Impaired regulation of force and firing pattern of single motor units in patients with spasticity

ANNELISE ROSENFALCK AND STEEN ANDREASSEN

From the Institute of Electronic Systems, Aalborg University Center, Aalborg, Denmark

SUMMARY Patients with spasticity were unable to maintain a constant force of the anterior tibial muscle. The force at maximal effort was reduced to less than 40% of normal, partly because motor units fired at a reduced rate even at high levels of contraction. Force and instantaneous frequency fluctuated slowly. The fast regulation of the firing rate, which characterises normal muscle, was absent. The variation between successive intervals was less than normal and the serial correlation coefficient between intervals increased.

Changes in the firing pattern and in the recruitment order of single motor units have been claimed to be characteristic of central motor lesions. A reduced firing rate was found in Parkinsonism and in patients with upper motor neuron lesions. Findings with respect to the firing pattern are conflicting. Kranz and colleagues found a slight decrease in the variability of the intervals in most motor units. A similar pattern was described by Freund et al. in patients with cerebellar lesions but only one third of the motor units were reported to show the same characteristic deviations from the normal firing pattern. Contrary to this they found increased variability of the intervals and negative serial correlation to be typical for patients with spastic hemipareses. The orderly recruitment of motor units according to size was reported to be disturbed in spastic patients. In the study presented in this report the firing pattern of single motor units in the anterior tibial muscle was investigated in 10 patients with spasticity.

Patients

The patients (table 1) were grouped as follows: four patients had a spastic hemiparesis due to a cerebral lesion (group P1). Six patients had spasticity due to multiple sclerosis; three had clinical findings suggesting cerebellar or cerebella...
Analysis

One hundred and twenty-two recordings from the 10 patients were selected for analysis. One third of the recordings had action potentials from two to three motor units. The potentials were classified automatically as belonging to one of the motor units according to their shape and their time of occurrence. This allowed analysis of the firing pattern of 160 different motor units from the 122 recordings. Twelve to 24 motor units were analysed per patient, except in one where six motor units were investigated. In recordings with action potentials from more than one motor unit several potentials coincide in time and superposition potentials are formed. It was therefore impossible to measure each interval in the action potential trains from different motor units without a manual or an automatic classification of the potentials. If an amplitude trigger had been used only about 80 of the 160 motor units in this material could have been analysed.

The patients had difficulty in keeping firing rate and force constant, as noted by Kranz. Therefore the statistical parameters generally used to describe the firing pattern are not adequate. Instead the variability of the intervals was measured by the parameters VAR, VARI and FSD, and the floating serial correlation coefficient FRHO, as described by Andreassen and Rosenfalck.13

Results

Torque and firing frequency The torque exerted at maximal effort was 40% or less of that exerted by normal subjects matched for body height, sex and age (table 1). The mean firing frequency recorded over 20 s was lower in the patients with spasticity than in normal subjects. It ranged from 5 to 13 Hz compared with 6 to 20 Hz in normals corresponding to mean intervals ranging from 75 to 200 ms in the

