Effect of experimental muscle pain on maximal voluntary activation of human biceps brachii muscle

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Muscle pain related to musculoskeletal disorders is a major clinical problem, but the neurophysiological mechanisms underlying muscle pain are not completely understood. Muscle pain induced by intramuscular injection of hypertonic saline is a well-established method to investigate the interaction between muscle pain and motor function in a healthy neuromuscular system (e.g., 2, 16, 26, 34, 49). Intramuscular injection of hypertonic saline activates mostly nonmyelinated small-diameter afferents (33, 43) and produces deep muscle pain described as aching and cramplike (2). It may also have a limited excitatory effect on large afferents (29).

In submaximal contractions, intramuscular hypertonic saline reduces electrical activity of the painful muscle and results in a redistribution of activity between muscle regions and muscles (14, 36). It is also known to reduce the discharge rate of low-threshold motor units in both the painful muscle and its synergists (15, 27, 47). Maximal motor output is also altered. For the knee extensor muscles, intramuscular injection of hypertonic saline significantly reduced maximal voluntary torque by ~20% but did not affect electrically evoked twitch torque (21). Hence, the authors concluded that the decrease in voluntary torque was mediated by central rather than peripheral mechanisms. Other studies using stimulation of the motor cortex or descending tracts have shown pain-related changes in motor responses. A reduction in the amplitude of motor-evoked potentials in response to transcranial magnetic stimulation (TMS) suggests a decrease in the excitability of the motor cortex (34). In contrast, experimental muscle pain increases the excitability of spinal motoneurons (39). Together, these results suggest that the observed decrease in maximal voluntary torque (21) is mediated at a supraspinal level. One possible explanation for the reduction in maximal torque is a decrease in voluntary activation associated with suboptimal drive from the motor cortex to the motoneurons. That is, voluntary output from the motor cortex is not maximal and is insufficient to drive motoneurons to produce maximal force from the muscle. In the present study, this possibility was directly tested with noninvasive stimulation methods.

Voluntary activation refers to the level of drive to contracting muscle during a voluntary contraction (17) and is commonly estimated using the twitch interpolation technique, in which a supramaximal electrical stimulus is delivered to the motor nerve (3, 18, 22, 29, 37) or motor point of the muscle (1, 5, 18, 30). When stimuli are delivered during maximal voluntary contractions (MVC), twitch interpolation tests the ability of subjects to activate the muscle fully. If extra torque can be evoked by the superimposed stimulus it suggests that either not all motor units were recruited by volition or they were firing at a suboptimal rate (1). On the other hand, if no extra torque is evoked by the superimposed stimulus during an MVC, then voluntary activation is considered to be complete. More recently, voluntary activation has been assessed by TMS (e.g., 20, 46, 54). Using this technique, any additional torque induced by the stimulus during an MVC suggests that the deficit in voluntary drive is located at or above the level of the motor cortex (54).

Other evidence of a central effect of muscle pain on the motor pathway comes from studies that used a force-matching task with the elbow flexors (44, 55). Using visual feedback, subjects performed a submaximal isometric contraction with one arm and attempted to match this torque with the other arm without visual feedback. Muscle pain induced by injection of hypertonic saline into biceps brachii resulted in subjects producing less torque with the painful arm than the nonpainful arm. Weerakkody and colleagues (55) proposed that nociceptors stimulated by injection of hypertonic saline reduced motor
cortex excitability and led to a mismatch between the sense of effort and motor output. In the present study, we attempted to test this more directly in a single arm task. We asked subjects to produce different levels of effort without visual feedback and measured the consequent motor output.

Hence, we tested the effect of experimental muscle pain induced by intramuscular injection of hypertonic saline into biceps brachii on maximal and submaximal voluntary contractions. In MVCs we tested voluntary activation and voluntary torque. Voluntary activation was assessed using motor-point and motor cortical stimulation in separate experiments. We hypothesized that evoked muscle pain would impair voluntary activation at a supraspinal level during maximal efforts and would reduce maximal voluntary torque. In submaximal contractions, we investigated the relationship between effort and actual submaximal torque output. We hypothesized that muscle pain would alter this relationship so that the same effort would lead to lower torque.

