Electrophysiological investigations in cranial hyperkinetic syndromes

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Chapter 2

Blink reflex recovery curves in blepharospasm, torticollis spasmodica and hemifacial spasm.

Eekhof JLA, Aramideh M, Bour IJ, Hilgevoord AAJ, Speelman JD and Ongerboer de Visser BW.

Abstract.

R1 and R2 blink reflex responses to single and paired stimuli were investigated in 23 control subjects, 21 patients with blepharospasm (BSP), 20 patients with torticollis spasmodica (TS), and 23 with hemifacial spasm (HFS).

For paired stimuli, we compared measurements of area and peak responses at two and three times R2 threshold. R1 and R2 indices were calculated as the average of the recovery values at 0.5-, 0.3-, and 0.21-s interstimulus intervals to test individual patients. Peak amplitude measurements at three times R2 threshold were optimal.

The R2 index was abnormal in 67% of BSP patients, 37% of TS patients, and 50% of HFS patients on the affected side and 20% on the unaffected side. A normal R2 index in one third of patients with BSP may indicate that different pathophysiological mechanisms are involved in this type of focal dystonia.

Keywords: blink reflex, blepharospasm, torticollis spasmodica, hemifacial spasm.


Introduction.

The blink reflex, evoked by electrical stimulation of the supraorbital nerve, consists of two components: an early ipsilateral reflex, R1, with a latency of about 10 ms; and a late bilateral reflex, R2, with a latency of about 30 ms. R1 is mediated through
Figure 1. Recordings of R1 and R2 blink reflex recovery curves from a control subject. (A) Average of six successive trials at each interstimulus interval, filtered and rectified. (B) Recovery curve of R1 responses and (C) of R2 responses from the same subject.
the pons by an oligosynaptic pathway ipsilateral to the side of the stimulation. Afferent impulses of R2 descend along the ipsilateral trigeminal spinal tract to a level caudal to the obex and ascend bilaterally via polysynaptic medullary pathways, which are probably located in the lateral bulbbar reticular formation. Motoneurons of the facial nerve constitute the final common efferent path.

Excitability of facial nerve motoneurons and brainstem interneurons can be examined by obtaining R1 and R2 recovery curves after application of two shocks (conditioning and test stimuli) to the supraorbital nerve at varying intervals. The recovery is then measured by expressing the size of the test response as a percentage of that of the first conditioning response at each interval.

An increased R2 recovery curve has been found in patients with parkinsonism, hemifacial spasm, and various focal dystonias. However, methodological aspects of obtaining reliable blink reflex recovery curves have received little attention and data of individual patients are not available. In this article, we investigated the impact of stimulation intensity on rectified and averaged peak amplitude and area measurements of recovery curves in a group of patients with blepharospasm (BSP), torticollis spasmodica (TS), and hemifacial spasm (HFS), and in a group of control subjects. We also calculated R1 and R2 recovery indices in all subjects as the average of recovery values at 0.5-, 0.3-, and 0.21-s intervals. This enabled us to study the blink reflex recovery of individual patients and to compare the results with the clinical findings and treatment outcomes.

Methods.

Twenty-three control subjects, 21 patients with BSP, 20 patients with TS, and 23 patients with HFS were included in this study, after they gave informed consent. General characteristics of the subjects are summarized in Table 1. The diagnosis was made by clinical observation and electromyogram (EMG) recordings with concentric needle electrodes inserted into the involved muscles. All patients with BSP had involuntary bursts of activities in the orbicularis oculi muscles. All patients with TS had involuntary EMG activity in at least one sternocleidomastoid muscle. Patients with HFS had twitching movements and synkinetic EMG activities between the orbicularis oculi and mentalis muscles of the affected side of the face, and none of them had a previous history of facial palsy. Severity of symptoms in BSP and HFS patients was assessed with a 4-point clinical scale and in TS patients with the Tsui-score. Responses to pharmacotherapy or injections with botulinum toxin type A (BTX, Dysport) were assessed in all patients by a 3-point scale, with 1 for no response and 3 for good response, as a combined opinion of patient and physician. Blink reflexes were recorded before treatment with the subjects in the supine position. Surface recording electrodes were placed over the lower portion of the ipsilate-
Table 1. Summary of the general characteristics of subjects.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of subjects</th>
<th>Most affected side (left/right/both)</th>
<th>Mean age (range)</th>
<th>Sex (M/F)</th>
<th>Mean duration in years (range)</th>
<th>Mean clinical scale (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>23</td>
<td>0</td>
<td>50 (19-74)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blepharospasm</td>
<td>21</td>
<td>0</td>
<td>64 (44-80)</td>
<td>7/14</td>
<td>8 (1-15)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>Torticollis</td>
<td>20</td>
<td>38176</td>
<td>49 (22-67)</td>
<td>5/15</td>
<td>9 (1-32)</td>
<td>11 (6-16)</td>
</tr>
<tr>
<td>Hemifacial spasm</td>
<td>23</td>
<td>36811</td>
<td>64 (33-80)</td>
<td>6/17</td>
<td>8 (1-30)</td>
<td>3 (2-4)</td>
</tr>
</tbody>
</table>

*Both is predominantly retrocollis for torticollis patients.

