Physiological characterisation of the “warm up” effect of activity in patients with myotonic dystrophy

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SUMMARY Contractile properties of adductor pollicis muscle were examined over a range of stimulation frequencies in patients with myotonic dystrophy and normal subjects. In patients, fresh muscle demonstrated impaired relaxation, weakness at all frequencies and selective loss of force and excitation at high frequencies. During stimulated “fatiguing” activity, patients showed improvements in force and relaxation which appeared to result from normalisation of membrane excitation. Normal twitch potentiation also occurred during activity suggesting intact excitation-contraction coupling. These electrophysiological findings help to characterise and explain the “warm up” effect described by patients.

Myotonic dystrophy is an inherited multisystem disease, including a muscle disorder which is characterised by weakness and slowed relaxation (myotonia) following a contraction. Myotonia is associated with abnormal and continued sarcolemmal membrane excitation but the precise mechanisms causing myotonia and weakness, and whether they are related, are not known. A frequent clinical observation is that both improve with exercise, this being known as the “warm up” phenomenon. Belanger and McComas suggested that the increase in strength was due to improvements in motoneuron activation by descending pathways that is, increased central drive. Previous studies with repeated contractions have documented improvements in force, excitation and relaxation time but during these investigations force, excitation and relaxation were not examined simultaneously and temperature was poorly standardised.

The aims of the present study were to investigate “warm up” and the mechanisms of myotonia and weakness quantitatively and simultaneously under more precisely controlled conditions. Contractile properties were examined in the adductor pollicis (AP), a particularly suitable muscle to study since myotonic dystrophy is primarily a disease of distal muscles. Part of this work has been presented to the Physiological Society and to the Medical Research Society.

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Methods

Experimental subjects
Nine normal volunteers (8 male) aged 25–34 years, and seven patients with myotonic dystrophy (6 male) aged 20–52 years, were studied. The clinical diagnosis of myotonic dystrophy was confirmed by electromyography and muscle biopsy. All subjects gave their informed consent for participation in this study which was approved by the Liverpool Area Health Authority Ethical Committee.

Contractile properties of muscle
Full details of the equipment and experimental procedures are described in a previous publication, thus only a brief description is given here. Prior to all experiments, muscle temperature was standardised by warming the hand and forearm in a water bath at 45°C for 10 minutes, and maintained throughout the experiment with a lamp. Contractions of AP were produced by supramaximal stimulation of the ulnar nerve at the wrist in a set frequency pattern, viz 1, 10, 20, 50, 100 and 1 Hz for 1 second each (10 Hz for 2 seconds). The resulting isometric forces were measured by a strain gauge attached to the thumb. The force signal produced was also differentiated with respect to time and used to calculate the maximal relaxation rate (MRR, that is, the maximum percentage (%)) after stimulation at 100 Hz. Surface electromyography (EMG) over AP was used to record the compound muscle action potential (CMAP) and the peak to peak amplitude was measured. Simultaneous oscillographic recordings of force, force differential, and the CMAP were termed the programmed stimulation electromyogram or PSEM (fig 1).

Experimental protocols
Activity without arterial occlusion A control PSEM was performed in fresh muscle and fatiguing activity consisted of 50 PSEMs, repeated at intervals of 12 s (that is with a 5 s rest between each one). Recovery was monitored using the
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Unoccluded

Ischaemic

Surface EMG

PSEM No

Force differential (MRR)

Force

Frequency Hz

Fig 1  Programmed stimulation electromyogram (PSEM) in a normal subject in fresh muscle (1st PSEM), at the end of unoccluded stimulated activity (50th PSEM) and at the end of ischaemic activity (15th PSEM).

PSEM at intervals of 0·5, 1, 2, 3, 5, 10 and 15 minutes after the end of activity.

Activity with arterial occlusion  A control PSEM was performed in fresh muscle. A sphygmomanometer cuff was inflated around the upper arm and maintained at 100 mm Hg above systolic blood pressure. After 3 minutes of ischaemic rest (during which time 50% oxygen depletion occurs, thus minimising oxidative metabolism1), fatiguing activity was commenced consisting of 15 PSEMs repeated as above. The cuff was then deflated and recovery monitored as above.