METHODS

Seven healthy subjects (4 men and 3 women; 33 ± 10 yr) participated in the first study, which involved motor-point stimulation. Four of these subjects (2 men and 2 women; 31 ± 3 yr) plus a further three (1 man and 2 women; 45 ± 7 yr) participated in the second study, which involved motor cortical stimulation. Six subjects (4 men and 2 women; 31 ± 4 yr) from the first study took part in an additional psychophysical experiment that involved graded submaximal efforts. The local institutional ethics committee approved the study, and written informed consent to the experimental protocol was obtained.

The study was conducted according to the Declaration of Helsinki.

Torque and EMG recordings. Subjects sat with the right arm positioned in an isometric myograph with an elbow angle of 90° (Fig. 1A). The forearm was supinated and the wrist was secured to the myograph by a strap. Elbow flexion torque was measured using a linear strain gauge (Xtran, Melbourne Australia; linear to 2 kN). In study 2, surface EMG from biceps brachii was recorded with adhesive Ag-AgCl electrodes (10-mm diameter) placed over the motor point and distal tendon. The EMG signals were amplified (×100) and band-pass filtered (16–1,000 Hz) using CED 1902 amplifiers (Cambridge Electronic Design, Cambridge, UK). Torque and EMG data were sampled at 1,000 and 2,000 Hz, respectively, and stored on a computer using a 12-bit analog-to-digital converter (CED 1401 Plus, Cambridge Electronic Design) and Spike 2 software (version 6.13; Cambridge Electronic Design).

Motor-point stimulation. In study 1, a single electrical stimulus of 100–µs duration was delivered by a Digitimer DS7AH constant-current stimulator (Digitimer, Welwyn Garden City, Herfordshire, UK) through surface electrodes (Ag-AgCl, 10-mm diameter) over biceps brachii. The active electrode was positioned over the motor point, and the reference was secured over the distal tendon. The resting twitch of maximal amplitude was determined by increasing the stimulus intensity until elbow flexor torque failed to increase despite an increase in current. To ensure a maximal response throughout testing, a supramaximal stimulus intensity (100–256 mA), which was 110% of the intensity that evoked a maximal twitch, was used.

Brachial plexus stimulation. In study 2, the brachial plexus was stimulated to determine the size of maximal compound muscle action potentials (Mmax) for biceps and triceps brachii. Single stimuli (100–µs duration) were delivered by a Digitimer DS7AH stimulator through surface electrodes (Ag-AgCl, 10 mm diameter). The active electrode was positioned over the supraclavicular fossa at Erb’s point and the reference on the acromion. The amplitude of Mmax was used to set the appropriate stimulus intensity for TMS (see next section).

TMS. In study 2, motor cortical stimulation was performed using a Magstim 2002 stimulator (Magstim, Dyfed, UK). A circular coil (13.5-cm OD) positioned over the vertex elicited motor responses (motor-evoked potentials, MEPs) in the biceps and triceps brachii. This position was marked to ensure consistent positioning of the coil during repeated stimulation. The direction of current flow activated the left hemisphere preferentially. Stimulator output was set to evoke strong MEPs (motor-evoked potentials) at 101% of the motor threshold. Subjects were instructed to grip a hand dynamometer to maximize voluntary contraction and to maintain this grip strength throughout TMS testing. The TMS coil was positioned over the vertex, as determined by MRI studies performed in a subset of subjects, with the axis of the coil parallel to the sagittal plane (130°, left hemisphere).

Subjects were seated in a comfortable armchair with the arm in a neutral position. Subjects were instructed to set the hand dynamometer to 50% of their MVC. Baseline MVCs were recorded, and the subject was then instructed to perform MVCs with the brachial plexus stimulation. After 1 min of stimulation, MVCs were repeated and the subject was then instructed to perform MVCs with the motor cortical stimulation. After 1 min of stimulation, MVCs were repeated and the subject was then instructed to perform MVCs without stimulation. MVCs were recorded after 1 min of voluntary contraction.