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient</th>
<th>Age (yr)</th>
<th>Duration of disease</th>
<th>Daily medication</th>
<th>Tmax (Nm)</th>
<th>Tmax (%)</th>
<th>Normal (Nm)</th>
<th>n</th>
<th>Ankle jerk</th>
<th>Knee jerk</th>
<th>Resistance to stretch</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>MH</td>
<td>59</td>
<td>7 days</td>
<td>6 mg diazepam</td>
<td>7-5</td>
<td>14</td>
<td>54</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P2</td>
<td>EP</td>
<td>72</td>
<td>40 days</td>
<td>None</td>
<td>5-0</td>
<td>14</td>
<td>34</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P3</td>
<td>AP</td>
<td>71</td>
<td>27 days</td>
<td>None</td>
<td>2-5</td>
<td>15</td>
<td>47</td>
<td>15</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>P4</td>
<td>IN</td>
<td>38</td>
<td>16 years</td>
<td>10 mg diazepam and antiepileptic drugs</td>
<td>None</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+ + + + + + + +</td>
</tr>
<tr>
<td>P5</td>
<td>IB</td>
<td>56</td>
<td>2 years</td>
<td>None</td>
<td>15-0</td>
<td>41</td>
<td>36</td>
<td>19</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>P6</td>
<td>GA</td>
<td>48</td>
<td>6 months</td>
<td>None</td>
<td>4-5</td>
<td>12</td>
<td>37</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>P7</td>
<td>PG</td>
<td>62</td>
<td>3 years</td>
<td>None</td>
<td>13-5</td>
<td>31</td>
<td>44</td>
<td>14</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>P8</td>
<td>SG</td>
<td>45</td>
<td>8 years</td>
<td>Corticotrophine</td>
<td>12-5</td>
<td>16</td>
<td>78</td>
<td>18</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>P9</td>
<td>NF</td>
<td>48</td>
<td>3 years</td>
<td>Corticotrophine</td>
<td>17-0</td>
<td>28</td>
<td>62</td>
<td>12</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>P10</td>
<td>BA</td>
<td>49</td>
<td>9 years</td>
<td>15 mg baclofen</td>
<td>5-5</td>
<td>15</td>
<td>37</td>
<td>18</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Tmax: Torque at maximal effort. Normal: Torque at maximal effort for normal subjects matched for body height, sex and age from Asmussen and Heebøll-Nielsen (1961). n is the number of motor units investigated. 0 normal; + increased reflexogenic zone, increased resistance to plantar flexion; + + increased tone and clonus; - absent tendon jerks.

Fig 1 Histograms of mean intervals determined from 160 recordings in patients with spasticity (P) and from 79 recordings in normal subjects (N).
Impaired regulation of force and firing pattern of motor units

Patients and from 49 to 160 ms in normal subjects (fig 1). Mean intervals longer than 160 ms were never encountered in the 97 motor units examined in normal subjects.13

The relation between torque and mean interval was plotted with the torque expressed in Nm (fig 2A), and with the torque expressed as per cent of the torque at maximal effort $(T_{\text{max}})$ for each patient (fig 2B). To compare the torque in Nm in patients and in normal subjects of different body height, sex and age the torques were normalised relative to a maximal torque of 60 Nm, which is the normal maximal torque for a 25 year old, 175 cm high male. When the torque was expressed in Nm most mean intervals fell within the range found in normal subjects. When the torque was expressed in per cent of the torque at maximal effort $(T_{\text{max}})$ for each subject, 97% of the mean intervals recorded in the patients fell above the regression line for mean intervals determined for normal subjects.

**Long term fluctuations** The patients were unable to maintain an isometric contraction of constant torque although they were given the same feedback as the normal subjects, the torque being displayed on a meter and the EMG by a loudspeaker. Torque and frequency fluctuated slowly (fig 3, P). In two thirds of the 122 recordings from the patients with spasticity the fluctuations in torque were $\pm 5$–20% of the average torque and in one third 20–80% of the average torque. The fluctuations in torque followed the fluctuations in frequency after a delay of 100 ms–500 ms. The fluctuations in instantaneous frequency were similar in different motor units recorded simultaneously (fig 4).

**Short term variations** The variability between successive interspike intervals was smaller in the patients with spasticity than in the normal subjects (fig 3). In the normal subjects a long interval was usually followed by a short and *vice versa* corresponding to a negative serial correlation. In the patients with spasticity a short interval was usually followed by a short, and a long interval by a long, corresponding to a positive serial correlation (figs 3 and 4). The