Table 1  Declines in force and excitation at the end of activity without circulatory occlusion in normal subjects and patients with myotonic dystrophy (mean, 1SD, Mann-Whitney U test)

<table>
<thead>
<tr>
<th>Stimulation Frequency (Hz)</th>
<th>Normals n = 6</th>
<th>Patients n = 6</th>
<th>Statistical Significance</th>
<th>Normals n = 6</th>
<th>Patients n = 6</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71, 15</td>
<td>120, 35</td>
<td>p &lt; 0·001</td>
<td>81, 22</td>
<td>96, 8</td>
<td>NS</td>
</tr>
<tr>
<td>10</td>
<td>93, 31</td>
<td>71, 19</td>
<td>NS</td>
<td>90, 18</td>
<td>110, 10</td>
<td>NS</td>
</tr>
<tr>
<td>20</td>
<td>66, 7</td>
<td>68, 13</td>
<td>NS</td>
<td>91, 11</td>
<td>121, 17</td>
<td>p &lt; 0·01</td>
</tr>
<tr>
<td>50</td>
<td>76, 5</td>
<td>83, 8</td>
<td>NS</td>
<td>68, 19</td>
<td>140, 48</td>
<td>p &lt; 0·01</td>
</tr>
<tr>
<td>100</td>
<td>72, 7</td>
<td>105, 22</td>
<td>p &lt; 0·01</td>
<td>42, 9</td>
<td>148, 70</td>
<td>p &lt; 0·01</td>
</tr>
<tr>
<td>1</td>
<td>49, 9</td>
<td>225, 140</td>
<td>p &lt; 0·05</td>
<td>73, 19</td>
<td>192, 94</td>
<td>p &lt; 0·05</td>
</tr>
</tbody>
</table>

Table 2  Declines in force and excitation at the end of activity with circulatory occlusion in normal subjects and patients with myotonic dystrophy (mean, 1SD, Mann-Whitney U test)

<table>
<thead>
<tr>
<th>Stimulation Frequency (Hz)</th>
<th>Normals n = 6</th>
<th>Patients n = 6</th>
<th>Statistical Significance</th>
<th>Normals n = 6</th>
<th>Patients n = 6</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
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<td>53, 26</td>
<td>p &lt; 0·05</td>
<td>72, 12</td>
<td>84, 23</td>
<td>NS</td>
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<tr>
<td>10</td>
<td>51, 47</td>
<td>94, 53</td>
<td>NS</td>
<td>62, 14</td>
<td>84, 32</td>
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<td>NS</td>
<td>20, 8</td>
<td>39, 12</td>
<td>p &lt; 0·05</td>
</tr>
<tr>
<td>100</td>
<td>21, 6</td>
<td>40, 20</td>
<td>NS</td>
<td>18, 9</td>
<td>52, 15</td>
<td>p &lt; 0·05</td>
</tr>
<tr>
<td>1</td>
<td>13, 6</td>
<td>109, 85</td>
<td>NS</td>
<td>70, 12</td>
<td>143, 69</td>
<td>p &lt; 0·05</td>
</tr>
</tbody>
</table>

N.B. The non-significance of some force differences,* despite their magnitudes, was due to the large variability caused by one patient with mild symptoms.
These protocols were performed in random order and at least one week apart to ensure full recovery of AP. Not all subjects underwent both protocols, the numbers involved in each experiment being shown in tables 1 and 2.

