EDITORIAL REVIEW

Physiological analysis of skeletal muscle weakness and fatigue

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Introduction

Over a century ago Duchenne summarized his life's work in the third edition of his famous book *De L'electrisation Localisée* (1872), which laid the foundation of electrophysiology of muscle and clinical myology. Primary muscle diseases are admittedly uncommon but, for the sufferers and their families, of grave import since for most no effective therapy is as yet available. However, skeletal muscle, which amounts to about 40% of the body mass, also reflects disordered function of a wide range of afflictions of body and mind in the common symptoms of weakness and fatigue. This review will indicate developments in techniques for investigating these symptoms and present a new diagnostic approach based on consideration of skeletal muscle as a machine, the prime function of which is to generate force.

Techniques for studying human muscle

**Needle biopsy**

This technique, with histochemical studies of muscle samples, has played an important part in recent understanding and classification of muscle disorders. Needle biopsy is a simple, harmless, rapid and repeatable diagnostic procedure (Edwards, 1971; Edwards, Maunder, Lewis & Pearse, 1973; Edwards & Maunder, 1977), which can also provide samples for chemical analysis (Edwards, Jones, Maunder & Batra, 1975; Edwards, 1977).

**Measurement of force**

The force of voluntary contractions can be measured at the bedside with a hand-held dynamometer ('myometer'; Edwards & McDonnell, 1974; Hosking, Bhat, Dubowitz & Edwards, 1976; Edwards & Hyde, 1977). The force of voluntary and electrically stimulated contractions of the quadriceps muscle has been measured with a strain gauge in a specially designed muscle-testing chair (Edwards, Young, Hosking & Jones, 1977b) or frame (Hosking, Young, Dubowitz & Edwards, 1978).

Electrical stimulation

When the motor nerve to a muscle is stimulated at a voltage at least 20% greater than that needed to achieve a maximum mechanical or electrical response ('supramaximal nerve stimulation') all muscle fibres are initially made to contract. The force generated depends on the frequency of stimulation and whether the muscle is fresh or fatigued. This approach has been used to study the contractile and electrical responses of small peripheral muscles with accessible motor nerves, e.g. adductor pollicis (Merton, 1954; Desmedt, Emeryk, Renoirte & Hainaut, 1968), abductor digiti minimi (Burke, Skuse & Lethlean, 1974) and extensor digitorum brevis (McComas, 1977). These muscles are not characteristically affected in most myopathies or dystrophies and so it was necessary to find a way of studying proximal muscle function. This was done by electrical stimulation with large pad electrodes (as in faradic stimulation by physiotherapists) of 20–30% of the quadriceps.

Absolute forces vary with the amount of muscle stimulated, and the contractility of the individual subject's muscle fibres, but the ratio of force obtained at different stimulation frequencies, and the time course of recovery after brief tetanic contractions, are reproducible, with very comparable results (Table 1) in both the quadriceps and adductor pollicis (Edwards *et al*., 1977b), and are independent of motivation (Young & Edwards, 1977).
TABLE 1. Contractile properties of human muscle in vitro and in vivo

Mean values (with SEM in parentheses) are shown, and are the values given by Edwards et al. (1977b) and Moulds et al. (1977).

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<th>In vitro</th>
<th>In vivo</th>
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<td></td>
<td>Isolated muscle preparation</td>
<td>Adductor pollicis</td>
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<tr>
<td>Force: tetanus 20 Hz/tetanus 50 Hz (%)</td>
<td>71.7 (2.8)</td>
<td>73.1 (2.8)</td>
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<tr>
<td>Relaxation time (ms) (SF₁₀)</td>
<td>104.8 (5.9)</td>
<td>95.8 (3.4)</td>
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Myothermalm measurements

Metabolic heat production in voluntary and electrically stimulated contractions has been measured with a thermistor or thermocouple probe (Edwards, Hill & Jones, 1975a; Edwards, 1975, 1977, 1978). The "myothermogram" (so named by analogy with the electromyogram which it is designed to complement as an investigation) gives a measure of the metabolic capacity of muscle, and indicates the improvement in energy economy of force maintenance in prolonged contractions (Edwards & Hill, 1975) associated with slowing of relaxation (Edwards, Hill & Jones, 1975a,b). Comparison of the rate of rise of muscle temperature in maximum voluntary and maximal electrically stimulated contractions (Edwards, 1975; 1978) offers a means of recognizing failure of central neural drive (see below).

Isolated human muscle preparations in vitro

Physiological studies of surgically obtained human skeletal muscle samples in vitro (Moulds, Young, Jones & Edwards, 1977; Gruener, 1977; Reuben, Wood & Eastwood, 1977) promise a new opportunity to describe the contractile characteristics of normal and diseased human muscle, in terms derived from studies of amphibian (Hill, 1965, 1970; Huxley, 1977) and mammalian muscle (Close, 1972), and greatly increase the opportunity of studying the effects of therapeutic agents.

