Somatosensory evoked potentials as a measure of experimental cerebral ischemia

KATHLEEN L. MEYER, M.D., ROBERT J. DEMPSEY, M.D., MARK W. ROY, PH.D., AND DAVID L. DONALDSON

Department of Neurosurgery, University of Kentucky Medical Center, Lexington, Kentucky

Somatosensory evoked potentials (SEP's) reflect the integrity of the central neuronal pathway, and as such may be used to assess function that remains during a variety of cerebral insults. To evaluate the natural history and utility of SEP's during experimental cerebral ischemia and infarction, SEP's were measured in 17 adult cats at 24 hours and 1 hour prior to right middle cerebral artery (MCA) occlusion, and again immediately afterward and at either 6 hours (five cats) or 24 hours (six cats) post-occlusion. Before occlusion of the right MCA, the SEP's were identical in the right and left hemispheres. After occlusion, there was a significant slowing of the interpeak latency of the first positive peak (P1) in the right hemisphere (3.53 ± 0.6 msec before compared to 3.99 ± 0.6 msec after occlusion, p < 0.001). Maximal slowing in right hemisphere P1 latency was seen in those animals in which the stroke extended into the thalamus (4.38 ± 0.1 msec). This was significantly slower than left hemisphere values (3.92 ± 0.32 msec, p < 0.01). The ipsilateral cortical components of the SEP's, the second positive peak (P2), and the major negative deflection (MN) were slowed in all cats immediately after right MCA occlusion compared to preocclusion measurements (p < 0.001). Severe infarcts in the mid-superior and posterior ectosylvian gyri (including the somatosensory cortex) resulted in a greater slowing of the latency of MN compared to less severe infarcts in that region (20.6 ± 3.9 msec versus 16.4 ± 1.1 msec, p < 0.05). There was a precipitous decrease in the amplitude or voltage of the ipsilateral P2-MN complex immediately after occlusion (5.32 ± 0.4 uV before compared to 0.98 ± 0.3 uV after occlusion, p < 0.001).

Therefore, the central latencies and cortical amplitudes of the SEP's are sensitive experimental tools as indicators of the onset and extent of a cerebral ischemic insult.

KEY WORDS • somatosensory evoked potentials • cerebral infarction • cerebral ischemia • brain edema • middle cerebral artery • thalamus

EXPERIMENTAL cerebral ischemia alters central nervous system (CNS) function and leads to infarction. While most studies of ischemia rely on evaluation of the size and distribution of the resulting infarct, in this study we evaluated somatosensory evoked potentials (SEP's) as a means of measuring neurophysiological function in the remaining viable brain during ischemia.

The SEP peaks in man and animals are presumed to be generated by specific CNS structures.1,3,7,11 Evoked potential components that are consistently identifiable, and their presumed origins are: 1) an early small positive voltage deflection representing Erb's point (brachial plexus); 2) a later positive deflection (P1) thought to be generated by the thalamus; and 3) a substantial positive-negative complex (P2-MN) thought to originate from the somatosensory cortex. Amassian2 and Dong, et al.,7 have suggested that subsequent peaks (P3 and P4) arise in association cortex. Additional waves, especially before P2, are described but not universally recorded. Allison and Hume1 evaluated the origins of these components in man and normal cats, using similar placement of recording electrodes. They found remarkable likeness in the evoked potentials except for negative polarity of the initial cortical complex in man.

Somatosensory evoked potentials have been well characterized in normal cats.1,7,11 Changes in the electroencephalogram (EEG), cerebral blood flow, and cerebral brain water and electrolytes have been assessed in the cat model of stroke.9,10,14,16 However, evoked potential changes that occur following experimental stroke produced by middle cerebral artery (MCA) occlusion in cats have not been described. Systematic evaluation of these changes should expand the utility of this model in assessing the variable pattern of cerebral infarction and ischemia.