RESULTS

Individual contributions. When the brachial plexus was stimulated, subjects reported a sharp pain in the elbow, and the MVC dropped by 5% (mean ± SD: 10.8 ± 4.6%) at 1 min (Fig. 2). MVCs were significantly lower than baseline MVCs at 5 min after stimulation (4.9 ± 3.3%, P < 0.05). When the motor cortex was stimulated, MVCs dropped by 7% (mean ± SD: 6.8 ± 3.6%) at 1 min, and MVCs were significantly lower than baseline MVCs at 5 min after stimulation (6.1 ± 3.9%, P < 0.05). MVCs were similar when the brachial plexus was stimulated as compared with when the motor cortex was stimulated.

Voluntary activation. MEP amplitudes were significantly lower when the brachial plexus was stimulated as compared with when the motor cortex was stimulated (−7%, P < 0.05). The decline in MEP amplitude was larger in the group that had a MVC drop at 5 min (−10%, P < 0.05) as compared with the group that did not have a MVC drop at 5 min (−6%, P < 0.05). The decline in MEP amplitude in the group that had a MVC drop at 5 min was larger in the group that had a MVC drop at 5 min (−10%, P < 0.05) than in the group that did not. The decline in MEP amplitude in the group that had a MVC drop at 5 min was larger in the group that had a MVC drop at 5 min (−10%, P < 0.05) than in the group that did not. The decline in MEP amplitude in the group that had a MVC drop at 5 min was larger in the group that had a MVC drop at 5 min (−10%, P < 0.05) than in the group that did not.

Correlation between effort and torque. The correlation between effort and torque was greater when the motor cortex was stimulated as compared with when the brachial plexus was stimulated (r2 = 0.76 vs. 0.54, P < 0.05).

DISCUSSION

The results of this study suggest that evoked muscle pain impairs voluntary activation and voluntary torque during maximal voluntary contractions. This finding is consistent with previous studies that have shown that pain impairs voluntary activation during submaximal voluntary contractions (25–27). This effect may be due to muscle pain reducing the level of effort that is required to perform a given task (27). This effect is likely to be more pronounced during maximal voluntary contractions because the level of effort that is required to perform a given task is higher during maximal voluntary contractions than during submaximal voluntary contractions.

In conclusion, evoked muscle pain impairs voluntary activation and voluntary torque during maximal voluntary contractions. This effect is likely to be more pronounced during maximal voluntary contractions than during submaximal voluntary contractions because the level of effort that is required to perform a given task is higher during maximal voluntary contractions than during submaximal voluntary contractions.
an MEP amplitude >60% Mmax in biceps and <15% Mmax in triceps during a brief maximal effort of the elbow flexors (53, 54). This stimulation intensity (40–60% stimulator output) remained constant for all measurements in an individual subject.

Protocol for studies 1 and 2. The effect of intramuscular injection of hypertonic saline on voluntary activation during isometric MVCs of the elbow flexors was assessed in two studies. Each study consisted of a pain session and a control session, separated by at least 1 wk, and the order of sessions was randomized between subjects. In the pain session of study 1, a bolus of 1 ml of 5% of hypertonic saline was injected into the belly of biceps before the 3rd and 4th sets of contractions, and in the control session, isotonic saline was injected (Fig. 1B). In each session, subjects performed six sets of three brief (~2 s) MVCs. Within a set, MVCs were separated by 1 min and sets were 5 min apart. Supramaximal electrical stimuli delivered over the motor point of biceps during and 4 s after each MVC evoked a superimposed twitch and potentiated resting twitch, respectively. In study 2, hypertonic saline was injected in the pain session but no injection was made in the control session. Similar to study 1, in the control and pain sessions, subjects performed six sets of three brief MVCs. In this study, each MVC was followed by brief (~2 s) submaximal contractions of 75 and 50% MVC at 4–s intervals. MVCs were separated by 75 s within a set and there was 5 min between sets. TMS was delivered during each contraction to evoke superimposed twitches. Muscle pain was rated on an 11-point modified Borg scale with descriptors (from 0 = infinitely small to 10 = extremely large) in rest periods between sets of contractions.