**Table 2. Short term variation VAR and floating serial correlation coefficient FRHO between successive intervals**

<table>
<thead>
<tr>
<th>Patient</th>
<th>n</th>
<th>VAR</th>
<th>P</th>
<th>FRHO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S</td>
<td>P</td>
<td>Mean</td>
</tr>
<tr>
<td>MH</td>
<td>15</td>
<td>0.131</td>
<td>0.031</td>
<td>0.02</td>
</tr>
<tr>
<td>EP</td>
<td>19</td>
<td>0.124</td>
<td>0.018</td>
<td>0.005</td>
</tr>
<tr>
<td>AP</td>
<td>15</td>
<td>0.126</td>
<td>0.020</td>
<td>0.02</td>
</tr>
<tr>
<td>IN</td>
<td>16</td>
<td>0.104</td>
<td>0.026</td>
<td>0.025</td>
</tr>
<tr>
<td>P1</td>
<td>55</td>
<td>0.124</td>
<td>0.032</td>
<td>0.001</td>
</tr>
<tr>
<td>IB</td>
<td>19</td>
<td>0.122</td>
<td>0.025</td>
<td>0.005</td>
</tr>
<tr>
<td>PG</td>
<td>24</td>
<td>0.168</td>
<td>0.037</td>
<td>NS</td>
</tr>
<tr>
<td>GA</td>
<td>14</td>
<td>0.241</td>
<td>0.041</td>
<td>0.001*</td>
</tr>
<tr>
<td>P2</td>
<td>57</td>
<td>0.171</td>
<td>0.056</td>
<td>NS</td>
</tr>
<tr>
<td>BA</td>
<td>18</td>
<td>0.116</td>
<td>0.024</td>
<td>0.005</td>
</tr>
<tr>
<td>NF</td>
<td>12</td>
<td>0.128</td>
<td>0.023</td>
<td>0.05</td>
</tr>
<tr>
<td>SG</td>
<td>18</td>
<td>0.104</td>
<td>0.033</td>
<td>NS</td>
</tr>
<tr>
<td>P3</td>
<td>48</td>
<td>0.136</td>
<td>0.031</td>
<td>0.001</td>
</tr>
<tr>
<td>All normal subjects</td>
<td>97</td>
<td>0.162</td>
<td>0.047</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Mean and standard deviation (S) of VAR and FRHO for the n motor units recorded in each patient and in the normal subjects. P is the significance of deviation of the mean from the mean in the normal subjects (NS = not significant).

*VAR greater than normal*
double discharges observed in one third of the recordings from muscles of normal subjects were rarely found in the patients with spasticity. The variability in intervals was described by FSD, VAR and VARI.\(^{13}\) As in normal subjects, FSD and VARI increased with the mean interval. In the patients with spasticity FSD tended to fall below the normal regression line (fig 5). This was even more pronounced for the values of VARI (fig 6). One patient with multiple sclerosis (GA) was an exception. In this patient all values of FSD and VARI fell above the regression line in normal subjects. The fluctuations in torque were the same as in other patients (10–50%), the level of contraction was low 1·5–10% of \(T_{\text{max}}\), and the mean intervals were shorter than in the other patients. The serial correlation between intervals was previously described by plotting the joint interval histograms and by calculating the serial correlation coefficient RHO.\(^{16-19}\)

In patients a short interval was followed by a short and a long interval by a long corresponding to a positive slope of the long axis of the contour ellipse in the joint interval histogram (fig 7, right). In normal subjects the slope of the long axis in the joint interval histograms was negative. A source of error is a slow change in frequency during the recording period. This could change a negative to a positive slope (Andresen and Rosenfalck,\(^{13}\) fig 6). A positive slope in the joint interval histogram is equivalent to a positive value of the serial correlation coefficient RHO. To avoid this error and to obtain a quantitative expression for the serial correlation between intervals a floating serial correlation coefficient FRHO was calculated relative to a "floating mean interval." FRHO increased with the mean interval as in normal subjects (fig 8).

In patients with cerebral lesions (Groups P1 and P2) 95% of the values of FRHO fell above the regression line for normal subjects, while the patients with spinal involvement (group P3) had normal values of FRHO. It may be argued that the increase in FRHO was due to the fluctuations in firing rate. If this was so FRHO should increase with the magnitude of the fluctuations. This was not found. When FRHO was plotted as a function of the size of the fluctuations in torque, there was no correlation. In addition there was no significant correlation between FRHO and the level of torque at which the recording was obtained.

In fig 9 the values of VAR and FRHO were plotted, ignoring the dependence of VAR and FRHO on the mean interval. Freund et al\(^{6}\)
Impaired regulation of force and firing pattern of motor units

Torque
Nm

Instantaneous
frequency Hz

Fig 4 Torque around the ankle joint and instantaneous frequency over a 20 s period for three different motor units extracted from the same recording. Patient with spasticity MH, male 59 years old.

