic (EMG) signals were recorded on a digital recorder (Sony PC 116 DAT; DC-2.5 kHz) then digitized (1 kHz for surface EMG, 2 kHz for intramuscular EMG) and analyzed with the Spike2 data analysis system (Cambridge Electronic Design, Cambridge, UK). The data are reported as mean \pm SD.

RESULTS

The average endurance time when the isometric contraction was sustained at 15% of maximum was 897 ± 416 s before immobilization, 2035 ± 1418 s immediately after immobilization, and 1136 ± 527 s after 4 wk of recovery for the subjects in the immobilization group. These endurance times were not statistically different. When the fatiguing contraction was performed immediately after 4 wk of limb immobilization however, 7 of 12 subjects experienced $\geq 100\%$ increase in endurance time (Fig. 1A). The average increase in endurance time of these subjects was 220%. In contrast, the endurance time of the other five subjects who completed the immobilization protocol (Fig. 1B) and the four subjects who comprised a control group (who performed the task on 3 occasions) did not change. There were two noteworthy features that distinguished the subjects who experienced an increase in endurance time from those who did not. First, the longer endurance time was associated with a unique pattern of muscle activation. Second, these subjects were all the women (6/6) in the study but only one of the men (1/6).

When the fatiguing contraction was performed both before immobilization and after 4 wk of recovery, the amplitude of the interference EMG increased progressively for all subjects (Fig. 2A). In contrast to this typical EMG profile, the postimmobilization performance of the subjects who experienced an increase in endurance time was associated with the pattern shown in Fig. 2B. All of the subjects who increased endurance time immediately after immobilization exhibited this EMG pattern. The two unique features of the pattern were no progressive increase in EMG amplitude despite reports from the subjects indicating an increase in the effort associated with the perfor-

mance and frequent changes in the population of activated motor units. The intermittent activation of motor units is more obvious when the record is displayed on an expanded time scale (Fig. 3). This unique pattern of muscle activity was not observed in the subjects whose endurance time did not change following limb immobilization.

Confounding the interpretation that the observed effect was because of gender were the differences in strength between the various groups of subjects. The MVC force (mean \pm SD) before immobilization was 228 ± 63 N for the subjects who increased endurance time and 330 ± 69 N for those who did not ($P < 0.05$). However, although the relative decline in MVC force after 4 wk of immobilization was greater for the subjects who experienced the increase in endurance time ($-26.0 \pm 11.9\%$ vs. $-12.8 \pm 18.1\%$), there were no differences between the two groups in the decrease of the absolute target force (-8.9 ± 5.6 N vs. -6.9 ± 5.4 N). Furthermore, the male subject who exhibited the same behavior as the women had an MVC force (353 N) that was intermediate for the men.

DISCUSSION

This study has two main findings. First, the postimmobilization increase in endurance time for an isometric contraction sustained at 15% MVC was exhibited by all the women but by only one man. Second, the prolongation of endurance time after 4 wk of immobilization was achieved with intermittent activation of the elbow flexor muscles and an absence of the typical progressive increase in EMG.

The literature on muscle fatigue suggests that women generally have longer endurance times than men, especially at low-to-moderate forces (Kahn et al. 1986; West et al. 1995; Zijdwind and Kernell 1994). For example, the endurance time of women was longer than that of men when performing an isometric contraction at 20% of maximum with the knee extensor muscles but not at 50 or 80% of maximum. Similarly, women were able to perform a greater number of repetitions with the elbow flexor muscles when lifting loads that were 50,