Study 3: psychophysical experiment. The third study consisted of a control session (no injection) and a pain session (injection of hypertonic saline) separated by 1 day. The control session was conducted before the pain session for all subjects. On each day, subjects initially performed three brief MVCs with visual feedback and verbal encouragement. The remainder of the test involved sets of 15 brief submaximal contractions (3 trials at 5 different levels of effort) without visual feedback. Within a set, contractions were separated by 10 s and the sets were 2 min apart. Before each contraction, subjects were instructed to “pull up with 5%, 10%, 25%, 50%, or 75% of your maximal effort.” Subjects were told not to adjust or correct their contractions once initiated. On each day, subjects performed a practice set of contractions during which they received verbal feedback from the experimenter (e.g., “that was too high”). Subjects then performed five to seven sets of recorded contractions. In the pain session, a single injection of 1 ml of 5% hypertonic saline was given before the 3rd set to induce muscle pain. For all subjects, muscle pain lasted ~5–10 min and that allowed two sets (30 submaximal contractions) to be performed continuously while pain persisted. Three recovery sets were completed after pain had subsided. In the control session, no injections were made, and five sets were collected in all subjects.

Data analysis and statistics. All measurements were made offline using Spike2 software (version 6.13; Cambridge Electronic Design). Voluntary activation was quantified by measurement of evoked torque responses following motor-point and transcranial magnetic stimulation. For motor-point stimulation, any increment in torque in response to stimulation during a maximal contraction was expressed as a fraction of the response to the same stimulus delivered to the potentiated relaxed muscle (Fig. 1C). Voluntary activation was quantified using this equation: voluntary activation (%) = [1 – (superimposed twitch/resting twitch)] × 100. The same equation was used to calculate voluntary activation following TMS, but the resting twitch was estimated rather than measured directly because of differences in cortical and motoneuronal excitability at rest vs. during contraction (54). A linear regression between the size of the evoked twitch and voluntary torque at 50, 75, and 100% MVC was used to estimate the resting twitch size. The y-intercept of the linear regression was taken as the amplitude of the estimated resting twitch (Fig. 1D) (54).

In the first and second studies, mean elbow flexion torque was calculated for the 100 ms immediately before each stimulus. Maximal torque and resting twitch data were normalized to the mean baseline value (average of sets 1 and 2). In the psychophysical experiment, the subject was asked to hold a contraction for ~2 s and the mean torque was calculated over 500 ms (from 50 ms before the peak torque to 450 after the peak torque).

For studies 1 and 2, voluntary activation, normalized maximal torque, and normalized resting twitch amplitude were analyzed with two-way repeated-measures ANOVA for comparison of session (control and pain) and time (baseline, baseline 2, pain 1, pain 2, recovery 1, and recovery 2) (Sigma Stat 2.01; Systat Software). Whenever the ANOVA revealed significant main effects and/or an interaction, post hoc tests were performed with Student-Newman-Keuls tests (SNK) to identify points where the significant differences occurred. For study 1, a paired Student’s t-test was used to compare the intensity of pain (mean value of sets 3 and 4) between the pain (injection of hypertonic saline) and the control session (injection of isotonic saline) and to compare the intensity of pain between the two injections of hypertonic saline in the pain session. In addition, for study 2, a paired t-test was used to compare the estimated resting twitch linear regression correlation coefficients (r) between the pain and the control session. For study 3, each normalized submaximal torque (5, 10, 25, 50, and 75% MVC) was analyzed using a two-way repeated-measures ANOVA with session (control and pain) and time (baseline, pain, recovery) as within-subject factors. In study 3, some subjects reported minimal pain during the first recovery set (set 5, Fig. 5C), and the set was not included in the analysis. To assess task performance in individual subjects, a linear regression between the requested and the voluntarily produced torque was obtained for each session. Data are represented as means ± SD in the text and means ± SE in the figures. Statistical significance was set at P < 0.05.

