Patients with spastic hemiplegia at different recovery stages: evidence of reciprocal modulation of early/late reflex responses.

I K Ibrahim, M A R El-Abd, V Dietz

Abstract
Reflex electromyographic (EMG) muscle responses were recorded from abductor pollicis brevis (APB) and tibialis anterior (TA) muscles of fifty patients with spastic hemiplegia. Responses in the muscles were evoked during voluntary muscle contraction (about 20% of maximum voluntary effort) by submaximal but suprathreshold electrical stimulation of the median (at the wrist) and common peroneal (at the neck of the fibula) nerves respectively. Three EMG peaks (R1, R2 and R3) could be recorded after the direct muscle response (M). There was only a slight difference in R1-R2 latency interval of about 5 ms between upper and lower limbs on the unaffected side of the patients making it unlikely that this late response of the lower limb involves a long loop pathway, although this possibility cannot be discounted for the later, R3, response. Reflex behaviour was analysed for three clinical identifiable recovery stages of voluntary movements in the spastic limbs (synergistic, isolated and useful movements). The major finding was that an increase in the amplitude of the early response “R1” was associated with a decreased amplitude and delayed latency of the late response “R2” on the spastic side. The amplitude of R1 in the three different recovery stages decreased significantly, whereas the amplitude of R2 increased significantly with improvement of the functional stage of the limb. A significant negative linear correlation was found between R1 and R2 amplitude changes in upper as well as lower limbs. A refractoriness of the motor neuron pool as a possible explanation for the decreased R2 amplitude could be discounted. These findings together with recent work on reflex development in children support the hypothesis of reciprocal modulation of early and late reflex signals by supraspinal motor centres.

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Upton et al1 have shown that early (V1) and late (V2) responses (in addition to direct muscle response) may be recorded in the intrinsic muscles of the hand, after stimulation of the ulnar or median nerves during a voluntary contraction, with latencies to onset of about 25 and 50 ms respectively. Although it was suggested that V1 was an unmasked H reflex, the origin of V2 could not be determined. Recently, interest has focused upon the behaviour and origin of the late components of mechanically and electrically induced reflexes.2 3 Milner-Brown et al5 interpreted the findings of Upton et al1 in such a way that they considered the possibility that V2 has a long-loop pathway via the motor cortex. Conrad and Aschoff8 supported this conclusion and also suggested that cutaneous signals also contribute to the afferent cortical input of the late response. Stanley7 has shown that both responses are evoked independently through reflex pathways: the first, with a mean afferent conduction velocity of 64 m/s and an estimated central delay of about 0.8 ms and the second with a mean afferent conduction velocity of 43 m/s and an estimated central delay of about 17 ms. The origin of the long-latency reflex response has been the subject of controversy.9 The supraspinal origin of the long-latency reflex responses has been considered by several workers,10–12 but questioned by others.13–16 Alternatively, there may be differences in the behaviour and pathways of this reflex in upper and lower limb muscles.17–19 as well as in proximal and distal muscles.20 In patients with spastic paresis, the behaviour of early and late reflex activity is altered in that reduced inhibition of the former is contrasted by a reduction or loss of the latter.21–23 The enhanced activity of the early stretch reflex is thought to arise from a reduction in reflex threshold without significant enhancement of the reflex gain.24–25 It was argued that the absence of long latency stretch reflexes is due to interruption of the long-loop (transcortical) pathway. Others attribute this (at least for leg muscles) to reciprocal modulation of monosynaptic and polysynaptic spinal reflex responses by brain centres.26–27

In the light of these views, the aim of this work was to quantify the behaviour of early and late reflex activities in spastic patients with different degrees of clinical recovery.

