Clinical Science and Molecular Medicine (1978) **54**, 609–614

Central and peripheral fatigue in sustained maximum voluntary contractions of human quadriceps muscle

B. BIGLAND-RITCHIE*, D. A. JONES, G. P. HOSKING AND R. H. T. EDWARDS†

Jerry Lewis Muscle Research Centre, Royal Postgraduate Medical School, London

(*Received* 9 *May* 1977; *accepted* 4 *January* 1978)

Summary

1. The fatigue of force that occurs during the first 60 s of a maximum voluntary contraction of the human quadriceps has been examined by comparing the voluntary force with that obtained by brief tetanic stimulation at 50 Hz in nine healthy subjects. In three subjects the voluntary force declined in parallel with the tetanic force whereas in the remainder it fell more rapidly, suggesting that central fatigue was present.

2. For those subjects who showed little or no central fatigue, surface electromyograph (EMG) activity remained approximately constant while the force declined by about 60%. In the others, EMG activity and force declined in parallel but when an extra effort was made the subjects could briefly increase their force and this was accompanied by a proportionately greater increase in EMG activity (generally up to the original value).

3. It is concluded that in sustained maximum voluntary contractions of the quadriceps (a) central fatigue may account for an appreciable proportion of the force loss, (b) surface EMG recordings provide no evidence that neuromuscular junction failure is the limiting factor determining the loss of force in this muscle.

*Present address: Quinnipiac College, Hamden, Conn. 06518, U.S.A.

†Present address: Department of Human Metabolism, University College Hospital Medical School, University Street, London WC1E 6JJ.

Correspondence: Professor R. H. T. Edwards, Department of Human Metabolism, University College Hospital Medical School, University Street, London WC1E 6JJ.

Key words: fatigue, muscle, quadriceps, voluntary contraction.

Abbreviations: EMG, electromyograph; MVC, maximum voluntary contraction.

Introduction

Force fatigue during maximum voluntary muscular contractions (MVC) may occur from failure either at the neuromuscular junction or at sites proximal or distal to this. Failure proximal to the junction may be the result of a decreased voluntary effort, change in motor neuron excitability (direct or due to inhibition of afferents from the muscle) or to presynaptic block. Which, if any, of these may limit the extent of voluntary contractions has been the subject of controversy in the last 50 years (Reid, 1928; Merton, 1954). A failure of transmission at the neuromuscular junction may arise from either a loss of excitability of the postjunctional membrane or from depletion of acetylcholine stores. Distal failure may arise if action potentials fail to propagate, if coupling between the action potential and the release of calcium fails within the fibre, or if the contractile elements fail to function correctly. We have examined the ability of normal subjects to maintain maximum voluntary isometric contractions of the quadriceps for periods up to 60 s. Force and surface electromyograph (EMG) activity have been measured and the response of part of the muscle to maximal electrical stimulation at different times during the MVC and has been used as an index of muscle contractility that is independent of central drive.

This work follows our previous studies of quadriceps muscle function (Edwards, Young, Hosking & Jones, 1977) and was designed to help answer the question 'Does the fatigue (i.e. failure to generate the required force) arise because the muscle machinery is failing, or because the subject is not willing to go on driving it with the same motivation as at the start?'.

Methods

Subjects

We studied nine healthy adult laboratory personnel (one female; ages 25–50 years) who were familiar with the procedures and gave their informed consent as required by the local Research Ethics Committee. Both legs were studied and no consistent differences in the ability to maintain force were detected.

Measurements of force

The blood supply to leg muscles is occluded during isometric contractions of more than about 20% of the maximal voluntary force (Barcroft & Millen, 1939; Edwards, Hill & McDonnell, 1972), but since many of the present experiments involved interruption of the contraction for brief periods of stimulation, a cuff around the upper thigh was inflated to 200 mmHg throughout to prevent any return of blood supply. The force produced by isometric contractions of the quadriceps muscle was measured with a strain gauge attached to the ankle while the subject was seated in an adjustable chair (Edwards *et al.*, 1977) and recorded on a u.v. oscillograph.

Surface EMG was recorded with two adhesive cup electrodes filled with electrode paste, one situated on the skin over the lower third of the vastus lateralis muscle, the other over the tendon on the lateral aspect of the knee. An earth electrode was placed on the lower leg. The EMG activity was amplified, rectified, smoothed with a time constant of 0·2 s and displayed on a u.v. oscillograph.