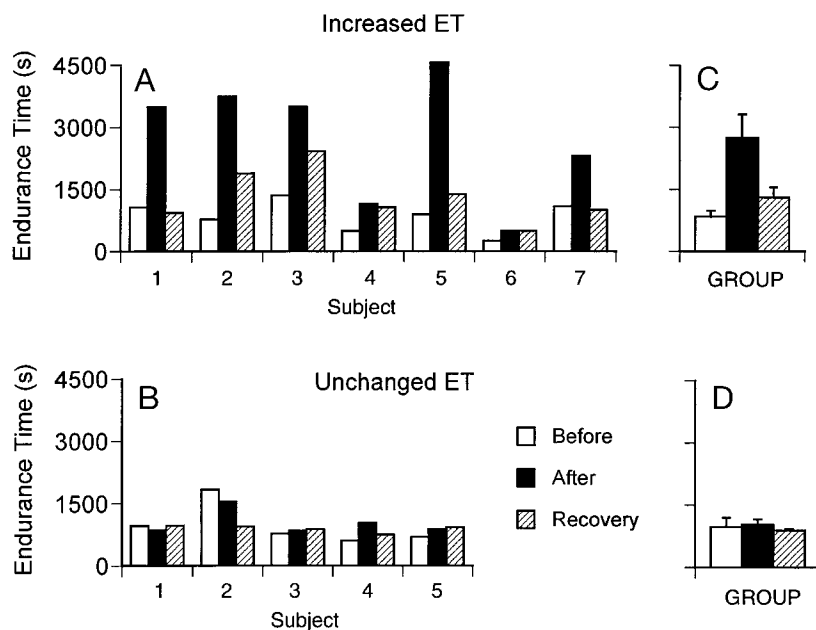


FIG. 1. Changes in the duration of a fatiguing contraction for 12 subjects who had the left arm immobilized in a fiberglass cast for 4 wk. The fatiguing contraction involved sustaining a low force (15% of maximum) with the elbow flexor muscles for as long as possible. Subjects performed the fatiguing contraction before immobilization, immediately after 4 wk of immobilization, and after 4 wk of recovery. Data is shown for 7 individual subjects who experienced $\geq 100\%$ increase in endurance time (ET) when the fatiguing contraction was performed immediately after the cast was removed (A) and 5 subjects whose endurance time did not change (B). Average endurance time is shown for the subjects who increased endurance (C) and for those who did not change (D).

60, and 70% of maximum but not with loads that were 80 or 90% of maximum (Maughan et al. 1986).

When an individual sustains an isometric contraction at a submaximal force, the typical finding is a progressive increase in the amplitude of the EMG (Fig. 2A) (Fuglevand et al. 1993). The increase in EMG probably represents the cumulative activation of motor units because the discharge rates of recruited motor units remain relatively constant during sustained isometric contractions at submaximal forces (Christova and Kossev 1998; Garland et al. 1994). Although subjects appear capable of recruiting motor units during such a task, the fatiguing contraction is terminated before activation of the entire motor unit pool, especially at low target forces (Fuglevand et al. 1993; Löscher et al. 1995; West et al. 1995).

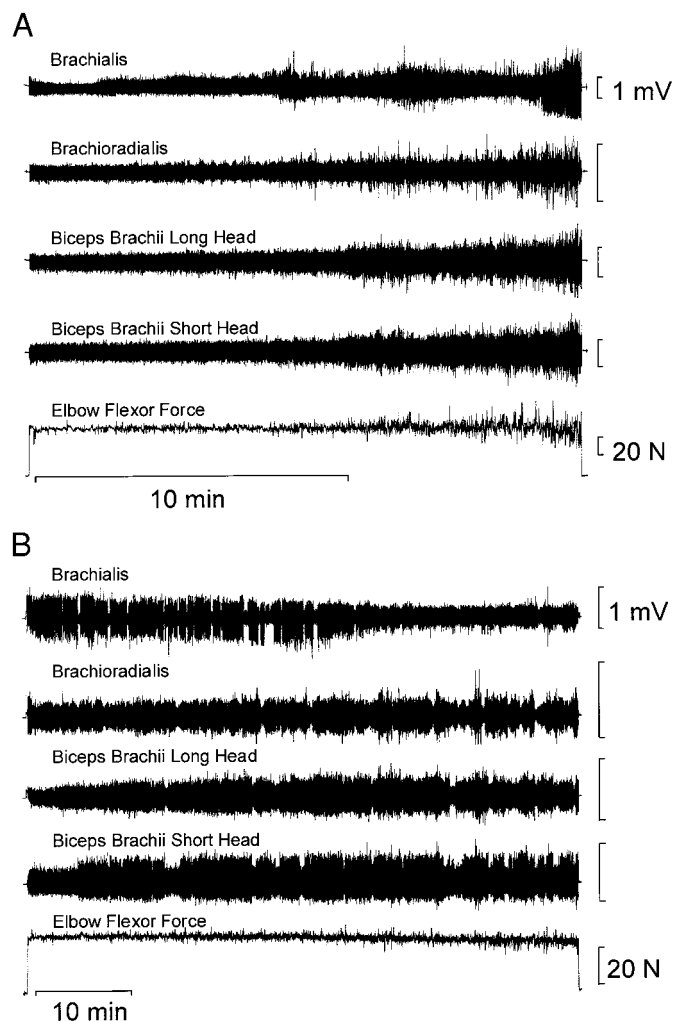


FIG. 2. EMG activity of the major muscles involved in the fatiguing contraction as performed by one subject before beginning the immobilization protocol (A) and immediately after the cast was removed (B). A: EMG amplitude for all 4 muscles increased progressively during the contraction. Bottom trace: net force exerted by the muscles. Despite attempts to keep the force constant, it became more tremulous as the fatiguing contraction progressed, which is indicative of the increasing effort that was required to perform the task. Subject was able to perform the task for 17.7 min. B: in contrast to the pattern of activity exhibited before immobilization, there was no progressive increase in the EMG signals, especially over the latter 60% of the fatiguing contraction. Furthermore, the EMG signals were characterized by intervals of reduced activity. On this occasion, the subject was able to sustain the force for 58.3 min.