RESULTS

In all studies, experimental muscle pain was induced by injection of 1 ml of 5% hypertonic saline into biceps brachii (Fig. 1B). As expected, injection of hypertonic saline induced significant pain in the muscle (pain rating of ~5 on a scale from 0 to 10). Subjects reported a deep, dull ache in the muscle after injection. Evoked muscle pain originated near the site of injection and diffused over a large area of the muscle belly. Figure 2 illustrates the time course of perceived pain following injection of hypertonic or isotonic saline.

Study 1: motor-point stimulation. Injection of hypertonic saline induced more pain than isotonic saline (mean pain rating of 4.5 ± 0.9 vs. 1.1 ± 0.9 across sets 3 and 4; P = 0.001). In the pain session, injection 1 induced more pain than injection 2 for all subjects (mean pain rating of 5.1 ± 1.2 vs. 3.8 ± 0.9 for sets 3 and 4; P = 0.01). Voluntary activation showed a significant main effect for session (P = 0.043) and an interaction (P = 0.036) but no significant main effect for time (P = 0.414). Hence, voluntary activation was lower in the pain than control session (mean voluntary activation across all sets was 97.7 ± 1.0% vs. 98.2 ± 0.7%, respectively; Fig. 3A). Comparison between sessions of corresponding sets of contractions showed a significant difference in voluntary activation for set 5 (P = 0.003; SNK, Fig. 3A), which was the first set after the pain had resolved. There was also a trend toward difference during pain (set 4, P = 0.072; SNK, Fig. 3A).

Experimental muscle pain caused a small but significant reduction (~5%) in maximal voluntary torque (Fig. 3B). In the two-way repeated-measures ANOVA, there were significant main effects for session (P = 0.008) and time (P < 0.001) and
an interaction ($P < 0.001$). Overall, MVC torque was lowered by $\sim 3\%$ for sets 3 and 4 compared with the baseline values (sets 1 and 2) and remained lower by $\sim 5\%$ for sets 5 and 6 during the recovery period ($P < 0.001$; SNK). Similar to voluntary activation, MVC torque was lower in the pain than control session. When corresponding sets were compared, there were significant differences during pain (sets 3 and 4; $P < 0.001$; SNK) and the recovery (set 5; $P = 0.03$, SNK).

The resting twitch was decreased in amplitude with time ($P = 0.002$) but was not altered by pain ($P = 0.70$), and there was no significant interaction ($P = 0.18$) between the factors (Fig. 3C). Resting twitch amplitude was decreased by $\sim 10\%$ during the recovery (sets 5 and 6) compared with the baseline values ($P < 0.03$; SNK).

**Study 2: TMS.** The level of pain induced in the pain session of study 2 was comparable to that in study 1 (mean pain rating of $4.6 \pm 1.3$ across sets 3 and 4), and injection 1 induced more pain than injection 2 for all subjects (mean pain rating of $5.3 \pm 1.2$ vs. $3.8 \pm 1.0$ for sets 3 and 4; $P = 0.01$). As there were no injections during the control session, there was no pain reported during sets 3 and 4 of this session. In contrast to voluntary activation assessed with motor-point stimulation, voluntary activation assessed with TMS was not altered by induced muscle pain (mean voluntary activation across all sets was $94.6 \pm 0.8$ vs. $94.5 \pm 1.1\%$ in the control and pain sessions, respectively; Fig. 4A). There were no main effects for session ($P = 0.86$) or time ($P = 0.09$) or an interaction between the factors ($P = 0.61$).