In this study, the SEP's were used to evaluate the degree of cerebral dysfunction after right MCA occlu-
TABLE 1

Right hemisphere infarct size at four brain levels *

<table>
<thead>
<tr>
<th>Brain Level</th>
<th>Distance From Frontal Pole (mm)</th>
<th>Infarct Size (%) At 6 Hrs</th>
<th>Infarct Size (%) At 24 Hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>posterior sigmoid gyrus (frontal)</td>
<td>0–5 mm</td>
<td>44.0 ± 13.4</td>
<td>43.0 ± 8.4</td>
</tr>
<tr>
<td>mid-suprasylvian gyrus (parietal)</td>
<td>5–10 mm</td>
<td>59.6 ± 13.4</td>
<td>54.2 ± 11.1</td>
</tr>
<tr>
<td>ectosylvian gyrus (temporal)</td>
<td>10–15 mm</td>
<td>62.8 ± 6.0</td>
<td>59.7 ± 12.6</td>
</tr>
<tr>
<td>posterior suprasylvian gyrus (occipital)</td>
<td>15–20 mm</td>
<td>56.4 ± 8.3</td>
<td>50.7 ± 9.3</td>
</tr>
</tbody>
</table>

* Infarct size is calculated as the percent of the right hemisphere not perfused. Values are means ± standard error of the means for five animals that survived 6 hours and for six animals that survived 24 hours.

sion in cats. The changes in SEP's were then correlated with the infarct size and edema resulting from the insult.

Materials and Methods

Seventeen adult cats of either sex, weighing an average of 2.6 kg, were used in these studies.

Somatosensory Evoked Potential Recordings

Prior to recording of SEP's, all animals were anesthetized with intramuscular ketamine (30 mg/kg). The dose was decreased after occlusion as the clinical condition warranted. The animals were placed on a warming blanket during SEP recording. Grass Type E2 platinum-iridium needle electrodes were used for SEP measurement.* Paired stimulating electrodes were placed over each distal median nerve proximal to the transverse carpal ligament. Recording needle electrodes were placed at each Erb's point and in the scalp overlying the primary sensory cortex bilaterally. The reference electrode was placed at the chin.

Square-wave stimuli (0.2-msec duration) were applied at a rate of 2 to 3/sec with a 1.6-msec pre-stimulus delay. Each median nerve was stimulated sequentially in an alternating fashion. Visible twitching of the forepaw determined the minimum stimulus intensity used. The evoked potentials resulting from 1000 to 2000 median nerve stimulations were measured at the recording electrodes and were averaged with a four-channel Nicolet LS 12/70 signal averager.† Evoked potentials were recorded at each Erb's point and at both cerebral hemispheres.

The time from stimulus to Erb's point, the time from stimulus to each major reproducible positive voltage deflection (P1–4), and the major negative voltage deflec-

* Grass Type E2 platinum-iridium needle electrodes manufactured by Grass Instrument Co., 101 Old Colony Ave., Quincy, Massachusetts.
† Four-channel Nicolet LS 12/70 signal averager manufactured by Nicolet Instrument Corp., 5225 Verona Road, Madison, Wisconsin.

**FIG. 1. Somatosensory evoked potentials (SEP's) recorded at the primary sensory cortex after median nerve stimulation in the normal cat. Stimulation is given at time zero, and the SEP's are recorded over a 51.2-msec interval. Times listed on the abscissa are the latencies between the stimulus and the individual peak. Interpeak latencies are the differences between the Erb's point latency (1.7 msec) and the absolute peak latencies.

MCA Occlusion Technique

For MCA occlusion, all animals were anesthetized with intravenous sodium pentobarbital (6.5 mg/kg) and were mechanically ventilated. Pancuronium bromide (0.2 to 0.4 mg, intravenously) and atropine sulfate (0.4 mg, intramuscularly) were administered preoperatively. The animals were hydrated perioperatively with intravenous lactated Ringer's solution (200 to 250 cc).

The right eye and orbital contents were excised. With the Zeiss OPMI-1 operating microscope‡ and a high-speed drill, a small craniectomy was made to enlarge the optic foramen. The proximal right MCA was exposed in the Sylvian fissure, and was then coagulated and transected proximal to the first lenticulostriate artery. Surgicel was placed over the exposed dural opening and the orbit was filled with methyl methacrylate.