Electrical stimulation

Stimulation of the quadriceps, either percutaneously with surface pad electrodes or by localized stimulation of the femoral nerve, was carried out as previously described (Edwards, Hill & Jones, 1975; Edwards *et al.*, 1977) with a short stimulus pulse duration (50 μs) so as to limit excitation to nerve branches in the muscle. Direct excitation of human muscle fibres required longer pulses (100–500 μs) when studied *in vitro* (Moulds, Young, Jones & Edwards, 1977).

Results

To maintain a maximal isometric contraction (MVC) of the quadriceps for 60 s takes a considerable effort. During the first 30 s discomfort is mild but between 30 and 45 s pain in the thigh becomes increasingly severe. There is a progressive change in the perceived sensations from the leg with the result that a subject, without visual feedback, is uncertain of the force exerted towards the end of the contraction. Pain in the thigh is not due to ischaemia alone since it largely disappears as soon as the contraction ceases, even when the cuff around the thigh remains inflated. To reduce variation due to pain the results presented here are all from subjects experienced in the experimental procedures.

Time course of a sustained MVC

Subjects were first asked to make a series of brief maximal contractions, the highest of which was taken as 100% MVC. Aided by visual feedback subjects were then asked to maintain a contraction as close as possible to this maximum for 60 s. During this period force fell to about 30% of the initial level, but the precise time course varied between individuals. The consistent performances of the two subjects with the greatest difference in the time course are shown in Fig. 1, the records having been made on several occasions over a 2 months period.

Central and peripheral fatigue

In one subject the maintained maximum voluntary force was compared with the force obtained by supramaximally stimulating the muscle via the femoral nerve. In the unfatigued muscle the MVC was matched by stimulating at 50 Hz, at which frequency a fully fused tetanus of the quadriceps develops (Edwards *et al.*, 1977). During each tetanus the stimulus voltage was increased to confirm that nerve stimulation was supramaximal. The subject then held a MVC which was interrupted every 15 s for a brief period of stimulation at 50 Hz (Fig. 2*a*).

The voluntary and stimulated contractions fell to a similar extent during the first 30 s. Thus fatigue during this period could only be due to a failure at or distal to the neuromuscular junction. After 45 s the voluntary force was less than the force produced by the test tetani, indicating that in this later period a loss of central neural drive contributed to the force fatigue.

Femoral nerve stimulation is painful and carries a risk of dislocating the patella, whereas percutaneous stimulation of about 50% of the quadriceps with large pad electrodes is quite acceptable (Edwards *et al.*, 1977). Heat measurements during stimulated and maximal voluntary contractions indicate that percutaneous stimulation can maximally activate a portion of the muscle (Edwards, 1975). The experiment was repeated with the same subject but, instead with percutaneous stimulation of the quadriceps at 50 Hz, activating 48% of the muscle (Fig. 2*b*, initial value).

During the first part of the MVC voluntary and stimulated force fell to a similar degree. Thereafter the voluntary force fell more than the tetanic force so that the stimulated contraction became 80% of the voluntary force after 60 s (Fig. 2*b*). The relative changes in the voluntary and stimulated forces were very similar to those seen in the same subject with femoral nerve stimulation (Fig. 2*a*). This indicates that percutaneous stimulation of a portion of the muscle can be used to determine function independently of central drive.

Possible fatigue of the central neural drive during 60 s MVC was assessed, with percutaneous stimulation, in all subjects. Central fatigue was considered to be present when the MVC force declined more rapidly than did the tetanic force produced by the brief stimulated contractions.

Of the nine subjects studied, four showed little or no central fatigue. In five it amounted to between

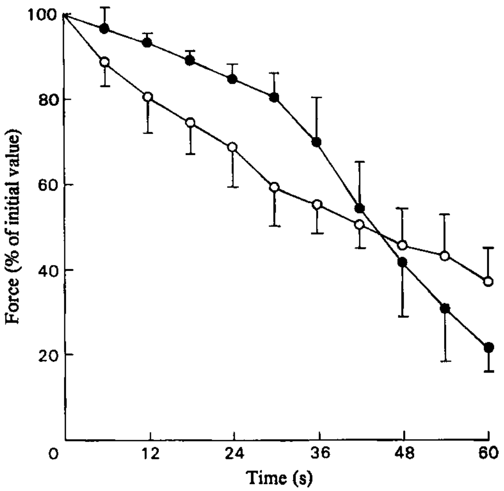

FIG. 1. Time course of uninterrupted maximum voluntary contractions (MVC) of the quadriceps. Subjects were asked to hold a MVC for 1 min. Points are the mean (±1 SD) of four separate contractions for subject D.O. (●), and six contractions for subject G.H. (○). Force is expressed as a percentage of the initial value.