Perception of voluntary contractions

The perceptual consequences of alteration of the contractile properties of muscle have long been studied in normal subjects (Waller, 1891; Mosso, 1915) in whom weakness of a muscle has been caused by work-induced fatigue, ischaemic fatigue, partial curarization and/or peripheral anaesthesia. Use of a psychophysical scale for estimating perception indicated that perception of 'effort' (and/or tension) was closely dependent on the force achieved, as partial curarization resulted in a subjective realization that performance capacity had been reduced but perception at forces within the range of performance was unchanged (Campbell, Edwards, Hill, Jones & Sykes, 1976). In contrast, recent weight-matching studies (Gandevia & McCloskey, 1977) indicated that the 'effort' (defined as voluntary neural drive to motor neurons) required to lift a weight was increased with partial curarization. 'Effort' was further increased when skin afferents were blocked by local anaesthesia, suggesting that the lifting motor-neurons were then deprived of a reflex potentiation of peripheral origin. Much has yet to be learned of the perceptions associated with muscular contraction, but techniques are now available for such studies.

Processes involved in voluntary muscular activity

The control chain for the processes which eventually lead to force generation are summarized in Fig. 1. Gradations of force can be achieved by

\[
\text{FORCE}
\]

\[
\text{Brain} \quad \downarrow
\]

\[
\text{Spinal cord} \quad \downarrow
\]

\[
\text{Peripheral nerve} \quad \downarrow
\]

\[
\text{Neuromuscular junction} \quad \downarrow
\]

\[
\text{Muscle cell membrane} \quad \downarrow
\]

\[
\text{Transverse tubular system} \quad \downarrow
\]

\[
\text{Calcium release} \quad \downarrow
\]

\[
\text{Actin–myosin cross-bridge formation} \quad \downarrow
\]

\[
\text{"Psyche"}
\]

Fig. 1. Voluntary contraction of human skeletal muscle: to this simple unitary scheme may be added reflex segmental and suprasegmental influences on the excitability of the spinal motor neurons and resultant efferent neural drive to muscle.
altering the activation of the contractile proteins (i.e. by changing stimulation frequency; see Fig. 3) but more importantly by altering the recruitment of motor units. It is generally believed that low-force contractions as in rhythmic exercise of low intensity are achieved by recruitment of only the type I fibres (Gollnick, Piehl & Saltin, 1974b; Gollnick, Karlsson, Piehl & Saltin, 1974a), which are characterized histochemically (Dubowitz & Brooke, 1973) as having a low myosin adenosine triphosphatase (ATPase) activity, high oxidative activity and physiological features (Close, 1972) of slow twitch time and relatively high resistance to fatigue. With high-force isometric contraction (Milner-Brown, Stein & Yemm, 1973) or intense rhythmic exercise (e.g. cycling with a power output approaching that of the maximum oxygen intake) increasing numbers of type II fibres (characterized by high myosin ATPase activity, high glycolytic but low oxidative capacity) are recruited (Gollnick et al., 1974a,b). The pattern of recruitment is reflected in the contraction and relaxation times of voluntary contractions. In dynamic contractions of the quadriceps the velocity of low-force contractions is significantly slower than for maximal contractions (Thorstensson, Grimby & Karlsson, 1976). The relaxation rate from brief isometric contractions follows the same pattern (Wiles, Jones, Young & Edwards, 1978). In general the type II fibres in human muscle have contraction/relaxation rates and myosin ATPase activities (Essen, Jansson, Henriksson, Taylor & Saltin, 1975) which are approximately double those of type I fibres.

Many everyday activities are carried out with a low force of contraction in which the firing frequency of the motor neurons and muscle cells is likely to be 10–30 Hz (Bigland & Lippold, 1954; Freyschuss & Knutsson, 1971; Grimby & Hannertz, 1977). In maximal contractions the frequency may briefly rise to over 100 Hz (Marsden, Meadows & Merton, 1971) but after a second or two will settle down to 50–80 Hz.

**Analysis of muscle weakness**

’Weakness’ is defined as a failure to generate the required or expected force on first testing or attempted performance. From the foregoing, the first and simplest reason for weakness is lack of motor drive, as failure to recruit motor units or to drive them at a sufficiently high frequency. This may be due to lack of motivation but can be due to neurological disorders. Brodal (1973) described his personal experiences of a ‘stroke’, in particular, the great ‘effort’ associated with the performance of everyday activities.

Viewed as a machine, human muscle itself can fail to generate the required force, for several possible reasons (Fig. 2).

**Impaired neuromuscular transmission.** This is well known in myasthenia gravis. Conventional EMG techniques (McComas, 1977) are well suited to investigate these conditions and confirmation of a positive result can often be obtained by administration of an anticholinesterase, e.g. edrophonium.