Like study 1, maximal voluntary torque was significantly reduced ($\sim 6\%$) during induced muscle pain (Fig. 4B). There was a significant main effect for time ($P < 0.001$) and an interaction ($P = 0.045$) but no main effect for session ($P = 0.079$). Overall, MVC torque was lower ($\sim 6\%$) for sets 3 and 4 compared with the baseline sets and remained lower ($\sim 4\%$) during the recovery (sets 5 and 6) ($P < 0.01$; SNK). Comparison of corresponding sets between sessions showed that MVC

Fig. 2. Time course and intensity of induced pain. Mean (solid lines) and SE (dashed lines) of pain rating with injection 1 of hypertonic saline (top traces) and isotonic saline (bottom traces) in study 1. The bar above the graphs shows approximate timing of MVCs. A similar time course was obtained with injection 2. However, injection 2 induced a smaller magnitude of pain than injection 1 for all subjects.

Fig. 3. Pooled ($n = 7$) data for voluntary activation, normalized maximal torque, and normalized resting twitch amplitude in study 1. Mean plots (mean $\pm$ SE) are shown before (baseline), during (pain), and after (recovery) experimental muscle pain induced by intramuscular injection of hypertonic saline (triangle) or control injections of isotonic saline (circle) into biceps brachii. *Data points (mean of both sessions) that are significantly lower than the baseline values ($P < 0.05$). †Significant difference between sessions at a given time point ($P < 0.05$). A: voluntary activation assessed with motor-point stimulation. B: maximal voluntary torque. C: resting twitch amplitude. Maximal torque and resting twitch amplitude were normalized to the mean baseline value.
torque was significantly lower for sets 3 and 4 of the pain session than the control session ($P < 0.002$ and $P < 0.02$, respectively; SNK).

The correlation coefficient ($r$) from the linear regression to determine estimated resting twitch amplitude was $r > 0.90$ in all instances (Fig. 1D). When compared between the pain and control session, the correlation coefficient was similar for all subjects ($P = 0.88$). Unlike the resting twitch evoked by motor-point stimulation, the estimated resting twitch evoked by TMS did not decrease significantly over time ($P = 0.27$) (Fig. 4C). However, like the motor point-stimulation twitch, neither the main effect for session ($P = 0.83$) nor the interaction ($P = 0.80$) were statistically significant for the estimated resting twitch. Hence, pain had no effect on the estimated resting twitch measured using cortical stimulation.

**Study 3: psychophysical experiment of evoked pain.** In studies 1 and 2, induced muscle pain had a small effect on maximal torque production and a negligible effect on voluntary activation during a maximal effort. In this study, subjects performed submaximal voluntary efforts to examine whether muscle pain changed the relationship between subjects’ effort and their torque output. Like studies 1 and 2, injection of hypertonic saline induced considerable pain in biceps brachii (mean pain rating of $4.2 \pm 1.2$ across sets 3 and 4). However, evoked pain had no significant effect on torque output during submaximal contractions of 5–75% MVC (raw traces for a single subject shown in Fig. 5A). Subjects performed the task well as the requested and voluntarily produced torques showed a strong correlation for both session ($r > 0.95$; shown for a single subject in Fig. 5B). For each level of voluntary effort, a two-way repeated-measures ANOVA of torque showed no interaction ($P > 0.41$) or main effects for time ($P > 0.0.07$) or session ($P > 0.62$) (Fig. 5C).

**DISCUSSION**

This study demonstrates that evoked muscle pain induced by intramuscular injection of hypertonic saline into biceps brachii had a minimal effect on voluntary activation when assessed with motor-point stimulation and no effect when assessed with motor cortical stimulation. Hence, the hypothesis that evoked muscle pain would impair voluntary activation at a supraspinal level was not supported by the data. Induced muscle pain had a small effect on maximal voluntary torque, but the psychophysical study revealed no significant effect of muscle pain on torque output during submaximal efforts.