Fig 5 Floating standard deviation FSD as a function of mean interval. 160 recordings from single motor units in 10 patients with spasticity. P1: MH ▲, EP ●, AP ●, IN ■; P2: IB ○, PG ●, GA ○; P3: BA ○, NF ▼, SG ●.

mentioned that "not all units recorded from one patient are similarly involved; some of them show the characteristic pattern, others do not or only weakly." This observation was confirmed in this study in the respect that most of the patients had some motor units, where VAR and FRHO fell within the normal range. It is therefore necessary to analyse several motor units in each patient, preferably 10 or more. However, the width of the histograms of VAR is not increased for the individual patients, when compared to the width of the histograms for individual normal subjects, and the width of the histograms for FRHO is only slightly increased for the patients. It is therefore likely that the firing pattern of all motor units in a patient is approximately equally affected, giving a shift in the mean values of the VAR and FRHO parameters, without a significant increase in the width of the histograms. If some motor units had been affected, while others had remained normal an increased scatter of the parameters VAR and FRHO would have been expected. The hypothesis, that the motor units are approximately equally affected, is also supported by the similar behaviour observed in motor units recorded simultaneously (fig 4).

Double discharges The double discharges observed during maintained contraction in one third of the motor units from muscles of normal subjects were rarely found in the patients with
Fig 6  Short term variation in instantaneous frequency $VARI$ as a function of mean interval. Recordings from single motor units in 10 patients with spasticity. $P_1$: $MH\blacktriangle$, $EP\bullet$, $AP\ast$, $IN\blacksquare$; $P_2$: $IB\bigcirc$, $PG\bigotimes$, $GA\blacklozenge$; $P_3$: $BA\blacklozenge$, $NF\blacktriangledown$, $SG\bigstar$.

Fig 7  Joint interval histograms for a normal subject (N) and for a patient with spasticity (P). In the normal subject (N) axis $a$ of the contour ellipse is smaller than axis $b$ corresponding to a negative serial correlation coefficient $RHO$ ($a = 9$ ms, $b = 12$ ms). In the patient with spasticity axis $a$ is greater than axis $b$ and $RHO$ positive ($a = 25$ ms, $b = 13$ ms). The floating serial correlation coefficient $FRHO$ is 0.1 smaller than $RHO$ in both plots due to the negative bias when calculating relative to a floating mean of 19 intervals. Same recordings as fig 3.

Fig 8  Floating serial correlation coefficient $FRHO$ between successive intervals as a function of mean interval. Recordings from single motor units in 10 patients with spasticity. $P_1$: $MH\blacktriangle$, $EP\bullet$, $AP\ast$, $IN\blacksquare$; $P_2$: $IB\bigcirc$, $PG\bigotimes$, $GA\blacklozenge$; $P_3$: $BA\blacklozenge$, $NF\blacktriangledown$, $SG\bigstar$. 

Impaired regulation of force and firing pattern of motor units

The reduction in force in hemiparetic patients has been attributed to different causes: disuse atrophy, vascular changes, arthropathy, α-motoneurone degeneration, pressure neuro-opacity, and an unspecified parietal mechanism (for references see McComas et al.29). The present finding of a reduced firing rate in patients with spasticity (fig 1) suggests that the torque is lower than normal, partly because most motor units fire at a rate where they produce unfused twitches. Similar reductions in firing rate were previously found in patients with upper motoneurone disease2-3 and in Parkinsonism.1 23 24

One might turn the question around and ask if the reduction of firing frequency is simply a consequence of the low torque. Considering the plot of torque in NNm and mean interval (fig 2A) this could be the case as the points fall around the regression line for the normal subjects. However, there are a number of motor units firing regularly at mean intervals above 160 ms, which is rarely found in normal subjects. Furthermore if each patient is used as his own reference, and the torque is plotted in per cent of his maximal torque, T_{max} (fig 2B), the majority of the points fall above the regression line for normal subjects indicating a reduction of firing frequencies. This presentation of the data is justified if disuse atrophy is considered a major reason for the reduced torque. It is also justified if the antagonists were cocontracting. The antagonists were not monitored during voluntary contractions and cocontraction could have been present, even though the patients could relax both agonists and antagonists at rest.

The reduced firing rates could be due to a change in membrane properties of the motor neurons, for example increased duration of the after hyperpolarisation. It could also be due to a bias in the sampling of motor units towards slow twitch units, which can fire continuously at low rates. The bias may be caused by preferential atrophy of fast twitch muscle fibres,25 or the patients may be unable to recruit the fast twitch motor units.