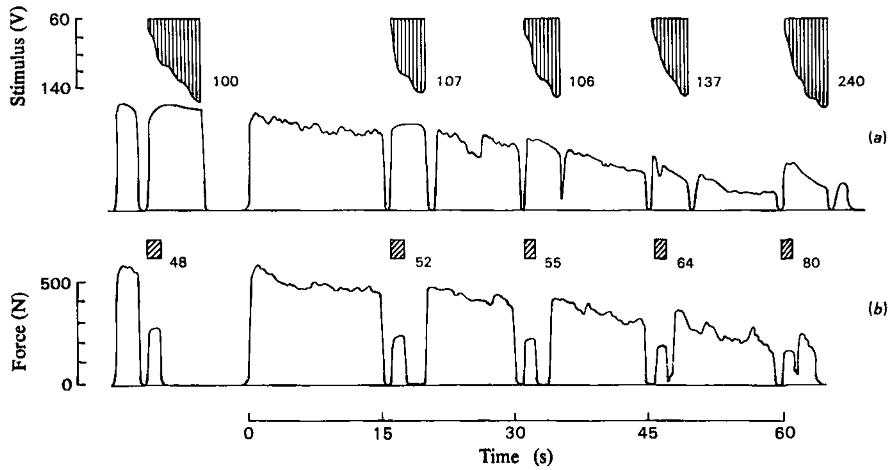

FIG. 2. Comparison of the force obtained by electrical stimulation with the voluntary force during a sustained maximum voluntary contraction (MVC) of the quadriceps. (*a*) Femoral nerve stimulation: stimulus marker (shaded area) gives a record of the stimulation voltage and duration. (*b*) Percutaneous stimulation. Duration of stimulation (at constant voltage) is indicated by the shaded areas. Force (newtons) and time scales apply to both records. Values given just below the stimulus markers are the tetanic force as a percentage of the voluntary force measured immediately before the tetani. Results in (*a*) and (*b*) are from the same subject.

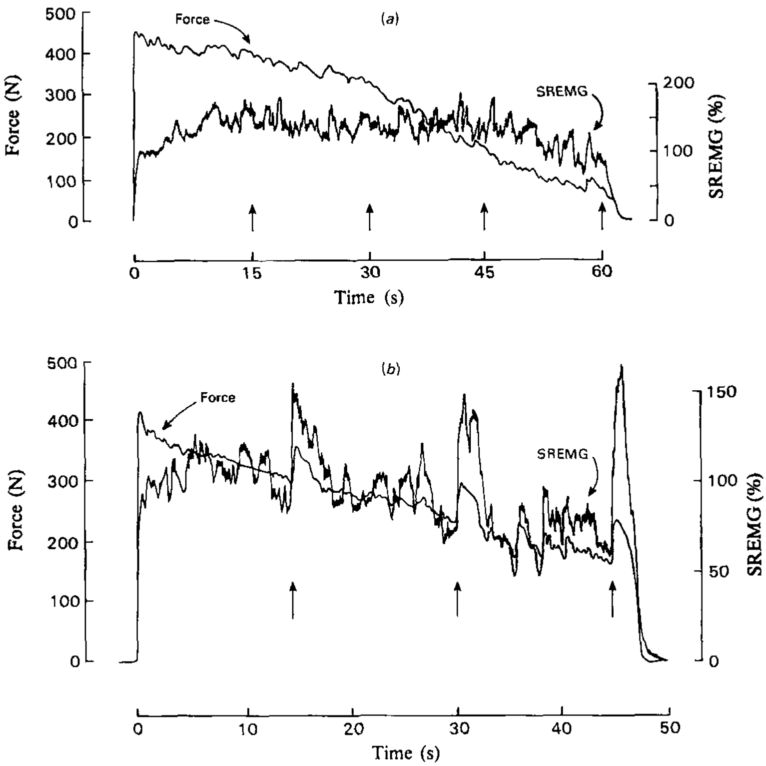

Fig. 3. Force and smoothed, rectified EMG (SREMG) during sustained maximum voluntary contraction (MVC) of quadriceps in (*a*) a subject (D.O.) with no central fatigue and (*b*) in subject D.J. with central fatigue; 'extra efforts' were made at times shown by the arrows. Force scale is in newtons. The smoothed, rectified EMG is given as a percentage of the value at the start of the MVC.