Table 2. Data of R2 recovery curve peak amplitudes at three times R2 threshold.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean at 10 s (%)</th>
<th>Mean at 3 s (%)</th>
<th>Mean at 1 s (%)</th>
<th>Mean at 0.5 s (%)</th>
<th>Mean at 0.3 s (%)</th>
<th>Mean at 0.21 s (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS</td>
<td>107 (41)</td>
<td>100 (41)</td>
<td>52 (22)</td>
<td>30 (15)</td>
<td>21 (11)</td>
<td>16 (07)</td>
</tr>
<tr>
<td>BSP</td>
<td>122 (53)</td>
<td>106 (24)</td>
<td>88 (28) *</td>
<td>61 (24) *</td>
<td>50 (25) *</td>
<td>49 (38) *</td>
</tr>
<tr>
<td>TS</td>
<td>118 (48)</td>
<td>120 (51)</td>
<td>61 (28)</td>
<td>44 (24) †</td>
<td>36 (21) *</td>
<td>19 (11)</td>
</tr>
<tr>
<td>HFS aff</td>
<td>114 (75)</td>
<td>98 (34)</td>
<td>68 (37)</td>
<td>49 (26) *</td>
<td>39 (26) *</td>
<td>39 (29) *</td>
</tr>
<tr>
<td>HFS unaff</td>
<td>120 (44)</td>
<td>108 (40)</td>
<td>60 (33)</td>
<td>39 (23)</td>
<td>26 (16)</td>
<td>24 (12) †</td>
</tr>
</tbody>
</table>

Mean = averaged value of R2 test response as a percentage of conditioning response for each interval. CS = control subjects, BSP = blepharospasm, TS = torticollis spasmodica, HFS aff = hemifacial spasm, affected side; HFS unaff = hemifacial spasm, unaffected side. * p < 0.01, † p < 0.05.
The supraorbital nerve was stimulated with the cathode placed over the supraorbital foramen and the anode 2 cm higher and lateral on the forehead. Impedance of the electrodes was always less than 5 kΩ. A Grass stimulator was used to apply constant current pulses with a duration of 0.2 ms. The low- and high-pass filters were set at 3 kHz and 1 Hz, respectively (6 dB/octave). The sweep time was kept at 200 ms. All responses were stored digitally on PDP 11/73 computer for further off-line analysis. The supraorbital nerve was stimulated initially with subthreshold intensity, which was gradually increased until the smallest R2 response could constantly be detected, i.e., R2 threshold. Blink reflexes evoked by single stimulus and recovery curves obtained by paired stimuli were recorded on the stimulation side at two and three times R2 threshold. After single stimulus, six successive responses were recorded on both sides in each subject. The affected side was examined in all HFS patients and the unaffected side in 20 of them. Using paired stimuli, six trials were performed at interstimulus intervals of 10, 3, 1, 0.5, 0.3, and 0.21 s on one side. In patients with BSP the most affected side or the side which was involved at the onset of the disease was examined preferentially. For each subject, the R1 and R2 recovery curves were obtained by plotting the size of the test response as a percentage of the conditioning response at each interstimulus interval (see figure 1).

The R1 recovery index was calculated in each subject as the mean recovery of peak amplitude values at interstimulus intervals of 0.5, 0.3, and 0.21 s, which appeared to be more sensitive than the index calculated from more than three intervals. The R2 recovery index was calculated in the same way. The upper limit of normal for R1 and R2 indices was defined as the mean + 2 SD. The values of R1 and R2 recovery indices were correlated to the clinical findings and treatment outcomes. Involuntary eyelid movements could be identified by the amplified sound signal. Responses with artifacts due to involuntary movements were rejected. Patients were requested to close their eyes gently during stimulation and to open them in between successive trials. Between successive trials, a rest period of at least 30 s, but often much longer in case of early and long-lasting habituation or severe spontaneous discharges, was maintained. In an off-line analysis, reflex responses were digitally band-pass filtered within a range of more than 100 Hz to minimize DC-offsets and slow eye drifts, and below 900 Hz to reduce the high-frequency noise. They were then full-wave rectified and for each interstimulus interval the average of six trials was computed. Peak amplitude and area of R1 were calculated within a window from 10 to 25 ms to avoid stimulation artifact, and those of R2 within a window from 32 to 90 ms. The average rest activity level was established within a window from 150 to 200 ms and subtracted from the average response.