‡ Zeiss operating microscope, Model OPMI-1, manufactured by Carl Zeiss, Inc., 1 Zeiss Dr., Thornwood, New York.
Evoked potentials in cerebral ischemia

Determination of Infarct Size

After SEP studies at 6 or 24 hours post-occlusion, all animals underwent intracardiac injection of india ink, after which they were immediately sacrificed with saturated KCl. The brain was removed at once and cut into four 5-mm coronal sections, from the frontal pole to the mid-occipital lobe (the post-suprasylvian gyri) (see Table 1). Photographs of each brain section were examined planimetrically. The cross-sectional area of the right hemisphere and of the infarct was determined for each section. The infarct size was then expressed as a percentage of the right hemisphere area.

Cerebral Edema Measurements

Immediately after sectioning of the brain, 1-cu mm samples were taken bilaterally from the medial frontal gray matter in the anterior cerebral artery distribution (the posterior sigmoid and anterior lateral gyri), the lateral parietal white and gray matter in the boundary area between the anterior cerebral artery and the MCA (the mid-suprasylvian gyri), and the lateral temporal white and gray matter in the MCA distribution (the posterior Sylvian and posterior ectosylvian gyri (see Table 2). A variable density kerosene-bromobenzene liquid gradient column was prepared as described by Marmarou, et al., 12,13 to determine brain-tissue specific gravity. Percent brain water content was then calculated for white and gray matter samples, presuming non-protein edema. 13

Data Analysis

A paired t-test was used to evaluate the effect of MCA occlusion on SEP's and edema formation. Significance was accepted at p < 0.05.

Results

Pre-Occlusion SEP's

Four positive peaks and one negative evoked potential peak were consistently noted before occlusion (Fig. 1). In the right hemisphere, the first positive deflection (P1) occurred 3.53 ± 0.06 msec and the second positive deflection (P2) 6.25 ± 0.08 msec after the Erb's complex. The major negative deflection (MN) was recorded at 9.10 ± 0.12 msec after the Erb's point potential. The third (P3) and fourth (P4) positive deflections occurred at 13.3 ± 0.76 msec and 23.6 ± 0.30 msec, respectively, after the Erb's complex. The peak-to-peak amplitude of the major positive-negative voltage complex (P2-MN) was 5.32 ± 0.44 μV.

Prior to MCA occlusion, there was no significant difference between hemispheres in the interpeak latencies or in the P2-MN interpeak amplitude. The SEP latencies did not change over time prior to right MCA occlusion. There was no significant difference between the interpeak latencies recorded at 24 hours and 1 hour prior to occlusion (Fig. 2).

Infarction

After right MCA occlusion, the 17 animals were observed for 6 hours (six cats) or 24 hours (11 cats). Five of the six animals in the first group survived 6 hours (16.7% mortality). Only six of the 11 animals in the second group survived the entire 24-hour period (45.5% mortality). Prior to sacrifice, the overall mortality rate was 35%.

The infarct size (percent of right hemispheric area not stained with ink on the coronal sections) increased progressively from anterior to posterior (Table 1). Thus, no stain was seen in 43.5% ± 7.0% of the most anterior section (the first 5-mm section) or in 56.9% ± 7.8% of the second section (5 to 10 mm posterior to the frontal pole). Infarct size was maximal (61.3% ± 6.2%) in the third slice through the posterior Sylvian and posterior ectosylvian gyri, including the somatosensory cortex, 10 to 15 mm posterior to the frontal pole (Fig. 3). The

---

§ Polar planimeter manufactured by Chicago Steel Tape, Chicago Heights, Illinois.
mean infarct size was decreased slightly in the fourth brain section through the posterior suprasylvian gyrus, 15 to 20 mm posterior to the frontal pole (53.3% ± 5.6%). There was no significant difference in infarct size at 6 or 24 hours in any of the sections. The infarct involved the posterior ectosylvian gyrus in all cats. The mid-ectosylvian and mid-suprasylvian gyri were involved to a lesser degree. The infarct extended deep to involve the thalamus in three cats.