**Analysis**

At all stimulation frequencies, force and CMAP were measured at the end of each stimulation period and where oscillation occurred (for example 10 Hz) the force was measured.
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through the middle of the oscillation. The mean force and CMAP at each frequency and the MRR after 100 Hz stimulation were measured on every 5th PSEM during activity without circulatory occlusion and on each PSEM during activity with occlusion. The results are expressed as a percentage of the equivalent part of the PSEM from fresh muscle. Frequency: force curves were calculated for fresh muscle and at intervals during activity by expressing all force values as a percentage of that at 100 Hz in fresh muscle. Results are expressed as mean, 1 SD in the text and tables, and as mean, 1 SEM in the figures (for clarity). Comparisons between the results for patients and normal subjects were made using the Mann-Whitney U test.

Results

Contractile properties of fresh muscle

There were remarkable differences between the fresh PSEM from normal subjects (fig 1) and that from patients (fig 2). Patients were weak at all frequencies, such as force at 100 Hz was 35, SD 13 Newtons in patients compared with 80, SD 17 Newtons in normal subjects. Excitation was also lower in patients such that their EMG recordings were made at higher sensitivity gains. In normal subjects, there was the expected post-tetanic potentiation at 1 Hz (pre- to post-tetanic increase to 151, SD 20%). Patients, however, showed a pre- to post-tetanic decline to 77, SD 55%. These changes in the post-tetanic twitch force were accompanied by corresponding changes in CMAP (pre- to post-tetanic increase in normal subjects to 101, SD 11%, and a decline in patients to 61, SD 31%). The MRR was substantially lower in patients; 3, SD 3 (range 0-6-8-6)% 10 ms⁻¹ than in normal subjects; 12-1, SD 0-7 (10-8-13-5)% 10 ms⁻¹.

Activity without arterial occlusion

Force In normal subjects, the PSEM at the end of activity was similar to that in fresh muscle but all constituents were smaller (fig 1). Force was reduced at all frequencies (table 1). In patients, force either actually increased (for example at 1 and 100 Hz) or was reduced less than in normal subjects (table 1). Force changes at 20 and 50 Hz were similar in normal subjects and patients (table 1). In patients there was little or no potentiation at 10 Hz. These differences in force changes are obvious when examining the frequency: force relationship during activity (fig 3). Despite the increases in force, patients remained relatively weak (for example after 3 minutes of recovery, force at 100 Hz was 37, SD 10 Newtons in patients but

Fig 4 Changes during unoccluded activity at 100 Hz in (a) force (b) excitation and (c) maximal relaxation rate in normal subjects (○) and patients (●) with myotonic dystrophy.
rapidly and increased MRR during relaxation during early recovery. Patients showed persisting improvements in the post-tetanic twitch in patients. During recovery, the reduced force at most low frequencies persisted both in normal subjects and patients; for example at 10 Hz after 10 minutes of recovery, 74, SD 10% and 75, SD 16% of fresh values respectively. In patients, improvements in force at 100 Hz (fig 4a) and the post-tetanic twitch continued during early recovery.

Excitation In normal subjects, CMAP declined at all stimulation frequencies while in patients, CMAP increased at most frequencies (table 1; for example 100 Hz, fig 4). The pre- to post-tetanic twitch changes in excitation at the end of activity had, as force changes, become similar in normal subjects (92, SD 4%) and patients (98, SD 4%) owing to the marked improvements in the post-tetanic twitch CMAP in patients. Improvements in excitation at 100 Hz (fig 4b) and the post-tetanic twitch in patients, continued during early recovery.

Relaxation In normal subjects, the MRR declined rapidly and then plateaued. In patients, however, the MRR increased before plateauing at values similar to those in normal subjects, and increased further during early recovery (fig 4c). Thus, at the end of activity, the PSEM of patients had assumed a "normal" appearance (fig 2).

Activity with arterial occlusion

Force The PSEM at the end of activity had become similar in normal subjects (fig 1) and patients (fig 2). Potentiation at 10 Hz occurred during activity (peak force in normal subjects was 189, SD 121%, and in patients 170, SD 47%) and recovery (154, SD 60% and 144, SD 64% respectively). At all frequencies, patients showed smaller reductions in force than normal subjects (table 2; for example at 100 Hz, fig 5).