The values of single stimuli and ratios of paired stimuli at all interstimulus intervals were compared between the patients and controls by means of t-test and nonparametric Mann–Whitney test. Nonparametric tests were used because most of the data were skewed. Differences and correlations with a p value smaller than 0.05 were considered significant. The same methods were used to compare the R1 and R2 recovery indices. Correlations were calculated between the R2 recovery index and the clinical findings.
Figure 2. Peak amplitude R1 recovery curves at three times threshold ± standard error of the mean.

Figure 3. Peak amplitude R2 recovery curves at three times threshold ± standard error of mean.
Results.

Neither peak amplitude nor area measurements of R1 and R2 responses, obtained by single stimulus at two and three times R2 threshold, differed significantly between the patients and controls.

Considering R1 and R2 responses obtained after paired stimuli, the calculated areas at two and three times R2 threshold showed more variability than peak amplitudes obtained at three times R2 threshold. Peak amplitudes measured at three times R2 threshold showed less variability than corresponding values obtained at two times R2 threshold. In the rest of the article, we will consider only the results of peak amplitudes of R1 and R2 responses obtained at three times R2 threshold.

R1 recovery curves of the control subjects and patients are shown in Figure 2. At intervals shorter than 1 s, variability of R1 responses in all groups appeared to be high and recovery curves in patients' groups were similar to those in control subjects. At intervals from 1 to 10 s, R1 recovery on the affected side in HFS patients showed significant enhancement, whereas they were normal in BSP and TS groups. The affected side in HFS patients also showed significant enhancement at the 10-s interval compared with the corresponding value on the unaffected side. R1 recovery on the unaffected side did not differ significantly from that of control subjects.

R2 recovery curves are shown in Figure 3, and the averaged data for each group in Table 2. At a 1-s interval, R2 recovery was significantly enhanced only in BSP patients, in whom it was also increased at intervals of 0.5-0.21 s. The TS group significantly differed from the control group at intervals of 0.5 and 0.3 s. The R2 recovery on the affected side in HFS patients was significantly enhanced at intervals from 0.5 to 0.21 s. In these patients, the R2 recovery on the affected side was also significantly enhanced at intervals of 0.3 and 0.21 s, compared with that of the unaffected side. This is shown in Figure 4. On the unaffected side only, the value at 0.21 s was enhanced although the curve from 0.21 to 0.5 s was positioned between that of the affected side and that of control subjects.

The results of R1 and R2 recovery indices are shown in Table 3. The upper limit of normal for R1 index was 126%. R1 index was abnormal in 6 patients with BSP (29%), in 6 patients with TS (32%), and in 5 patients with HFS (23%). The upper limit of normal for R2 index was 40%. One TS and 1 HFS patient were excluded because of lacking data. Indices were abnormal in 14 patients with BSP (67%, 5 with an abnormal R1 index), in 7 patients with TS (37%, 3 with an abnormal R1 index), in 11 patients with HFS on the affected side (50%, 4 with an abnormal R1 index), and in 4 patients with HFS on the unaffected side (20%). Three of the 4 patients with an abnormal R2 index on the unaffected side also had an abnormal index on the affected side.
Table 3. The results of R1 and R2 recovery indices in individual subjects.

<table>
<thead>
<tr>
<th>Group</th>
<th>Nos</th>
<th>R1 (%)</th>
<th>R2 (%)</th>
<th>R1 and R2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS</td>
<td>23</td>
<td>-</td>
<td>1 (4)</td>
<td>-</td>
</tr>
<tr>
<td>BSP</td>
<td>21</td>
<td>6 (29)</td>
<td>14 (67)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>TS</td>
<td>19</td>
<td>6 (30)</td>
<td>7 (37)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>HFS aff</td>
<td>22</td>
<td>5 (22)</td>
<td>11 (46)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>HFS unaff</td>
<td>20</td>
<td>-</td>
<td>4 (35)</td>
<td>-</td>
</tr>
</tbody>
</table>

See Table 2 for abbreviations. * Upper limit of normal for R1 index was 126%, and that for R2 index was 40%.

Figure 4. Peak amplitude R2 recovery curves at three times threshold ± standard error of mean.
No correlations were found between the R2 index and the duration or severity of symptoms, age, and response to treatment with botulinum or medication.

Discussion.