Twitch interpolation has been the most widely used technique to investigate voluntary activation during a maximal effort (e.g., 3, 5, 11, 19, 20, 24, 42, 45, 54). In the present study, both motor-point and motor cortical stimulation were used to assess how voluntary activation of the elbow flexors was affected by experimental muscle pain induced by intramuscular injection of hypertonic saline into biceps brachii. Neither method of stimulation showed a convincing impairment of activation following injection of hypertonic saline although motor point stimulation revealed a very small decrease in activation in one set of contractions after resolution of the muscle pain. As motor cortical stimulation gives a more linear relationship between voluntary force and the evoked superimposed twitch, particularly for high contraction strengths (e.g., 20, 54), it should be more sensitive.
were normalized to the MVC value. Intramuscular injection of hypertonic saline into biceps brachii. Torque data during (pain), and after (recovery) experimental muscle pain induced by voluntary torque during submaximal efforts (5–75% MVC) before (baseline),

Figure 5: Psychophysical experiment. A: example of torque traces recorded from 1 subject during the pain session. Gray and black traces are efforts before and during experimental muscle pain, respectively. B: relationship between requested and produced torque before (circle) and during (triangle) experimental muscle pain for the same subject. C: mean plots (mean ± SE; n = 7) for voluntary torque during submaximal efforts (5–75% MVC) before (baseline), during (pain), and after (recovery) experimental muscle pain induced by intramuscular injection of hypertonic saline into biceps brachii. Torque data were normalized to the MVC value.

The period of ischemic rest allows neurons in the motor pathway to recover from repetitive activation but does not allow the muscle to recover. It has been proposed that the impairment in voluntary activation during ischemia could be due to the activity of group III and IV muscle afferents (18, 51) which are activated by the muscle metabolites accumulated during the fatiguing contraction as well as by ischemia (31). Motoneuron firing rates are low during brief MVCs performed when the muscle is held ischemic (6, 56). However, for the elbow flexors, fatigue-sensitive small-diameter muscle afferents do not directly inhibit spinal motoneurons (10, 50) and may actually facilitate them (37). Hence, the low motoneuron firing rate and poor voluntary activation when these afferents fire may occur through actions at a supraspinal level to impair voluntary descending drive (10). In the present study, muscle pain was induced by injection of hypertonic saline, which is also known to activate small-diameter group III and IV muscle afferents (33, 43, 52). However, it is possible that muscle fatigue, ischemia, and hypertonic saline activate different populations of muscle afferents and have different effects on motor function. This possibility is supported by the finding that characteristics of pain (intensity, duration, and quality) induced by hypertonic saline in tibialis anterior were different from those during ischemic contraction (22). In addition, in the arm, fatigue-sensitive muscle afferents facilitate biceps motoneurons but inhibit triceps motoneurons whereas those activated

than motor-point stimulation to a slight reduction in voluntary activation if the reduction is due to suboptimal output from the motor cortex. Thus the lack of change here emphasizes that any failure of drive was not at a supraspinal level. These findings are surprising given the previous result that experimental muscle pain substantially reduced (~20%) maximal voluntary torque of the knee extensors (21). For the elbow flexors, we found a much smaller reduction of MVC torque (~5%). One explanation for the discrepancy may be that voluntary activation of quadriceps muscle is relatively low (~85–95%) (3, 7, 8, 23, 28, 45, 48) compared with the elbow flexor muscles (94–98%) (1, 3, 11, 18, 24, 41, 45). Herbert and Gandevia (25) developed a model of twitch interpolation for abductor pollicis and found a sigmoidal relationship between the level of excitation of the motoneuron pool and muscle force. According to the model, large increases in drive are needed to make small increases in measured voluntary activation when voluntary activation is already high. Hence, if the elbow flexors are close to the plateau of the sigmoidal relationship and the knee extensors are on a steeper portion of the curve, then similar decreases in motoneuron drive to the muscles may result in larger decreases in voluntary activation and force for the less well activated muscle (i.e., knee extensors.)

One complication with the present data is that subjects became fatigued during the test sessions despite long periods of rest between contractions. Muscle fatigue is evident from the fall in maximal torque over time in the control as well as pain sessions. A peripheral component to this fatigue is confirmed by a gradual decline in resting twitch amplitude (study 1, Fig. 3C). This decrease was not significant for the estimated resting twitch (study 2), which is calculated from superimposed twitches elicited during maximal and submaximal contractions and contrary to the twitch after motor-point stimulation, is unlikely to be sensitive to low-frequency fatigue (13, 40).