Excitation Changes at most low frequencies were similar in both groups but at high frequencies (for example 100 Hz, fig 5b) and the post-tetanic twitch, excitation was reduced less or actually increased in patients during activity (table 2) and became obviously potentiated during early recovery (for example at 100 Hz fig 5b).

Relaxation The MRR declined in normal subjects while in patients it initially increased before declining to values similar to those in normal subjects (fig 5c). During early recovery, the MRR again increased in

Fig 5 Changes during ischaemic activity at 100 Hz in (a) force (b) excitation and (c) maximal relaxation rate in normal subjects (O) and patients (●) with myotonic dystrophy.
patients before declining towards the abnormal resting values (fig 5c).

**Discussion**

**Contractile properties of fresh muscle**

The highly characteristic appearance of the PSEM from fresh myotonic muscle was the result of impaired relaxation, failure of force maintenance at high frequencies and absence of post-tetanic twitch potentiation. The associated reductions in CMAP imply excitation propagation failure. However, although activity substantially increased excitation in myotonic patients, it remained below the normal range suggesting that there may also be a loss of motor units. Several mechanisms have been postulated to explain post-tetanic potentiation in normal muscle, but its absence in fresh myotonic muscle is probably the result of excitation failure rather than a defect in these mechanisms (see below). The considerable variation in MRR, in fresh myotonic muscle, was not unexpected since clinical myotonia may vary markedly by patients.

**Changes during activity and recovery**

**Force and excitation** The relationship between force and excitation in normal subjects has previously been discussed. Increases in force in patients were associated with improvements in excitation which occur due to a “conditioning” effect of preceding activity on the muscle membrane, as previously demonstrated. The normal capacity for twitch potentiation after activity, shown in the present study, was also observed by Belanger and McComas and appears to result from the improvements in excitation (table 1, 2). This suggests that excitation-contraction coupling, which is necessary for potentiation, is intact in myotonic dystrophy.

**Relaxation** Reductions in myotonia, indicated by increases in MRR, appeared to be related to increases in excitation. Changes in excitation and MRR, however, became dissociated during both early activity and early recovery. These dissociations might be explained by temperature changes since myotonia, in myotonic dystrophy, is known to be worse in the cold and improved with increasing temperature. Thus, in the present study, dissociations occurred at times when changes in thermal energy production and loss within the muscle would be greatest, that is during early activity and recovery respectively. The cause of impaired relaxation may be more temperature sensitive than that for force or excitation therefore producing “lags” in their rates of change, relative to MRR.

The initial increase in MRR, despite circulatory occlusion (fig 5c), suggests that oxygen and oxidative energy substrate supply are not vital to “warm up”. The subsequent decline in MRR appears to represent true fatigue changes with suppression of “warm up” due to metabolite accumulation.

**Fatiguability of dystrophic muscle**

In the present study force loss at the end of activity was less in patients suggesting that dystrophic muscle is less fatiguable. However, during activity two processes were occurring simultaneously in the dystrophic muscle, that is, “warm up” and fatigue. “Warm up” could presumably involve progressive recruitment of previously rested contractile elements where in normal muscle full activation is achieved upon initial stimulation. Furthermore, since the maximal force capacity of fresh myotonic muscle cannot be established, interpretations regarding fatiguability are not possible. This point is emphasised in early recovery where improvements in force, excitation and MRR continue until the beneficial effects of “warm up” begin to wear off.

**Mechanisms of myotonia and weakness**

Myotonia is thought to result from a defect which reduces the potential difference across the sarcolemmal membrane but the precise mechanism is unknown. The reduced potential difference renders the membrane less stable and liable to repetitive depolarisation on minimal mechanical or electrical stimulation, as when inserting a needle EMG electrode into a muscle. This produces characteristic abnormal action potentials, or “after discharges”. Slight movement of the electrode causes further abnormal EMG activity. The production of these disruptive “after discharges” during voluntary activity could severely hamper the effective propagation of normal action potentials along the muscle membrane, as suggested by the pre- to post-tetanic depression of the CMAP in the fresh myotonic PSEM (fig 2).

