Level of consciousness as a conditioning factor of F wave generation in stroke patients

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Abstract

Objective: The current study aimed to investigate whether the level of consciousness influenced the F wave generation, as an independent factor.

Methods: Forty-three patients with acute stroke were divided according to their level of consciousness in two groups; to those with Glasgow scale (GCS) score 3–7 indicating coma (group I) and those with GCS score 8–15 (group II). A series of 40 electrical stimuli were delivered to the ulnar nerve bilaterally in order to obtain F waves. The following variables were estimated and then compared between groups: F persistence, F wave latency, amplitude and duration. All studies were performed within 3 days from the onset of the stroke symptoms.

Results: The main finding to emerge was the significantly reduced F wave persistence in the group of patients with low GCS score as opposed to patients allocated in the group with GCS score 8–15. This result is referred to F waves obtained from both the affected and unaffected limb. F wave minimum latency was also prolonged in the group with low GCS score, whilst the comparison of all other F wave variables revealed no significant differences between groups I and II. F wave persistence measurements did not differ between the affected and unaffected sides. Stroke location and type (ischemic or hemorrhagic) were not associated with alterations of F wave measurements.

Conclusions: Our results on stroke patients suggest that generation of F waves, expressed by the F wave persistence is associated with the level of consciousness.

Significance: F wave study may be useful as an objective measure in documenting the severity of consciousness impairment.

Keywords: Level of consciousness; Glasgow scale; Stroke; F waves

1. Introduction

F waves are late muscle responses elicited by backfiring of antidromically stimulated motor neurons. Their measurements are helpful in evaluating motor conduction along the entire length of the peripheral axons, including the most proximal segment (Kimura, 2001). F wave study has become part of the routine neurophysiological investigation of peripheral nerves (Fisher, 1992; Mersrati and Vecchierini, 2004; Panayiotopoulos and Chroni, 1996) and has been proven to be particularly useful in diagnosis of polyneuropathies. Furthermore, on research grounds mainly, changes of F wave parameters also have long been described in central nervous system (CNS) diseases such as Parkinson, ALS and stroke (Abbruzzese et al., 1985; de Carvalho et al., 2002; Fisher, 1992). Several studies have focused on F wave abnormalities recorded from limbs affected by upper motor neuron diseases during acute, but mainly chronic phases. Increased F wave amplitude, duration or frequency that have been observed in spasticity, were attributed to imbalance of central impulses in favor of excitatory resulting in enhanced anterior horn cells excitability (Eisen and Oodusote, 1979). In contrast, during the initial
phase of an acute cerebrovascular accident, reduced $F$ wave on the affected limbs has less often been demonstrated (Fierro et al., 1990; Fisher, 1992).

Although the results of focal brain deficits to the corresponding lower motor neurons were studied, the possible influence of $F$ waves by the general status of brain function has received little attention. This study aimed to investigate whether reduced level of consciousness, as a result of an acute cerebrovascular accident, could modify $F$ wave generation.

2. Patients and methods

2.1. Study design

This was a single-center, prospective study, which was conducted in accordance with the principles of the Declaration of Helsinki. The selection of the patients was initiated after approval of the study protocol by the Institutional Review Board of Patras Medical School. For overall enrolled patients, written informed consent for participation in the study was obtained either from the patient himself if she/he presented satisfactory alertness and cognitive function, or from a family member or a first degree relative.

2.2. Patients selection

Forty three patients, 32 males (74.4%) and 11 females (25.6%) with mean age 65.4±11.8 years (range 22–82), admitted at the Neurology Department of Patras University Hospital with a diagnosis of acute stroke, were included in the current study. On examination, all participants demonstrated either hemiparesis or hemiplegia, whilst none of them had either increased reflexes and tone or decreased activation of antigravity antagonist muscles on the contralateral, unaffected side. The motor performance of comatose patients was based on the motor response to stimuli, muscle tone, tendon reflexes and plantar responses. The side of the brain damage (right or left), the location (cerebral cortex, basal ganglia or brain stem) and the type of stroke (ischemic or hemorrhagic), were established from the clinical neurological examination performed on admission, using the Scandinavian Stroke Scale (Scandinavian Stroke Study Group, 1985) and the findings of the neuroimaging examinations (brain computerized tomography and/or magnetic resonance imaging). The level of consciousness of enrolled patients was assessed by Glasgow Coma Scale (Jennett and Teasdale, 1977). Patients were divided by cut point of eight in two groups: patients in comatose state (group I, GCS score from 3 to 7) and patients with normal, mild or moderate reduced level of consciousness (group II, GCS score from 8 to 15).