While our study shows no convincing impairment of voluntary activation of the elbow flexors with muscle pain, the firing of small-diameter muscle afferents has been reported to impair activation in other circumstances. Voluntary activation declines progressively during a sustained MVC and remains low when the muscle is held ischemic at the end of the contraction (18). The period of ischemic rest allows neurons in the motor pathway to recover from repetitive activation but does not allow the muscle to recover. It has been proposed that the impairment in voluntary activation during ischemia could be due to the activity of group III and IV muscle afferents (18, 51) which are activated by the muscle metabolites accumulated during the fatiguing contraction as well as by ischemia (31). Motoneuron firing rates are low during brief MVCs performed when the muscle is held ischemic (6, 56). However, for the elbow flexors, fatigue-sensitive small-diameter muscle afferents do not directly inhibit spinal motoneurons (10, 50) and may actually facilitate them (37). Hence, the low motoneuron firing rate and poor voluntary activation when these afferents fire may occur through actions at a supraspinal level to impair voluntary descending drive (10). In the present study, muscle pain was induced by injection of hypertonic saline, which is also known to activate small-diameter group III and IV muscle afferents (33, 43, 52). However, it is possible that muscle fatigue, ischemia, and hypertonic saline activate different populations of muscle afferents and have different effects on motor function. This possibility is supported by the finding that characteristics of pain (intensity, duration, and quality) induced by hypertonic saline in tibialis anterior were different from those during ischemic contraction (22). In addition, in the arm, fatigue-sensitive muscle afferents facilitate biceps motoneurons but inhibit triceps motoneurons whereas those activated...
by hypertonic saline excite both the flexor and extensor motoneurons pools (37, 39).

In the present study, the small fall in the MVC without a significant pain-related change in either peripheral force production or in voluntary activation is puzzling. We can speculate on two possible solutions. First, there could be increased cocontraction of the antagonist muscles. As noted above, the elbow extensor motoneurons are facilitated by injection of hypertonic saline into biceps (39). In other studies, changes in antagonist activity are variable and may depend on the specific task (12, 14). Second, there could be a drop in voluntary activation that is too small for the twitch interpolation technique to detect. However, voluntary activation measured with TMS should be more sensitive than voluntary activation measured with motor-point stimulation as it is more linearly related to the strength of voluntary contractions (53). Thus, if there is a small undetected decrease of voluntary activation, the site of impairment is likely to be subcortical. Furthermore, as the motoneurons of the elbow flexors are facilitated by intramuscular hypertonic saline (39), the impairment should be premotoneuronal. A possible site would be the propriospinal interneurons, as a substantial part of voluntary drive may be conveyed via the C3–4 propriospinal system (9) and transmission through the system is altered during fatiguing contractions (38).

A further indication that experimental muscle pain may have a central effect on the motor pathways comes from the work of Weerakkody and colleagues (55). In their study, subjects performed a torque-matching task with the elbow flexors when biceps of one arm was made sore by injection of hypertonic saline. When the sore arm was used to match a torque produced by the other arm, the result was consistently low. It was proposed that pain afferents reduced the excitability of the motor cortex and hence reduced the motor output to the painful arm for a given sense of effort. To determine whether muscle pain alters the relationship between the sense of effort and the production of muscle force in a single-arm task, we had subjects produce voluntary efforts ranging from 5–75% maximal. On the control day, a strong correlation between the sense of effort and the production of muscle force in a single-arm task, we had subjects produce voluntary efforts ranging from 5–75% maximal effort. The present study thus showed by motor-point stimulation after pain had resolved.

In summary, experimental muscle pain induced by intramuscular injection of hypertonic saline caused a small reduction in maximal voluntary torque of the elbow flexors. During the muscle pain, there was no significant impairment of voluntary activation in maximal contractions despite a small reduction shown by motor-point stimulation after pain had resolved. Furthermore, evoked muscle pain did not alter the link between the sense of effort and torque production during submaximal contractions (5–75% maximal effort). The present study thus suggests that evoked muscle pain has a limited effect on motor output to the elbow flexors during voluntary contractions.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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