Possible membrane defects in myotonic dystrophy include: increased Na$^+$ conductance, failure of the Na$^+$/K$^+$ pump mechanism and abnormalities of membrane ATPases. However, abnormalities of ionic channels (Cl$^-$, K$^+$ and Na$^+$), demonstrated by voltage clamp experiments in different myotonic syndromes (reviewed by Rüdel and Lehmann-Horn), have yet to be conclusively demonstrated in myotonic dystrophy. Furthermore, postulated mechanisms causing myotonia in myotonic dystrophy appear different from those in other myotonia; for example reduced membrane Cl$^-$ and K$^+$ conductance occur in animal myotonia and in human myotonia congenita but not in myotonic dystrophy. Extrapolation between myotonic syndromes is therefore potentially misleading.

Weakness in myotonic dystrophy is due to a pri-
ary defect within the muscle since the possibility of a primary neurogenic cause appears to have been excluded.\textsuperscript{2} 18 25 26 Part of the weakness is due to dystrophy\textsuperscript{27}–\textsuperscript{29} with the severity of histological changes correlating with clinical weakness.\textsuperscript{30} It has been suggested that excitation-contraction coupling failure\textsuperscript{31} may contribute to weakness in myotonic dystrophy.\textsuperscript{32} Absence of potentiation of force at 10 Hz during unoccluded activity in patients in the present study, despite increased excitation, appears to support this suggestion. However, the potentiation of force which occurs during activity in normal muscle, and which is thought to be due to increased fusion of tetani caused by slowing of MRR,\textsuperscript{15} would have been prevented by the rapid increase in MRR which occurred in the patients (fig 4c). Furthermore, the normal capacity for twitch potentiation observed in patients once “warm up” has occurred suggests normal excitation-contraction coupling (see above).

Mechanism of “warm up”
Demonstration of “warm up” with supramaximally stimulated contractions (thus excluding volition) confirms that it is due to peripheral and not central changes, such as increased motoneuron recruitment as suggested by Belanger and McComas.\textsuperscript{2} The mechanism by which activity alters excitation and contractile performance in myotonic muscle can presently only be discussed speculatively. In normal human muscle, a potent cause of force failure is thought to be accumulation of K\textsuperscript{+} in the t-tubules\textsuperscript{34} which also contributes to myotonia in the myotonic goat\textsuperscript{1} 35 and reduces the duration of warm up in chemically induced myotonia in the mouse diaphragm.\textsuperscript{36} Alternatively, reduction in extracellular Na\textsuperscript{+}, rather than K\textsuperscript{+} accumulation, might cause fatigue in normal muscle,\textsuperscript{34} and is known to cause failure of action potential propagation in normal frog muscle.\textsuperscript{37} Thus, the normalising effect of “conditioning” activity could be due to removal of K\textsuperscript{+} from the t-tubules and/or restoration of normal extracellular Na\textsuperscript{+} concentrations.

Another possible explanation for “warm up” is a decrease in intracellular pH during activity.\textsuperscript{38} Concentrations of inorganic phosphate (Pi) increase during activity and are thought to inhibit membrane and myofibrillar ATPases causing reduced excitation and force.\textsuperscript{38} Since, during recovery, Pi returns towards normal values before pH\textsuperscript{39} this may explain the further increases in force, excitation and MRR during early recovery in patients. The very marked and immediate increases (particularly in excitation) after occluded activity appear to indicate that conditioning of the membrane occurs despite the obvious suppression of “warm up” during fatiguing activity.

The present study suggests that myotonia and some of the weakness in myotonic dystrophy result from abnormal excitation. It appears that activity renders the sarcosomal membrane less unstable such that disruptive depolarisation occurs less easily, allowing normal relaxation and membrane excitation propagation to occur. This permits more complete activation with the resulting improvements in force. Use of the present technique to assess the effects of certain drugs (for example membrane stabilising agents) with specific effects to isolate different factors may elucidate further the mechanisms involved in myotonic dystrophy.

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