General principles of recording R1 and R2 recovery curves have been described by Kimura. However, technical aspects vary considerably among different studies. In this study, recordings and data calculations were fully computerized and blink reflexes were evoked under standard conditions, while responses with involuntary eyelid movements were rejected. Between successive trials, a rest period of at least 30 s was maintained. Often longer rests, up to several minutes, were necessary due to fast habituation of R2 and involuntary movements.

With these carefully controlled measuring conditions, our data revealed that recovery curves of peak amplitudes, recorded at three times R2 threshold intensity, are less variable than those of area measurements or those obtained at lower stimulation intensity.

The peak amplitude and area measurements of R1 and R2 responses after single stimulation showed no significant differences between the patients and controls, conforming to the results of Pauletti et al. Our results also confirm the findings of Auger and Esteban and Molina-Negro in patients with HFS, who also explicitly avoided stimulation during eyelid spasms. These results provide additional evidence that blink reflex circuits are functionally intact in patients with BSP, TS, and HFS.

R1 recovery curves were normal in all patients' groups at intervals shorter than 1 s. At larger intervals, the R1 recovery curve in the HFS group was enhanced. Valls-Solé and Tolosa found no significant difference in R1 recovery curves between HFS patients and controls. To our knowledge, the features of R1 recovery curves at intervals larger than 1 s have never been examined before.

R2 recovery curves were enhanced in all patients' groups. This was most evident in BSP patients at intervals of 1 s or shorter. In TS patients, values at intervals of 0.5 and 0.3 s showed enhancement. Our results are similar to those found by Berardelli et al in patients with BSP, and by Nakashima et al in TS patients. In HFS patients, R2 recovery curve was enhanced at intervals of 0.5 s or shorter on the affected side, which is in agreement with the results of Valls-Solé and Tolosa. We calculated the indices of R1 and R2 responses as the mean of the recovery values at 0.5-, 0.3-, and 0.21-s intervals, which enabled us to test individual patients.
The R2 recovery index was abnormal in two thirds of patients with BSP, in one third of patients with TS, in one half of patients with HFS on the affected side, and in one fifth with HFS on the unaffected side. Previous studies\textsuperscript{16,103,135,138} did not report on results in individual patients. The finding of a normal R2 recovery index in one third of patients with BSP was unexpected, because BSP affects the orbicularis oculi muscles, which participate in the blink reflex. BSP can begin unilaterally and may be asymmetrical.\textsuperscript{44} Although we recorded only unilaterally, we preferentially examined the most involved side or the side involved at the onset of the disease to prevent this problem. One possible explanation is that physiologically BSP is not a homogeneous disease entity and that probably different pathophysiological mechanisms are involved. Clinical and electrodiagnostic investigations are consistent with this assumption.\textsuperscript{45,46} Most HFS patients had abnormal R2 index on the affected side only, but some had abnormal R2 index bilaterally. This indicates bilateral involvement of the brainstem in at least some patients, as was also established by Valls-Solé and Tolosa.\textsuperscript{138}

No correlations were found between recovery index and clinical data such as patients' age, duration and severity of symptoms, and the response to treatment with, among others, the botulinum toxin. We were unable to confirm the correlation between duration of symptoms and abnormal R2 recovery in HFS patients, as reported by Valls-Solé and Tolosa.\textsuperscript{138}

In patients with Parkinson's disease, Kimura\textsuperscript{82} showed normal R1 recovery curves and enhanced R2 recovery and suggested that this may be due to hyperexcitability of the brainstem interneurons. The same recovery features have been reported in patients with BSP, TS, and HFS.\textsuperscript{16,135} In patients with HFS, however, enhanced R1 and R2 recovery curves would be expected because many authors favor hyperexcitability of the facial motoneurons as the cause of involuntary contractions.\textsuperscript{34,99} The fact that in all three groups those patients with an abnormal R2 index also had an abnormal R1 index indicates that this diagnostic test cannot be applied to distinguish between these disorders. We also assume that an abnormal R1 recovery does not necessarily point to an enhanced excitability of the facial motoneurons, but is probably also dependent on the state of excitability of the oligosynaptic pathway through which R1 response is relayed.

An abnormal R2 index in one third of patients with TS, without eyelid spasms, and a normal R2 index in some patients with BSP may indicate that there is no causal relationship between the state of excitability of the blink reflex circuits and the occurrence of involuntary discharges in the orbicularis oculi muscles.

Based on the results of the present study, we conclude that (i) R1 and R2 blink reflex amplitudes do not differ in the patients and controls; (ii) R2 peak amplitude recovery curves should be recorded at three times R2 threshold; and (iii) the fact that one third of patients with BSP had normal R2 recovery indices may indicate that different pathophysiological mechanisms are involved.