Ischemic edema (brain water content) was greater in the right hemisphere than in the left for each section (Table 2). It was maximal in the right ectosylvian gyrus gray matter at both 6 hours (88.0% ± 1.2% H2O) and 24 hours (87.5% ± 0.7% H2O) following right MCA occlusion, and was significantly elevated at both times as compared to the opposite hemisphere (p < 0.001). A significant gradient of edema within the right hemisphere similar to that gradient seen with the size of infarct was also noted (p < 0.05). The least amount of edema was noted in the right posterior sigmoid gyrus gray matter (86.6% ± 1.4% H2O at 6 hours, and 84.1% ± 1.2% H2O at 24 hours). An intermediate increase in water content was noted in the right mid-suprasylvian gyrus gray matter at 6 hours (87.8% ± 2.4% H2O) and to a lesser extent at 24 hours (85.3% ± 1.5% H2O).

White matter edema was also maximal in the right posterior ectosylvian gyrus at 6 hours (79.9% ± 1.4% H2O) and 24 hours (77.5% ± 0.8% H2O). Less ischemic edema was seen in the right mid-suprasylvian gyrus white matter at 6 hours (77.8% ± 0.7% H2O) and at 24 hours (74.4% ± 2.1% H2O).

The ischemic area and resulting edema were therefore maximal in the ipsilateral posterior ectosylvian gyrus in both the white and gray matter. The ipsilateral mid-suprasylvian gyrus was an intermediate or boundary zone of ischemia and edema affecting cortex greater than white matter. The right posterior sigmoid gyrus and the entire left hemisphere, representing areas of separate vascular supply, were relatively unaffected by right MCA occlusion.

### Post-Occlusion SEP's

**Right Hemisphere Recordings.** Immediately after occlusion of the right MCA, all 17 cats demonstrated slowing of the interpeak latency on the right hemisphere recordings (Fig. 2). The least effect was noted in the Erb’s point-P1 latency (increased from 3.53 ± 0.06 msec to 3.99 ± 0.11 msec, p < 0.001). However, this effect was greatest if the infarction included the right thalamus (Table 3). Slowing of the interpeak latency was most marked in the Erb’s point-P2 latency (increased from 6.25 ± 0.08 msec to 12.66 ± 0.71 msec, p < 0.001) and the Erb’s point-MN latency (increased from 9.10 ± 0.12 msec to 17.6 ± 1.3 msec, p < 0.001). The animals with infarcts involving more than 70% of the posterior suprasylvian and posterior ectosylvian gyri (including the somatosensory cortex) had a significantly slower post-occlusion Erb’s point-MN latency than animals with a smaller area of infarction (20.6 ± 3.9 msec versus 16.4 ± 1.1 msec, p < 0.05). Neither P3 nor P4 could be identified at this time.

At 6 hours after MCA occlusion, the interpeak latency showed evidence of improvement (Fig. 2) in the Erb’s point-P2 (decreased to 9.77 ± 1.1 from 12.66 ± 0.71, p < 0.001) and Erb’s point-MN components (decreased to 14.7 ± 2.7 from 17.6 ± 1.3 msec, p < 0.05) but deteriorated slightly in the Erb’s point-P1 component (slowed to 4.63 ± 0.26 msec, p < 0.01). Again, peaks P3 and P4 could not be identified.

Twenty-four hours after right MCA occlusion there was continued slowing of the Erb’s point-P1 component (increased to 6.23 ± 1.24 msec). This latency was significantly slower than immediately post-occlusion

### TABLE 2

Focal ischemic edema in various regions of the brain*

<table>
<thead>
<tr>
<th>Brain Level</th>
<th>At 6 Hrs</th>
<th>At 24 Hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rt Hemi-</td>
<td>Lt Hemi-</td>
</tr>
<tr>
<td></td>
<td>sphere</td>
<td>sphere</td>
</tr>
<tr>
<td>posterior sigmoid gyrus</td>
<td>86.6 ± 1.4</td>
<td>85.6 ± 2.4</td>
</tr>
<tr>
<td>mid-suprasylvian gyrus</td>
<td>87.8 ± 1.5</td>
<td>82.8 ± 0.8</td>
</tr>
<tr>
<td>posterior ectosylvian gyrus</td>
<td>88.0 ± 1.2</td>
<td>83.7 ± 1.1</td>
</tr>
<tr>
<td>white matter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mid-suprasylvian gyrus</td>
<td>77.8 ± 0.7</td>
<td>77.7 ± 2.1</td>
</tr>
<tr>
<td>posterior ectosylvian gyrus</td>
<td>79.9 ± 1.4</td>
<td>77.6 ± 1.7</td>
</tr>
</tbody>
</table>