**Impaired excitation–contraction coupling.** This failure of activation of the contractile process despite adequate membrane excitation is thought to cause the weakness of familial hypokalaemic periodic paralysis (Engel & Lambert, 1969) and may also contribute to the weakness in some forms of myotonia (Wiles & Edwards, 1977). This is also a pharmacological action of the drug dantrolene sodium (Ellis & Bryant, 1972; Moulds, 1977; Young & Edwards, 1977), which is used to treat spasticity.

**Impaired energy supply.** The supply of energy for muscular contraction has to be viewed in quantitative terms. In the brief contractions in which weakness and fatigue are clinically assessed, as for the brief everyday activities of holding, lifting, rising from a chair, the immediate energy sources are muscle ATP and phosphorylcreatine (PC). For activities lasting less than 10 s these local stores are used. For intense activities lasting...
10–45 s a considerable demand is made on the local glycogen stores with resulting accumulation of lactate. In studies of isolated animal muscle contraction force is logarithmically related to muscle ATP (Murphy, 1966), and linearly related to PC content (Spande & Shottelius, 1970). Measurements of muscle ATP and PC content in needle biopsies from patients referred because of symptoms of weakness and fatigue were not infrequently a little reduced (Edwards et al., 1975), but rarely to the degree which might be responsible for weakness in light of the above animal studies. Even a Duchenne dystrophy is seems unlikely that weakness can be simply attributed to impaired energy supply (Edwards, 1977).

**Contractile machinery.** Loss of contractile machinery of muscle due to destructive disease processes, as in the dystrophies, or disuse atrophy (without gross destruction) after immobilization of a limb after a fracture (Sargeant, Davies, Edwards, Maunder & Young, 1977), or in metabolic myopathies due to steroids, hypo- or hyperthyroidism or vitamin D deficiency (Dubowitz & Brooke, 1973), is far more important than either of the two foregoing mechanisms. In these latter conditions there is often obvious atrophy of the type II fibres.

Gross muscle bulk, as yet a difficult characteristic of the machine to assess quantitatively, has been measured by ultrasound scanning (Ikai & Fukunaga, 1968) and the effects of strength training on muscle cross-sectional area assessed (Ikai & Fukunaga, 1970).

Only after exclusion of the above features can impairment of the force per unit cross-sectional area of the muscle fibres be assumed to contribute to weakness. So far this possibility is only of theoretical interest, as the measurement of force in a known number of fibres under conditions of optimum and uniform activation is technically formidable. Studies with isolated human muscle preparations (Moulds et al., 1977; Gruener, 1977) or isolated, skinned fibre preparations (Reuben et al., 1977) may in the future allow this to be carried out.

**Analysis of muscle fatigue from experimental studies in normal subjects**

'Fatigue' is defined as a failure to generate the required or expected force during sustained or repeated contraction. There are many associated physiological changes (e.g. slowing of relaxation) but an important feature is that fatigue generally recovers either spontaneously, or by appropriate alteration of the experimental conditions.

The first requirement is to establish whether the failure to sustain the expected or required force is due to failure of neural drive (fatigue 'in the mind' or at least in the nervous system rather than in the muscle). Comparison of the force of voluntary with electrically stimulated contractions has allowed the recognition of a measure of 'central fatigue' in experiments in which well-motivated subjects sustained contractions of the quadriceps under conditions of local ischaemia for 60 s (Bigland-Ritchie, Jones, Hosking & Edwards, 1978).

'Peripheral' (as opposed to 'central') fatigue can take two forms, according to the response to stimulating at low and high frequencies. The striking observation is that the frequency/force curve (Fig. 3) possesses a steep part at low and a plateau at high frequencies. Fatigue can be experimentally produced so that at low frequencies the force is strikingly reduced though the maximum tension achieved with high-frequency stimulation is essentially unchanged (Edwards, Hill, Jones & Merton, 1977a). This form of fatigue ('low-frequency fatigue') may be due to alteration in excitation–contraction coupling, with less force per membrane action potential. The opposite effect, a shift of the curve to the left (indicating potentiation), can occur when the relaxation rate of muscle is slowed by cooling (Fig. 4), and also in hypothyroidism.

Such alterations of the position of the frequency/force curve have important implications for the forces generated at the low-stimulus frequencies.
Muscle weakness

Relaxation speed

Force

Frequency Tw 10 20 50 100
Warm

Cold

Tw 10 20 50 100 (s')
Warm

FIG. 4. Programmed stimulation of the author's adductor pollicis via the ulnar nerve. Notice the effects of cold (immersion of the arm and hand in water at 16°C for 15 min) on the contractile properties of the muscle. Relaxation speed (differentiated force signal) was reduced as expected but notice also potentiation of the 10 Hz tetanus (cf. Fig. 3) and striking high-frequency fatigue (i.e. failure of the 100 Hz tetanus when 50 Hz tetanus is almost the same as in warm muscle). Tw, Twitch.

of motor innervation (10–30 Hz) in the submaximal contractions (Grimby & Hannerz, 1977) used in many everyday activities.