The fluctuations in torque were reflected in the firing pattern. We found similar changes in the firing pattern in all motor units examined (figs 3 and 4). The fluctuations in instantaneous frequency preceded the fluctuations in torque by 100 ms–500 ms. Even though the torque fluctuated more than normal, the short term variation between intervals was less than normal in the patients with spasticity. The large variation between successive intervals and the negative values of FRHO found in the normal subjects

**Fig 9** Histograms for VAR and FRHO for 160 motor units recorded from 10 patients with spasticity. n : number of motor units. Below data pooled from the 10 patients P_{1} + P_{2} + P_{3}.

spasticity. Double discharges were rarely found at the onset of a contraction, where they are frequently found in normal subjects. This is in accordance with the observation that the patients were unable to correct changes in torque quickly.

**Discussion**

The torque recorded in patients with spasticity differed in two respects from normal: maximal torque was 40% or less of that in normal subjects; during submaximal contraction the fluctuations in torque were larger and slower than in normal subjects.
was suggested to be an expression of a feedback mechanism that keeps the torque constant by fast corrections of the frequency. In the patients with spasticity this mechanism was impaired and the instantaneous frequency drifted up and down. The reduced variability was previously found in hand muscles of patients with spasticity and in patients with cerebellar lesions. Poor utilisation of feedback from muscle receptors could explain the lack of fast control and the corresponding fluctuations in torque. This is in accordance with the enhancement of low frequency tremor (below 8 Hz) in the masseter muscle of monkey after deafferentation. In man, Burke et al. recorded from single muscle spindle afferents in the peroneal nerve during slow shortening of the anterior tibial muscle and showed that feedback from spindles may control irregularities in the shortening. The hypothesis of poor utilisation of peripheral feedback is consistent with the finding that the second EMG burst M2 in response to a sudden perturbation of the thumb is absent when the long loop reflexes are disturbed by lesions in the afferent or efferent branches. The increase in the modified serial correlation between successive intervals FRHO which we have found in the patients with spasticity can be interpreted the same way.

Cocontraction of the antagonist creates a "myotatic unit," where afferent input from the antagonist increases the efficiency of the reflex regulation of the firing pattern. If cocontraction were present in the patients an increased regulation of the firing pattern would be expected, thus making the present finding of a reduction of the regulation more striking.

"Phasic" and "tonic" motor units
In the 160 motor units classified from 122 recordings from patients with spasticity we never observed disturbances in the recruitment order as described by Grimby et al. They found that "phasic" units are recruited as "tonic" units fatigue. Usually we did not attempt to continue the recording until the patients fatigued and this could account for our inability to confirm their finding. The 20 s recording periods used for analysis were however selected from 1-4 min recordings in the normal subjects and in the patients with spasticity. In these longer recordings we failed to find motor units firing in high frequency bursts corresponding to the firing pattern of the "phasic" motor units found in normal subjects and in patients with spasticity. In the present study units recorded a high levels of contraction showed the same firing pattern as other units. We found in accordance with Clamann, Gillies, Tanji and Kato and Gydkov and Kosarov that the firing rate of "tonic" motor units with low recruitment threshold could be increased considerably during increasing contraction. Grimby and Hannerz and Borg et al. have not included force recordings in their illustrations of the firing pattern, this makes the interpretation of a "phasic" firing pattern uncertain. None of the data in the present study (firing rate, VAR and FRHO) distinguish between "tonic" and "phasic" units. This is in accordance with other investigations of the firing pattern in normal subjects which failed to confirm the original finding by Tokizane and Shimazu that "tonic" and "phasic" units can be distinguished by their firing pattern. When two or three motor units were extracted from the same recording they behaved similarly (fig 4), with respect both to long term and short term fluctuations. The similar behaviour of all motor units in individual normal subjects and in individual patients with spasticity also was confirmed by the finding of the narrow width of the histograms of VAR and FRHO (fig 9).

Distinction between spinal and supraspinal lesions
In patients with cerebral lesions 95% of the values for FRHO fell above the normal regression line. The increase in serial correlation coefficient FRHO was less pronounced in the patients with spinal involvement. Whether the changes in VAR and FRHO can be used to localise the site of the lesion needs further investigation of patients with well-defined lesions in the central nervous system.

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Impaired regulation of force and firing pattern of motor units


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*Annelise Rosenfalck and Steen Andreassen*


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A Rosenfalck and S Andreassen

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