Methods
Subjects
Experiments were conducted on both sides of 5 apparently healthy volunteers aged between 37 and 50 years, and 50 stroke patients (32 males and 18 females) with spastic hemiplegia. The patients’ ages varied from 25 to 71 years [mean (SD) 57.4 (9.8) years].
Table Patients with spastic hemiplegia at different recovery stages: evidence of reciprocal modulation of early/late reflex responses

<table>
<thead>
<tr>
<th>Upper limb functional stage</th>
<th>SYN</th>
<th>ISOL</th>
<th>USEF</th>
<th>Total (UL)</th>
</tr>
</thead>
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<tr>
<td>SYN</td>
<td>n = 24</td>
<td>n = 16</td>
<td>n = 10</td>
<td>n = 50</td>
</tr>
<tr>
<td>n = 17 34%</td>
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<td>32%</td>
<td>20%</td>
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<td>26%</td>
<td>20%</td>
<td>0</td>
<td>combined groups</td>
</tr>
<tr>
<td>USEF</td>
<td>n = 10</td>
<td>n = 10</td>
<td>0</td>
<td>Total (patients)</td>
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<tr>
<td>n = 50 100%</td>
<td>100%</td>
<td>20%</td>
<td>0</td>
<td></td>
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</tbody>
</table>

Recovery stage of voluntary movements in upper and lower limbs and the distribution of the combined groups among the studied cases. n = number, UL = upper limb, LL = lower limb, SYN = synergistic movement, ISOL = isolated movement and USEF = useful movement.

duration of the symptoms varied from 6 to 60 months (mean (SD) 16·1 (10·2) months).

The right to left ratio of the spastic side was 36/14. The stroke was caused in most instances by a thrombosis (n = 49) and only one case was attributed to an embolism.

Each of the patients satisfied the following criteria: 1) exclusive unilateral motor disorder; 2) clinical signs of upper motor neuron syndrome at the affected side, that is, extensor plantar response, increased muscle tone and exaggerated tendon tap reflexes; 3) no clinical evidence suggesting the presence of any other neuromuscular disease (such as, neuropathy); 4) The patient had suffered the stroke at least six months previously so that adaptation to the existing neurological deficits could be guaranteed. In all patients the sensations were not clinically affected. The unaffected side of the patients was clinically normal (the so-called unaffected side is described as frequently abnormal). The stage of recovery of the spastic upper and lower limbs of the patients was classified into one of the following groups: stage (I) of synergistic movement characterised by flexion synergy in the upper limb and extension synergy in the lower limb. In these instances the patient moves the whole limb synergistically when he or she tries to move one joint. Stage (II) of isolated movement in which the patient is capable of performing independent joint movements. Stage (III) in which the patient can perform functionally useful movements. For upper limb these movements include manual and finger dexterity (the ability to work with the hand in grasping, placing and turning motions and the ability to manipulate small objects with the fingers), whereas in the lower limb complete clearance of the foot from the ground during walking can be achieved. The table shows the distribution of these three recovery stages of voluntary movement in the upper and lower limbs and the distribution of the combined groups among the cases studied.

Recordings

The reflex potentials were recorded from the abductor pollicis brevis (APB) and tibialis anterior (TA) muscles.

For APB muscle recording, the subject was seated comfortably with the forearm and hand lying palm upwards on a pillow. Two 9 mm silver/silver chloride disc surface recording electrodes were positioned so that the active recording electrode was over the belly of the muscle and the reference recording electrode was at the metacarpal joint of the thumb. The ground electrode was placed at the wrist between the stimulating and the recording electrodes.

For TA muscle recording, the subject lay comfortably in a supine position with the lower limb to be tested lying straight and slightly elevated by a sandbag placed under the calf muscles. Bipolar surface recording electrodes were placed 3 cm apart over the belly of the muscle at the junction of the upper and middle third of the leg. The active recording electrode was proximal to the reference one. The ground electrode was placed between the stimulating and recording electrodes.

Stimulations

Two silver electrodes were used for nerve stimulation. They were covered with saline-soaked felt and spaced 2·5 cm apart in a holder. The electrodes were placed on the skin overlying the nerve at the point at which the lowest motor activation threshold could be achieved. To study TA muscle the stimulating electrodes were positioned over the common peroneal nerve behind the neck of the fibula whereas for the investigation of the APB muscle the electrodes were situated over the median nerve at the wrist. The stimuli were rectangular voltage pulses, 0·5 ms in duration and delivered at 0·5 Hz. The intensity was submaximal but suprathreshold (about 55 V) and just evoked a weak visible muscle contraction. Toennies Electromyographic apparatus was used for stimulation and recording.