10 and 30% of the force loss after 60 s of sustained, uninterrupted contraction. With practice, the degree of central fatigue generally became less though these subjects were not able completely to overcome it.

Surface EMG activity during sustained MVC

The smoothed, rectified EMG activity and force were measured at intervals throughout the contraction in seven of the subjects (Fig. 3). To show how these vary the ratio of the smoothed, rectified EMG divided by the force (here called the E/T ratio) as first used by Stephens & Taylor (1972) is shown in Fig. 4. The subjects could be divided into two groups. In group 1, where the smoothed, rectified EMG declined roughly in proportion to the fall in force (resulting in relatively constant E/T ratios), all the four subjects showed central fatigue when previously tested, as described above. In group 2 the smoothed, rectified EMG increased during the first 10–15 s and then remained high while the force fell to between 20 and 35% of the

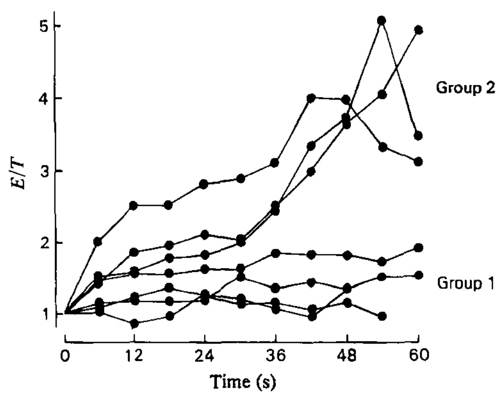

Fig. 4. Relationship between smoothed, rectified EMG (SREMG) and force during prolonged maximum voluntary contraction (MVC) in seven subjects. The SREMG is divided by force (E/T ratio, ordinate) and the value at the start of the contraction expressed as 1·0. Group 2 subjects exhibited no central fatigue but were in brief extra efforts able to achieve E/T ratios close to those found in group 2 subjects.

fresh MVC. This gave E/T ratios three to five times the control value at the end of the contraction. The three subjects in this group had previously shown no central fatigue.

Subjects were asked to maintain a MVC and, at 15 s intervals, to make a brief extra effort. Subject D.O., typical of those exhibiting little or no central fatigue, showed the initial rise in smoothed, rectified EMG to a value which was then maintained until near the end of the contraction (Fig. 3*a*). When asked, he could produce virtually no extra force nor was there any increase in the smoothed, rectified EMG. The second subject (D.J.), in whom approximately 10% central fatigue had been demonstrated, showed the same initial rise in smoothed, rectified EMG but after about 10 s the smoothed, rectified EMG and force fell at the same rate (Fig. 3*b*). When this subject made an extra effort both smoothed, rectified EMG and force increased momentarily but with a greater proportional increase in the electrical activity. If the E/T ratio was expressed as 1·0 at the start of the contraction, it became 1·4 just before the first extra effort, increasing to 1·7 during this brief effort. After 30 s the value before was again 1·4, increasing to 2·0 during the brief effort and for the last effort the values were 1·7 and 2·9 respectively. Although the 'before' values are similar to those seen for the group 1 subjects shown in Fig. 4, values during the brief extra efforts approached those maintained by group 2 subjects. All the subjects showing a fall in smoothed, rectified EMG during the contraction could increase the level proportionately more than the increase in force during the extra efforts, thus briefly increasing the E/T ratio.

Discussion

Our studies show that changes occurring proximal to the neuromuscular junction (i.e. central fatigue) can consistently account for up to 30% of the total force loss even in apparently well-motivated subjects during sustained contractions of the quadriceps. All subjects who showed evidence of central fatigue could overcome this in brief extra efforts. The results demonstrate that fatigue cannot be all attributed to factors at, or distal to, the neuromuscular junction, without first ascertaining, particularly when studies are done on naive subjects, that central components are not also present.