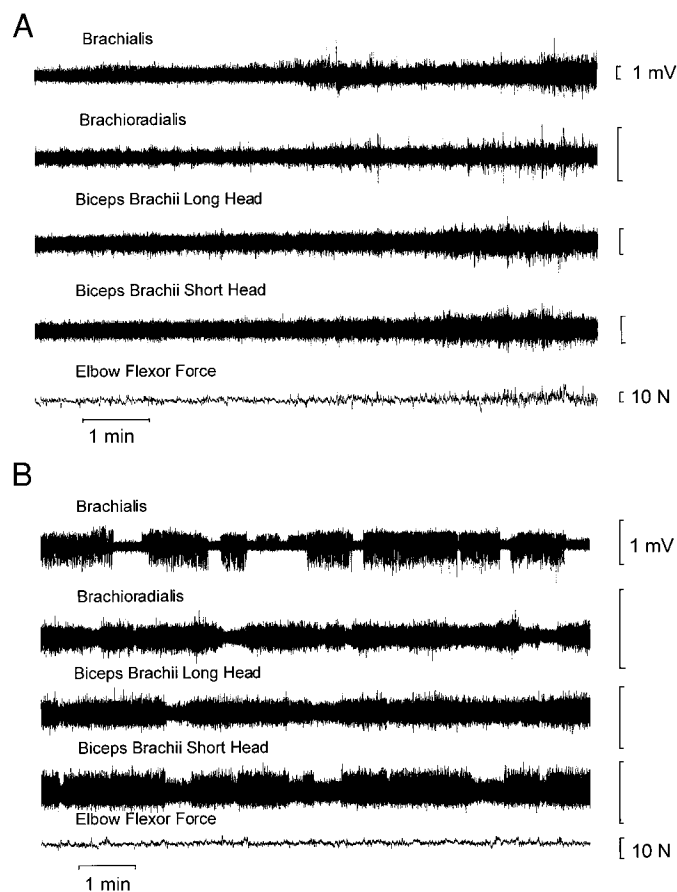


FIG. 3. Expanded view of the performances shown in Fig. 2 to emphasize the absence (A) and presence (B) of the intermittent pattern of activity during the postimmobilization fatiguing contraction. Intermittent activity (B) was exhibited by all the subjects who increased endurance time (6 of 6 women and 1 of 6 men), but only when the task was performed immediately after the cast was removed. In contrast, those subjects whose endurance time did not change (5 of 12) used a pattern of a progressive increase in EMG with no intermittent activity (A). Furthermore, the intermittent activity was not observed in the fatiguing contraction performed by any subjects before immobilization or after 4 wk of recovery. The record for brachialis comprises the most discrete bursts of activity because it was obtained with an intramuscular electrode that had a smaller recording volume than the surface electrodes used for the other muscles.

In combination with previous findings, the absence of a progressive enhancement in the EMG suggests that the postimmobilization increase in endurance time involved neither the recruitment of additional motor units nor a gradual increase in discharge rate of the activated motor units. Rather, the EMG activity appeared to be comprised of bursts of motor unit activity (Fig. 3B). Although alternating motor unit activity has been observed previously in a fatiguing contraction (Fallentin et al. 1993; Tamaki et al. 1998), this is the first study of an intervention-induced change in the activation pattern, the significance of which is underscored by the possible role of gender in the adaptation.

Participation in a 4-wk intervention of limb immobilization evoked an adaptation that enhanced the differences due to gender in the fatigability of muscle. This effect does not appear to have been because of short-term (monthly) hormonal differences between women and men as the women were tested at different phases of the estrous cycle and yet showed similar changes in endurance time and pattern of muscle activation. In

addition, each woman was tested at the same time points in two consecutive cycles, and yet there were substantial differences in the experimental outcomes.

The gender effect might represent an interaction between the responses evoked by the imposed restraint of limb immobilization and neuromodulatory action of the enkephalinergic, dopaminergic, and serotonergic systems. The responses associated with limb immobilization have been reported to involve a reorganization of the motor cortex area serving the muscles in the immobilized limb (Liepert et al. 1985), a decrease in multiunit activity in the amygdala (Henke 1985), discrete reductions in noradrenaline levels and dopamine turnover in the hypothalamus (Fuxe et al. 1983), heightened extracellular levels of 5-hydroxyindoleacetic acid in several brain areas (Clement et al. 1998), an increase in the number of junctional and extrajunctional nicotinic acetylcholinergic receptors in the immobilized limb (Suliman et al. 1997), and an increase in oxidative stress in skeletal muscle (Kondo et al. 1992). Perhaps the mechanisms mediating such adaptations interacted with central neuromodulators (Chaouloff 1997; Marder 1998) to evoke a gender-specific pattern of motor unit activity.

These findings underscore three fundamental features of the neuromuscular system. First, a relatively modest reduction in muscle usage can evoke marked adaptations in the neuromuscular system. Second, adaptations of the neuromuscular system after limb immobilization appear to differ between women and men. Third, the mechanisms underlying the association between the sense of effort and motor unit recruitment were disturbed, especially for women, immediately after the cast was removed.

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