Testing procedure

During the testing, the subject was instructed to mildly contract the muscle under investigation so that the electrical activity recorded remained at approximately 20% of maximum voluntary effort measured on the unaffected side, and to make the contractions as isometric as possible by maintaining the force. Stimuli were delivered only while the subject was contracting his muscle consistently. Muscle electrical activity was amplified (band width of 1·5 Hz to 5 kHz) and averaged automatically (time locked to each stimulus) over 64 or 128 or 256 sweeps (depending upon the size of the evoked responses). In figures where EMG recordings are shown, two such averaged responses have been superimposed. The latencies (in ms) of reflex responses were measured as the time from the stimulus artifact to the point at which the recording deflects from the base line. The amplitudes (in µV) were measured peak to peak for the largest response. To analyse the amplitude changes of reflexes between the three groups, response amplitude was normalised by dividing the spastic side value by the unaffected
Further recordings were made from APB muscles of two healthy subjects and three patients (unaffected side) during isotonic contractions. The subject was instructed to abduct and adduct the thumb smoothly and alternatively perpendicularly to the palm. The frequency of movement (0.3 Hz) was controlled by auditory signals from a mechanical metronome. Stimuli were delivered only during the abduction movement.

Statistical methods

Statistical analysis of data was performed using an SPSS/PC™ package run on a computer system. The different tests used were: paired t test, one way analysis of variance (ANOVA), multiple range test (Scheffe's test), correlation coefficient (r) (Pearson test), and linear regression.

Results

REFLEX EMG RESPONSES
a) Unaffected side

Distinct, early (R1) and late (R2) waves (in addition to the direct muscle “M” response) could be recorded from APB and TA in all patients and healthy subjects. A later (R3) wave was infrequently observed and could be recorded from APB in only 9 patients and from TA in only 3 patients.

Figure 1 shows two superimposed averaged EMG reflex patterns from the unaffected and the spastic upper and lower limbs in a stage I

Figure 2  EMG responses in a stage II patient (capable of isolated movements). R2 has a delayed latency and a decreased amplitude on the spastic side.
The reflexes in spasticity

Subject (capable of synergistic movements only). The reflex potentials started with a negative wave and were always biphasic. The main deflection was negative for APB and positive for TA. The mean (SD) latencies of APB and TA were; for R1 28·9 (2-3) ms and 31·4 (3-0) ms respectively, for R2, 48·9 (5-7) ms and 57·5 (5-1) ms respectively and, for R3 was 68·1 (14-5) ms and 90·7 (15-8) ms respectively. The mean (SD) amplitude of R1 in APB and TA was 161·3 (90-7) μV and 132·9 (64-0) μV respectively, of R2, 94·6 (45·2) μV and 65·1 (35·4) μV respectively and, of R3, 45·5 (9-5) μV and 60·25 (49-9) μV respectively.

These latency and amplitude values for R1 and R2 are about the same as those obtained from healthy subjects. It was noticed that R1 latency in the unaffected lower limb was slightly longer than that of the unaffected upper limb. This difference (about 2·5 ms) can be explained by the limb length differences. R2 and even later EMG peak, R3, latencies in the unaffected lower limbs are considerably longer than that of the unaffected upper limbs (about 10 ms for R2 and about 20 ms for R3) a latency that cannot be explained solely by difference in limb length.

b) Spastic side
The major finding on the spastic side of patients was an increased amplitude of R1 and a decreased amplitude with increased latency of R2 compared with the unaffected side.

R1 was observed in all spastic upper and lower limbs while R2 could be seen in the APB and TA muscles of 26 and 25 patients respectively. R3 was not usually observed from the spastic side. It is seen from fig 1 that the spastic side R1 wave had a very high amplitude in comparison to that of R1 recorded from the unaffected side, whereas R2 was not present. These recordings were taken from a stage I patient. Figure 2 displays another example of the EMG reflex pattern of both the unaffected and spastic upper and lower limbs but in this case from a stage II patient (capable of performing isolated movements). Although the R2 wave is present on the spastic side it shows an increased latency and diminished amplitude in comparison with the unaffected side at this stage of functional recovery.