Patients with diabetes mellitus, alcohol abuse, positive family history of hereditary neurological diseases or other conditions related to neuropathy, were withdrawn from the study. Patients under mechanical ventilation or receiving sedative drugs and patients in which thrombolisis for acute stroke was performed, were also withdrawn from the study sample.

All $F$ wave studies were performed within 3 days from the onset of the stroke symptoms. All subjects were examined reclining on a couch with the arm in a supine position. Complete relaxation of the examined limb was ensured by audio feed-back and the skin temperature was maintained between 32 and 34 °C. The ulnar nerve was stimulated bilaterally at the wrist and the elicited compound muscle action potential (CMAP) was recorded with surface electrodes over abductor digiti minimi muscle. Forty consecutive supramaximal stimuli were then delivered to each nerve with a frequency of 1 Hz and the obtained $F$ waves were stored for subsequent analysis. Acquisition conditions included a filter setting of 2–10 kHz, a sweep speed of 10ms per division and an amplifier gain of 0.1–0.5 mV per division for the $F$ waves, and 0.5–5 mV for the CMAP.

The following $F$ waves variables were estimated: $F$ wave latency, amplitude (peak to peak), duration (from onset of deflection to return to the baseline) and for each nerve studied the minimum, average and maximum values were calculated. $F$ wave persistence that is the number of definable $F$ responses per 40 stimuli, expressed as a percentage, was also assessed. Only those $F$ waves with an amplitude of 40 μV and higher were measured. A sample of 40 stimuli was considered appropriate in order to explore the full potential of $F$ wave study (Chroni et al., 1994).

2.3. Statistical analysis

Descriptive statistics were generated for all variables. For each variable, the mean values of both groups were compared using Student’s $t$ test. For the amplitude values that were not normally distributed, the Mann–Whitney U non-parametric test was applied. For comparison of more than two groups, the one-way ANOVA test was used. All tests were two-sided and significance was set at $P<0.05$ level. Statistical analyses were performed using the SPSS for Windows (release 10.0; SPSS Inc., Chicago, IL).

3. Results

Clear recordings were obtained from all 43 patients, while three of them were studied twice. Twenty one (48.8%) of them suffered an ischemic stroke, and 22(51.2%) a hemorrhagic stroke. The location of the stroke was cerebral cortex in 16(37.2%), basal ganglia in 19(44.2%) and
brainstem in 8(18.6%). The demographic and clinical characteristics of the patients in each of the two groups recognized are described in Table 1.

Analysis was based on pooling of F-wave data from affected and unaffected side in a total of 46 person-studies or 92 nerves. CMAP (direct response) was present and its parameters were within normal limits in all studies. F wave persistence(%) was significantly lower (P = 0.0001) in patients with GCS score 3–7(33.4 ± 33.2) as opposed to patients with GCS score 8–15(68.5 ± 25.9). In group I, F waves were unobtainable bilaterally in four patients (two of them had a basal ganglia hemorrhagic lesion; one had a brainstem ischemic and the other had a cortical hemorrhagic lesion) and on the affected side in three patients (two of them had brainstem ischemic and one cortical hemorrhagic lesion). In group II, F waves were absent on the affected side in three patients (one had a basal ganglia ischemic, one had basal ganglia hemorrhagic lesion and another had cortical ischemic lesion), whereas none in this group had bilaterally absent F waves. Hence, a total of 10 patients had absent F waves on the affected side, whilst four of them had also unobtainable F waves on the unaffected side. Analysis of F wave measurements obtained from the remaining nerves where F wave were present, showed that F wave minimum latency was prolonged in group I compared to group II (P = 0.03). All other F wave variables did not differ significantly between groups (Table 2). When only the measurements from the affected side were analysed, F wave persistence (P < 0.0001) and F wave minimum latency (P < 0.04) were significantly different between groups I and II, whereas all other F wave parameters showed no such differences. Comparison of the F wave data, irrespective of the GCS group, between the affected and unaffected side, failed to demonstrate a significant difference (Table 3).

Data were also divided into groups according to the type and location of the stroke. None of the F wave parameters showed statistical significant result in these comparisons (P values for type groups > 0.14 and P values for location groups > 0.24).