Failure of the contractile force at high-stimulation frequencies ('high frequency fatigue') occurs in myasthenia gravis, in myotonia (Wiles & Edwards, 1977) and also with partial curarization (Heisterkamp, Skovsted & Cohen, 1969), as well as being a feature of experimentally produced ischaemic fatigue and cooling of muscle in normal subjects (Fig. 4). In sustained maximum voluntary contractions of the first dorsal interosseous muscle the smoothed rectified surface EMG fell proportionately to the loss of force when the synchronous action potential evoked by electrical stimulation of the ulnar nerve was unchanged. This led Stephens & Taylor (1972) to conclude that the critical step in experimental fatigue lay in the neuromuscular junction. Studies in man (B. Bigland-Ritchie, R. H. T. Edwards & D. A. Jones, unpublished work) involving electrical stimulation at different frequencies interposed during the course of sustained maximum voluntary contractions, and parallel studies in isolated curarized mouse muscle, suggest that failure of electromechanical activation distal to the neuromuscular junction may also play a role in this form of experimental ischaemic fatigue in man.

The practical implication of high-frequency fatigue, whether due to impaired neuromuscular transmission, as in Wedenski inhibition (Katz, 1966), or possibly from imbalance of K⁺ and Na⁺ exchange in the transverse tubular system and interfibre spaces (B. Bigland-Ritchie, R. H. T. Edwards & D. A. Jones, unpublished work), is that a ceiling is set to all attempts to secure maximum activation of the muscle whether by voluntary effort or electrical stimulation. In assessing the mechanical properties of human muscle (Edwards et al., 1977b) this form of fatigue must be recognized if errors in the interpretation of the frequency/force curve and comparisons between electrically stimulated and voluntary contractions are to be avoided.

Impaired energy exchange may underlie fatigue by affecting the contractile process or energy-requiring ion pumps of cell membranes. Fatigue follows anoxia and poisoning with enzyme inhibitors in animal muscle (Murphy, 1966; Spande & Shottelius, 1970) but the extent to which failure of energy supply is responsible for fatigue in human muscle is unclear. It is, however, well known that substantial depletion of the phosphorylcreatine stores occurs in sustained ischaemic contractions (e.g. Edwards et al., 1975a). Phosphorylcreatine stores recover only if the circulation is restored, and approximately follow recovery in force (Harris, Edwards, Hultman, Nordesjö, Nylin & Sahlin, 1976).
Practical relevance and future opportunities

The suggested scheme for analysing muscle weakness (Fig. 2) not only facilitates diagnosis, but may point to the functional abnormality and perhaps to appropriate therapy. Patients with muscle weakness can be classified according to the structure and function found on clinical assessment, and laboratory investigation.

Destruction of contractile machinery. This may be present with or without abnormal contractile properties of muscle: e.g. muscular dystrophies, rhabdomyolysis, severe inflammatory muscle disease.

Contractile machinery intact but not functioning properly. For example, myotonia congenita, periodic paralysis.

Contractile machinery reduced in size but no obvious destruction (i.e. shrinkage of muscle fibres). For example, disuse atrophy, myopathy of osteomalacia.

Contractile machinery intact but control mechanisms impaired. For example, 'psychogenic weakness', 'effort syndrome' (Lewis, 1918), impaired neural motor control.

The recognition that muscle can become bigger and stronger, spontaneously or in response to treatment, raises the important therapeutic possibility of optimizing long-term protein repair processes in muscle. Hypertrophy of muscle with physical training or physiotherapy has been followed by repeated needle biopsies (MacDougall, Ward, Sale & Sutton, 1977; Andersen & Henriksson, 1977), as has the recovery of patients with osteomalacic myopathy treated with vitamin D. Improvement in contraction force of the quadriceps has been found to follow the time course of increase in muscle fibre size (Young, Brenton & Edwards, 1978).

Recognition of those conditions in which the contractile machinery is intact but not functioning properly (often exhibiting high- or low-frequency fatigue) is important because of the quite different therapeutic challenge of seeking to optimize short-term membrane permeabilities and intracellular activation processes.

In patients, 'weakness' and 'fatigue' of psychogenic origin can be fairly confidently diagnosed once it is recognized that the properties of the muscle 'machine' are normal, or only showing evidence of disuse. Demonstration to the patient that the contractile properties of their muscles are normal independently of volition can serve as the first positive step in rehabilitation.

Key words: muscle mechanics, fatigue, myopathy.

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References


REUBEN, J.P., WOOD, D.S. & EASTWOOD, A.B. (1977) Adapta-