The mean (SD) latencies of the R1 wave in APB and TA muscles on the spastic side [29·1 (2-6) and 31·6 (2-7) ms respectively] were about the same as those obtained from the unaffected side. However, the mean latencies of the R2 wave in APB and TA muscles on the spastic side [55·9 (8-9) and 60·1 (7-7) ms respectively] was increased compared with the unaffected side (p < 0·001 for APB, and p < 0·05 for TA).

Figure 3 shows that the mean (SD) amplitude of the R1 wave of APB and TA on the spastic side [521·1 (426-3) and 423·4 (348-1) μV respectively] was considerably increased (p < 0·001) compared with the unaffected side. The mean (SD) amplitude of the R2 wave of APB and TA on the spastic side [51·8 (26-1) and 38·7 (22-0) μV respectively] was significantly decreased compared with the unaffected side (p < 0·01).

QUANTIFICATION OF R1 AND R2 RESPONSES IN THE THREE FUNCTIONAL STAGES
Figure 4 shows that the mean amplitude (normalised data) of R1 in each of the three functional groups decreases significantly (p < 0·01), while the mean amplitude of R2 increases significantly (p < 0·01) with improvement of the functional stage of the limb.

This reciprocal activity was further quant-
fied using scatter plots and regression line correlating the amplitude change (normalised values) of R1 and R2 (fig 5). A significant negative linear correlation was found between both responses in APB \((r = -0.74; p < 0.001)\) as well as TA \((r = -0.56; p < 0.01)\) muscles. The normalisation of the data to the unaffected side was responsible for uncovering this significant correlation as using the absolute values of amplitude of the spastic side revealed insignificant negative correlation in APB \((r = -0.1 p > 0.05)\) as well as in TA \((r = -0.23 p > 0.05)\). This is due to the wide range of normal R1 and R2 amplitudes (see amplitude values). The R1-R2 amplitude (absolute values) correlation on the unaffected side was found to be insignificant in APB \((r = 0.29 p > 0.05)\) as well as in TA \((r = 0.18 p > 0.05)\).

The prevalence of R2 responses was different in each of the recovery stages in the upper \((n = 26)\) and lower \((n = 25)\) limbs. Figure 6 shows that R2 seldom appears in poorly functioning limbs (stage I) but is much more evident as recovery progresses through stages II and III in which the limb can at least perform isolated movements. It was also noticed that in spastic limbs where R2 was not seen there was a large R1 peak. The R2 latency changes among the three groups were insignificant (not shown in a Fig).

R1 AND R2 RESPONSES DURING ISOTONIC CONTRACTIONS OF HEALTHY APB MUSCLE
The influence of the type of muscle contrac-

tion upon the amplitude of the reflex response in APB muscles of two healthy sub-
jects and the unaffected side of three patients was investigated. It was evident that during

Discussion
The main findings of our study were: 1) evidence for a different origin of late response
“R2” in upper and lower limb muscles; 2) increased amplitude of R1 associated with
decreased amplitude and delayed latency of
R2 in spastic limbs, and 3) correlation of reci-
procal behaviour of R1 and R2 response amplitudes in the different recovery stages of
hemiplegia.

Possible origin of late response
For the early response (R1) an oligosynaptic spinal pathway can be assumed for both
upper and lower limb.14 Also for the late response (R2) in hand muscles a transcortical
pathway is most probable according to earlier
works.8,10,20 This may be different for the
lower limb muscles.16 In this study an R1-R2
interval of about 20 ms in hand and of about
25 ms in leg muscles was found. The differ-
ence (about 5 ms) between the upper limb
and the lower limb argues against the possi-
bility of a transcortical pathway for R2 in
lower limb as (using the fastest conducting
fibres) an extra delay of 10 ms (in small indi-
viduals) to 20 ms (in large individuals) is
needed for an impulse to travel the distance
between the lumbar and cervical motor neu-
ron pools twice during the reflex transmission
(for calculation see Darton et al18). Further-
more, following muscle stretches, the M1-M2
interval was shown to be about the same in
hand and foot muscles.14 The calculated,
R1-R3 interval in the hand (about 40 ms)
and in the leg (about 60 ms) makes a tran-
cortical pathway for R3 possible also for
lower limb muscles.