Fig. 1 demonstrates the F wave persistence measurements in three patients who were twice studied. Patients no 1 and 2 had a hemorrhagic cortical stroke. When GCS decreased from seven to four and three respectively, F wave on the affected as well as the unaffected limbs disappeared. Patient no 3 had an ischemic cortical stroke. Improvement of GCS from eight to normal (15) was accompanied by considerable increase of F persistence bilaterally.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Group 1(GCS 3–7)</th>
<th>Group 2(GCS 8–15)</th>
</tr>
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<tbody>
<tr>
<td>No of patients</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.4 ± 11(41–80)</td>
<td>65.4 ± 13(22–82)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>12/5</td>
<td>18/8</td>
</tr>
<tr>
<td>Type of stroke (isc/hem)</td>
<td>9/8</td>
<td>12/14</td>
</tr>
<tr>
<td>Location (cortex/ b.ganglia/ brain stem)</td>
<td>5/7/5</td>
<td>3/9/14</td>
</tr>
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Table 2

<table>
<thead>
<tr>
<th></th>
<th>Group I GCS: 3–7</th>
<th>Group II GCS: 8–15</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Number of nerves</td>
<td>38</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>F persistence (%)</td>
<td>33.4 ± 33.2</td>
<td>68.5 ± 25.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>(0.93)</td>
<td>(0.100)</td>
<td></td>
</tr>
<tr>
<td>Duration (ms)</td>
<td>27</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Amplitude (µV)</td>
<td>Average 181 ± 127</td>
<td>173 ± 129</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>Min 86 ± 54</td>
<td>74 ± 42</td>
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<tr>
<td></td>
<td>Max 390 ± 354</td>
<td>382 ± 303</td>
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<td></td>
<td>(53–464)</td>
<td>(58–641)</td>
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<td>(40–30)</td>
<td>(50–200)</td>
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<td></td>
<td>(80–1500)</td>
<td>(90–1800)</td>
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<td>(2.1–9.8)</td>
<td>(3.0–8.7)</td>
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<td></td>
<td>(1.2–8.0)</td>
<td>(1.4–5.2)</td>
<td></td>
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<tr>
<td></td>
<td>(2.5–16.2)</td>
<td>(4.7–15.0)</td>
<td></td>
</tr>
</tbody>
</table>

For each value the mean ± SD(range) based on pool F wave data from affected and unaffected side, are given.

a Mann–Whitney U, instead of Student t test, was used.

For each value the mean ± SD are given.

4. Discussion

F wave has repeatedly served as a marker of motor neuron excitability, providing information for diverse central and peripheral nervous system diseases (Abbruzzese et al., 1985; Fisher et al., 1978; Mesrati and Vecchierini, 2004) and evaluates the effects of various drugs (Dueck et al., 2003; Zhou et al, 1998). The final level of motor neuron pool excitability constitutes the summation of multiple excitatory and inhibitory central influences. F wave study was suggested to be particularly useful for assessing motoneuron inhibition rather than excitability (Lin and Floeter, 2004).

Early after unilateral cerebral lesion F wave persistence, amplitude and duration was found to be decreased in the clinically affected limbs (Fisher et al., 1978; Mesrati and Vecchierini, 2004). These findings were associated with reduced muscle tone and attributed to decreased central excitability. The opposite state of motor system, i.e. spasticity in the context of a chronic upper motor neuron lesion, is accompanied by increased F wave persistence, mean and maximal amplitude and duration, which has been interpreted as disinhibition of central influences (Eisen and Odusote, 1979; Fisher, 1992; Uncini et al., 1990).

All the above was dealt with the direct effect of motor pathways on the corresponding lower motor neuron pool. In the current study, accurate measurements of motor performance and its relation with F wave data was not attempted since many patients were in deep coma. Instead, we sought to investigate a different aspect of F waves in a group of patients with unilateral deficit (hemiparesis). We were mainly interested in studying the F wave responsiveness in relation to the general functional state of the brain and specifically to the level of consciousness. Our main finding was the significant reduced F wave persistence in those patients with low GCS score, irrespective of the type, or location of the underlying lesion. Regarding only the nerves with absent F waves, it should be noted that six of the 43 patients had asymmetrically absent F waves in the affected side, while this did not apply to any of the patients on the unaffected side. It is interesting however that, when considering all nerves with either absent or reduced F wave persistence, the finding of low F wave persistence in group I patients was evident in both the affected and the unaffected limbs with no inter-side statistical differences. Moreover, four patients with GCS score below eight demonstrated absent F waves in the affected as well as the unaffected side despite normal direct responses. Other stroke characteristics, such as location and type, do not influence F wave responsiveness, supporting further the view that F wave persistence is influenced by the overall brain function.

With the exception of prolonged F wave minimum in the comatose patients (group I), all other parameters appeared to be unimpaired by GCS score. The latter implies that the level of consciousness affects F wave generation in an ‘all or none’ matter, without interfering in the firing properties of specific neuron sub-populations.

There is a possibility that in comatose patients, motor impairment of the unaffected side that could not be detected by the standard clinical examination, exists and could be responsible for the F wave abnormalities. Even if this is so, low F wave persistence indicates the severity and expansion of brain damage that would otherwise have remained obscure. However, the following pieces of evidence support the view of a direct link of level of consciousness to the F wave generation. The incidental observation of F wave suppression during a vasovagal attack of a healthy subject and their reappearance following recovery, draw our attention to the possible effect of consciousness on F wave generation (Chroni and Panayiotopoulos, 1996).