* Values are means ± standard error of the means for five animals that survived 6 hours and for six animals that survived 24 hours.
Evoked potentials in cerebral ischemia

TABLE 3
Erb's point-P1 latencies in the right hemisphere*

<table>
<thead>
<tr>
<th>Time of Recording</th>
<th>No. of Cats</th>
<th>Latency (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>before stroke</td>
<td>17</td>
<td>3.53 ± 0.06</td>
</tr>
<tr>
<td>immediately after stroke involving the thalamus</td>
<td>3</td>
<td>4.38 ± 0.1</td>
</tr>
<tr>
<td>immediately after stroke in all other animals</td>
<td>14</td>
<td>3.89 ± 0.13</td>
</tr>
</tbody>
</table>

* Values are means ± standard error of the means.

(p < 0.01). The latencies of the Erb's point-P2 (increased to 14.07 ± 1.9 msec) and Erb's point-MN components (increased to 16.4 ± 2.01 msec) approximated those seen immediately post-occlusion. There was no significant difference between the Erb's point-P2 and Erb's point-MN latencies immediately after occlusion and at 24 hours after occlusion (Fig. 2).

The peak-to-peak amplitude of the right hemisphere P2-MN component was measured immediately post-occlusion (Fig. 4). There was a significant decrease to 0.98 ± 0.27 µV, or 18.4% of the pre-occlusion P2-MN amplitude (p < 0.001). Six hours post-occlusion there was a further decrease in amplitude to 0.29 ± 0.09 µV, or 5.5% of the pre-occlusion value. The P2-MN amplitude remained depressed at 24 hours (0.49 ± 0.24 µV; 8.6% of pre-occlusion amplitude).

Light Hemisphere Recordings. The left hemisphere interpeak latencies and P2-MN interpeak amplitude were also measured immediately and 6 hours or 24 hours after right MCA occlusion (Figs. 2 and 4). There was no significant change in the left hemisphere Erb's point-P2 or the Erb's point-MN latencies either before or after right MCA occlusion for the entirety of the observation period. The amplitude of the P2-MN complex recorded in the left hemisphere increased to 6.57 ± 0.67 µV after contralateral MCA occlusion, or to 125% of the pre-occlusion value. This increase in amplitude was unchanged at 6 hours (6.54 ± 1.51 µV, or 124.6% of the pre-occlusion level). There was a further increase in amplitude at 24 hours (to 8.33 ± 1.63 µV), significantly larger (158%) than the pre-occlusion amplitude (p < 0.05).

Left Versus Right Hemisphere Recordings. During the entire experiment there was a significant difference between the Erb's point-P2 and Erb's point-MN latencies as recorded on the left compared to those recorded on the right (p < 0.05). Unlike that of the cortical components P2 and MN, the latency of the left hemisphere Erb's point-P1 component increased for the first 6 hours after stroke in parallel with the right Erb's point-P1 latency (Fig. 2), and had the same latency as the right. This relationship was not present in animals in which the area of infarction involved the right thalamus (Table 3). The right Erb's point-P1 latency was then significantly longer than the left hemisphere Erb's point-P1 latency immediately after right MCA occlusion (p < 0.01). The amplitude of the P2-MN complex increased on the left after the contralateral MCA occlusion, and was significantly different from the amplitude measured in the right hemisphere after occlusion (p < 0.001).