In experiments on the first dorsal interosseous muscle Stephens & Taylor (1972) found that the smoothed, rectified EMG and force declined in parallel, resulting in a constant E/T ratio (smoothed, rectified EMG divided by force) during the first 60 s of the contraction. They interpreted this to show that fatigue was mainly due to failure of neuromuscular transmission, having excluded central fatigue because the evoked synchronous muscle action potential was also shown to decrease. Although a number of our subjects showed a constant E/T ratio with contractions of the quadriceps, we believe that for these subjects this constancy could be accounted for by central fatigue. For subjects without central fatigue the smoothed, rectified EMG, after an initial rise, remained fairly constant at a time when the force was falling, so that the E/T ratio increased throughout the contraction. Those subjects with evidence of central fatigue could briefly increase their E/T ratios to about the same level by making brief extra efforts. Our findings for the quadriceps therefore differ in this respect from those of Stephens & Taylor (1972) for the first dorsal interosseous.

The smoothed, rectified EMG signal recorded during a contraction depends on the number, size and distribution of active units in the muscle, the size of the individual fibre action potentials, the firing frequency and the degree of synchronization of motor unit activity. The influence of these on the surface recorded signal is not known, and we are therefore reluctant to speculate about the site of failure on the basis of smoothed, rectified EMG data.

It was noticed that towards the end of a sustained MVC subjects with little central fatigue appeared actually to improve their voluntary performance as compared with their response to stimulation at 50 Hz. However, this effort seems likely to arise from a diminished response to stimulation at 50 Hz rather than an improvement in voluntary performance. Parallel studies on the adductor pollicis (B. Bigland-Ritchie, R. H. T. Edwards & D. A. Jones, unpublished work) have shown that fatigued muscle responds to stimulation at 20 Hz better than at 50 Hz. As a practical consideration, if muscle contractility is to be tested during the course of a prolonged MVC, a 50 Hz tetanus is appropriate at the start of the contraction but after about 30–45 s stimulation at a lower frequency (20 Hz) is a better match to the force of the voluntary contraction, so giving more reliable information. This suggests that in order to maintain optimum force during a fatiguing contraction the firing frequency of motor neurons must decline, as has been observed (Marsden, Meadows & Merton, 1971). The smoothed, rectified EMG might therefore be expected to fall somewhat even without any neuromuscular block.

In any investigation involving prolonged MVC of the quadriceps the possibility of central fatigue must be taken into account. We suggest that this should be checked by comparing the voluntary force with tetani at 50 Hz during the first 30 s of the contraction, and at a lower frequency thereafter. It would appear that central neural drive progressively falls during sustained MVC but that subjects can overcome this tendency to various degrees.

Acknowledgments

This work was supported by the Wellcome Trust and the Muscular Dystrophy Group of Great Britain and also in part by grant NS 09960 from the U.S.P.H.S. to B.B.-R.

References

BARCROFT, H. & MILLEN, J.L.E. (1939) The blood flow through muscle during sustained contraction. *Journal of Physiology (London)*, **97**, 17–31.

EDWARDS, R.H.T., HILL, D.K. & MCDONNELL, M. (1972) Myothermal and intramuscular pressure measurements during isometric contractions of the human quadriceps muscle. *Journal of Physiology (London)*, **224**, 58P–59P.

EDWARDS, R.H.T. (1975) Muscle fatigue. *Postgraduate Medical Journal*, **51**, 137–143.

EDWARDS, R.H.T., HILL, D.K. & JONES, D.A. (1975) Heat production and chemical changes during isometric contraction of the human quadriceps muscle. *Journal of Physiology (London)*, **251**, 303–315.

EDWARDS, R.H.T., YOUNG, A., HOSKING, G.P. & JONES, D.A. (1977) Human skeletal muscle function: description of tests and normal values. *Clinical Science and Molecular Medicine*, **52**, 283–290.

MARSDEN, C.D., MEADOWS, J.C. & MERTON, P.A. (1971) Isolated single motor units in human muscle and their rates of discharge during maximal voluntary effort. *Journal of Physiology (London)*, **217**, 12P–13P.

MERTON, P.A. (1954) Voluntary strength and fatigue. *Journal of Physiology (London)*, **123**, 553–564.

MOULDS, R.F.W., YOUNG, A., JONES, D.A. & EDWARDS, R.H.T. (1977) A study of the contractility, biochemistry and morphology of an isolated preparation of human skeletal muscle. *Clinical Science and Molecular Medicine*, **52**, 291–297.

REID, C. (1928) The mechanism of voluntary muscular fatigue. *Quarterly Journal of Experimental Physiology*, **19**, 17–42.

STEPHENS, J.A. & TAYLOR, A. (1972) Fatigue of maintained voluntary muscle contraction in man. *Journal of Physiology (London)*, **220**, 1–18.