Several publications have focused on F wave study, conditioned by impaired alertness. F waves are decreased during sleep, especially in stage REM, a fact, which can be attributed to the influence of surpaspinal reticular formation on motor neuron pool excitability. Moreover, F wave min latency was longer during sleep than during wakefulness (Ichikawa and Yokota, 1994). It was found that intravenous anesthetic, propofol, and volatile anesthetic, isoflurane, reduced F wave amplitude and persistence with no change of CMAP measurements and the action of these drugs on the spinal cord was associated with anesthesia-induced immobility (Zhou et al., 1998; Dueck et al., 2003). Particularly, in the case of propofol, it has been proposed that it induces a suppression of motor neuron excitability in humans, producing a concentration-dependent reduction of F wave persistence (Kakinohana et al., 2002). In support to our findings, F-waves were not recorded from the frontalis muscles in 10 unconscious patients with cerebrovascular accident (Ishikawa et al., 2000). Along the same lines, in a
case of heat stroke, F waves remained absent despite normalization of other peripheral nerve parameters, implying the direct influence by central control (Bakshi and Maselli, 1998).

Experimental evidences on healthy subjects and patients, have documented that F wave persistence and amplitude are clearly influenced by motoneuron excitability, reflecting influences of descending inputs and/or spinal circuits (Fisher et al., 1978). Therefore, it is conceivable that comatose patients, in which muscle tone is usually reduced, may present F wave alterations. The effects of spinal segmental inputs on F wave generation cannot be excluded in the absence of deafferentation. However, it seems reasonable to assume that in our subjects, selected to exclude confounding conditions, supraspinal control is responsible for the observed F wave findings. The question raised now, is whether there is a causative relation between decreased level of consciousness and reduced F wave persistence or both events merely share a common pathophysiology. There is no adequate evidence to support either possibility. It is well known that reticular formation in the brainstem can influence directly or indirectly the lower motor neurons via reticulospinal pathways, thus modifying most forms of motor activity and tone (Carpenter and Sutin, 1983). On the other hand, reticular formation also controls the state of alertness and wakefulness through ascending inputs to cerebral cortex (Carpenter and Sutin, 1983). Bearing these in mind, one could postulate that either anatomical derangement (as occurred in patients with stroke), or functional derangement (as occurred in subjects under anesthesia), involving the region of brain stem reticular formation could be correlated with F wave abnormalities in comatose patients. The role of cerebral hemispheric lesions should also be considered. The patients studied were carefully selected to demonstrate hemiparesis or hemiplegia on only one side. However, the remote effects of an infarct in one hemisphere that can functionally impair the opposite intact hemisphere, a phenomenon known as diaschisis (Reggia, 2004), may produce bilateral F wave deficits.

Amongst various methods for assessing level of consciousness in acute stroke (Weir et al., 2003), the widely used GCS was adhered in the current setting, dividing patients (cut point of eight) to those in coma and those with either normal or mild, moderate reduced level of consciousness. This grouping was based on definition of coma that in our subjects, selected to exclude confounding conditions, supraspinal control is responsible for the observed F wave findings. The question raised now, is whether there is a causative relation between decreased level of consciousness and reduced F wave persistence or both events merely share a common pathophysiology. There is no adequate evidence to support either possibility. It is well known that reticular formation in the brainstem can influence directly or indirectly the lower motor neurons via reticulospinal pathways, thus modifying most forms of motor activity and tone (Carpenter and Sutin, 1983). On the other hand, reticular formation also controls the state of alertness and wakefulness through ascending inputs to cerebral cortex (Carpenter and Sutin, 1983). Bearing these in mind, one could postulate that either anatomical derangement (as occurred in patients with stroke), or functional derangement (as occurred in subjects under anesthesia), involving the region of brain stem reticular formation could be correlated with F wave abnormalities in comatose patients. The role of cerebral hemispheric lesions should also be considered. The patients studied were carefully selected to demonstrate hemiparesis or hemiplegia on only one side. However, the remote effects of an infarct in one hemisphere that can functionally impair the opposite intact hemisphere, a phenomenon known as diaschisis (Reggia, 2004), may produce bilateral F wave deficits.

An association of F wave persistence with GCS scores was revealed from reported data. To our knowledge this is the first study that brought out the innovative idea of a potential supplementary value of F waves in documenting the severity of impairment of consciousness. Further studies, possibly on patients with no motor deficits, are necessary to elucidate this clinically important issue.

References