Discussion

Somatosensory evoked potentials were characterized in this study by interpeak latencies, since limb length and extremity temperature can affect the conduction time of an electrical impulse after peripheral nerve stimulation. The interpeak latencies we measured in our animals corresponded to those described by others.17 Erb's point (the brachial plexus) was revealed to be similar to P10 in man. The P1 component, with a latency of 3.5 ± 0.06 msec in the cat, correlated with the P15,16 (thalamic) component described in man. The P2 component had a latency of 6.25 ± 0.08 msec in the cat, and was comparable to N20, the first cortical peak observed in man, but with opposite polarity.1

After right MCA occlusion, the Erb's point-P1 latency increased bilaterally in all cats immediately post-occlusion and 6 hours after occlusion. In three cats, the area of infarction extended deep into the thalamus. In these animals the ipsilateral P1 component, measured immediately after occlusion, occurred significantly later...
than in cats with a more superficial infarction (p < 0.001) (Table 3). In these animals with thalamic infarcts, the right hemisphere P1 latency was also significantly different from the P1 latency recorded on the left (p < 0.01). This difference was not noted in the animals with more superficial infarcts. This prolongation of the ipsilateral Erb’s point-P1 interpeak latency in cats with deep thalamic infarcts, which supports the hypothesis of thalamic generation of P1,6,7,11 is useful for defining the extent of an infarct.

The right hemisphere Erb’s point-P2 and Erb’s point-MN interpeak latencies demonstrated the greatest slowing after ipsilateral MCA occlusion. Similar slowing was not demonstrable in the same latencies recorded from the left hemisphere. In cats with primarily cortical infarcts, a delay in the generation of the P2-MN complex was seen. The animals with larger infarcts involving more than 70% of the hemisphere at the level of the ectosylvian gyrus had an even greater slowing of the ipsilateral Erb’s point-MN interpeak latency 1 hour post-occlusion as compared to animals with a smaller infarct size (p < 0.05). Slowing of the interpeak latency to these cortical peaks consistently indicated the onset of ischemia. No correlation was demonstrated between the interpeak latencies and the degree of edema.

The right hemisphere P2-MN amplitude decreased in all cats immediately after MCA occlusion. Branston, et al.,4 described a significant correlation between the depression of the evoked potential amplitude and decreasing local cerebral blood flow. Disappearance of the evoked potentials occurred with a decrease in flow below a critical level. Hossmann and Schuier10 demonstrated a 60% decrease in EEG amplitude within seconds of MCA occlusion. As in their study, no significant improvement in the P2-MN amplitude was noted in our animals in the 24-hour period after MCA occlusion.

Meldrum and Brierley14 studied the effect of profound hypotension on SEP’s. Similarities exist between their model and cats with permanent occlusion of the MCA. In their study, severe hypotension was associated with a decreased amplitude and prolonged latency of the cortical signal. Increasing severity of hypotension correlated with increasing SEP abnormality and with more severe metabolic derangements. Thus, both our present study and that of Meldrum and Brierley demonstrate the sensitivity of evoked potentials to changes in cerebral perfusion.

The amplitude of the P2-MN complex was significantly increased in the left hemisphere immediately after the onset of right hemisphere ischemia. This amplitude increase in the contralateral hemisphere may have been due to the elimination of inhibition from right hemisphere association fibers. Hossmann and Schuier10 demonstrated similar increases in the EEG intensity after permanent MCA occlusion.

Oclusion of the right MCA resulted in an infarction that varied in size between animals. The area of infarc-

Conclusions

Somatosensory evoked potentials appear to be a valuable tool in the study of experimental ischemia. Loss of the P2-MN amplitude is a sensitive measure of the onset of ischemia. Changes in the interpeak latencies with experimental stroke correlate with the size and location of the infarction. Monitoring of SEP’s allows assessment of neurophysiological functioning during the period of ischemia and extends the ability to study stroke beyond simple measurement of the size of an infarction.

References


Evoked potentials in cerebral ischemia


Manuscript received January 16, 1984.
Accepted in final form August 16, 1984.
Address reprint requests to: Kathleen L. Meyer, M.D., Department of Neurosurgery, University of Kentucky Medical Center, 800 Rose Street, Lexington, Kentucky 40536.