Reflex behaviour in spasticity
The short-latency reflex “R1” could be
obtained in all patients. Its latency was simi-
lar to that of the unaffected side, however, its
amplitude was usually larger. This R1
enhancement corresponds to the well-known
exaggerated tendon tap reflexes in spasticity.
For some time it has been suggested that
increased gamma-motor neuron drive is
responsible for the exaggerated reflexes, how-
ever, microneurographic recordings of single
muscle spindle afferents in humans have pro-
vided no evidence of overactivity of afferent
spindle discharges due to exaggerated fusimo-
tor drive in spastic patients. The enhanced amplitude of monosynaptic stretch reflex in spastic paresis may arise from a reduction in reflex threshold without significant enhancement of the reflex gain. The most probable cause for this may be a decreased presynaptic inhibition of la fibres as suggested in other studies.

In this work, the late reflex response R2 was either absent or reduced in amplitude and its onset was delayed on the spastic side. The absence of a long-latency response in spastic patients has been previously described in APB following electrical stimulation of the median nerve, and in the triceps surae and the wrist flexors following stretch. The possibility that the cortical lesion had disrupted the pathway for R2 as suggested elsewhere is unlikely for lower limb muscles according to our observations. In our study response patterns with an absent R2 component were associated with large R1 peaks (fig 1). A similar change to that observed in spastic patients with large short-latency and small long-latency reflex responses has also been described in young children with immature CNS. As an explanation for the absence of the late reflex response, it was argued that an increased motor neuronal refractoriness after a large early response may have limited subsequent later overactivity. This hypothesis is based on the observation that in normal subjects the long-latency response decreased in amplitude as the short-latency response became larger by increasing the acceleration of the stretch. However, our work shows that among healthy subjects and the unaffected limbs there were examples of large R1 waves associated with large R2 responses during isotonic contraction. Under this condition several R1 amplitudes in healthy subjects and the unaffected limbs were in the range of those seen in spastic limbs where R2 was absent (figs 1 and 7). In healthy subjects and unaffected limbs, however, the amplitude of R2 was also increased. Furthermore, following muscle stretches in spastic patients it could be shown that exaggerated early reflexes cannot account for the depression of the late responses. Thus motor neuronal refractoriness is unlikely to be the sole cause of the R2 depression in spasticity. It is assumed that both responses are modulated reciprocally by a supraspinal mechanism. The dynamic R1–R2 relationship described in normal subjects seems to be static in patients with spastic paresis.

Relation between reflex responses and the stage of recovery

In our study it was found that the R2 response is generally observed in stage II and III, that is, when the limb is at least capable of performing isolated movements (fig 6). When it appeared in poor functioning limbs it was usually of very low amplitude. The defective R2 reflex may therefore contribute to disturbed motor control in spastic patients. This suggestion agrees with the loss of long-latency reflex modulation during functional arm movements of spastic limbs which has been described recently. Correlation of the reflex activity to the clinical stages of recovery has shown a reciprocal relationship between R1 and R2 amplitudes. From stage (I) of synergistic movement to stage (III) of useful movement, R1 amplitude decreased while that of R2 increased significantly in a proportional manner (fig 4). This is also underlined by a significant negative linear correlation between both responses in upper as well as in lower limbs (fig 5). This negative correlation was statistically insignificant in previous work probably because the correlated data were not normalised to the response recorded on the unaffected side of the patient. A similar insignificant correlation was also found in this study when absolute amplitude values were used. The normalisation was performed in our work to account for the wide range of reflex amplitudes observed. A reciprocal modulation of R1 and R2 reflexes seen here in spastic patients during different stages of recovery was also described for small children during development where a progressive decrease of short-latency reflex response (E1) was associated with the progressive increase of longer-latency reflex response (E2) (evoked by cutaneous stimulation) with increasing age in children.

Our findings support the proposal of reciprocal modulation of these reflex mechanisms, the function of which depends on supraspinal control. The close relationship between the stage of recovery and the behaviour of early and late reflexes we describe in spastic patients may serve for the documentation of the course of rehabilitation by simple electrophysiological means.

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