Correlation Between Somatosensory Evoked Potentials and Neuronal Ischemic Changes Following Middle Cerebral Artery Occlusion


SUMMARY In an attempt to determine the usefulness of evoked potentials as a measure of focal cerebral ischemia, we examined somatosensory evoked potentials (SEP’s) and morphological neuronal changes in cats following unilateral middle cerebral artery (MCA) occlusion. Fifteen adult cats underwent transorbital occlusion of the MCA under halothane anesthesia. In seven cats the ipsilateral SEP’s were abolished after middle cerebral artery occlusion, and did not show any recovery after 6 hours. The same seven cats showed the greatest area of moderate and severe ischemic neuronal changes, ranging from 21 to 64% (mean 39 ± 14%) of the total ipsilateral cortical area. The remaining eight cats showed a complete flattening or decreased amplitude of the SEP after occlusion, but demonstrated a considerable recovery in the amplitude of the primary cortical potential during the six hours of the study. All these cats had ischemic areas of less than 15% (mean 9 ± 3%) of the total ipsilateral cortex. These results demonstrate that the disappearance of the SEP and their failure to recover correlate with the extent and degree of histological cerebral ischemia.

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SOMATOSENSORY evoked potentials (SEP’s) are commonly employed to monitor cerebral and spinal cord function in patients.1 Symon and his colleagues have utilized SEP’s as a measure of focal cerebral ischemia in primates and have demonstrated a good correlation between abolition of the SEP and reduction in local cerebral blood flow.2-4 Recently, SEP’s have been applied to canine and feline models to study cerebral ischemia.5,6 In an attempt to explore the relationship between evoked potentials and histological focal cerebral ischemia, we examined SEP’s and ischemic neuronal changes in cats following unilateral middle cerebral artery occlusion.

Material and Methods

Fifteen adult cats (mean weight 3.2 kg) were studied. The anesthetic technique and method of SEP recording were identical during implantation of the occlusive device and the acute experiment.

Anesthetic Technique

Each animal was sedated with ketamine HCl (30 mg/kg intraperitoneally) and atropine sulphate (0.2 mg intraperitoneally), intubated, paralyzed with gallamine triethiodide (0.3 mg/kg) and artificially ventilated with air and oxygen (FIO2 0.6). Anesthesia was maintained with halothane (0.75-1.25%) adjusted to keep the blood pressure constant at approximately 120/80. A cephalic venous catheter was inserted and 0.9% saline infused at 4 ml/hr. A femoral arterial cut-down catheter was placed. Body temperature was measured with a rectal probe and kept near 37.5°C with a warming blanket. A capnograph was used to continuously monitor end-expired CO2 which was kept between 30-35 mm Hg. Arterial blood gases were drawn to check the adequacy of oxygenation, confirm the accuracy of the end-tidal CO2 monitor, and measure pH. Base deficit was corrected when necessary with intravenous sodium bicarbonate (1 mEq for each 5 mEq/l base deficit).

Implantation of Microtourniquet Occlusive Device

The head was immobilized in the sphinx position using skull pins. The left proximal middle cerebral artery was exposed via the supero-medial transorbital approach and the microtourniquet placed around the artery as previously described.7 The tourniquet was not tightened. Bilateral scalp SEP’s were recorded before and after implantation to verify that the surgical procedure did not affect the evoked potentials. Following tourniquet implantation, the animals were observed during the one week recovery period and no neurologic deficits were noted.

Somatosensory Evoked Potential Recording

Paired stimulating needle electrodes were placed over the median nerve proximal to the transverse carpal ligament. Scalp recording electrodes were positioned on the coronal suture one centimeter lateral to the midline. The reference electrode was placed on the glabella. Square wave stimuli of 0.2 msec duration and 10 mamps were delivered at 4.1/sec to each median nerve while evoked potentials were recorded from the contralateral scalp. Visible twitching of the appropriate paw was observed in all cases before giving the gallamine. The SEP’s were recorded with a Nicolet CA1000 Signal Averager. The band pass filter was set between 5-3000 Hz, recording duration of 20 msec and sensitivity of 50 microvolts. Two hundred and fifty-six responses were averaged and stored on a floppy disc for subsequent analysis. To ensure reproduc-
ibility, two separately averaged SEP's from each hemisphere were made during each data collection period.

Latencies of the major positive (P) and negative (N) cortical deflections were determined. The amplitude of the primary cortical potential was measured from the peak of the major positive deflection to the trough of the major negative deflection (fig. 1). For purposes of data analysis the amplitude of the post-occlusion cortical potential was also expressed as a percentage of the pre-occlusion value.

Acute Experiment

One week following implantation of the microtourniquet each cat was again anesthetized as outlined above. The tourniquet was exposed and baseline SEP's recorded. Some cats received a single intravenous bolus of lidocaine (5.0 mg/kg) fifteen minutes before occlusion as part of a study whose results will be reported separately. Then the left middle cerebral artery was occluded by tightening the tourniquet. SEP's were recorded every five minutes after occlusion for 30 minutes and then at 30 minute intervals over the next 5½ hours. Halothane anesthesia was maintained over this entire period.

Perfusion-fixation

Six hours after middle cerebral artery occlusion and without releasing the tourniquet, each animal was euthanized with pentobarbital (20 mg/kg). Perfusion was performed through a left ventriculostomy using 500 ml of isotonic saline followed by 500 ml of 10% phosphate buffered formalin as outlined previously. The brains were fixed in situ for a minimum of one week. Then they were removed and immersed in formalin for one to three months before processing.

Histological Examination of the Brains

An eight micron coronal section 3 mm posterior to the temporal lobe tip, through the optic chiasm was processed and stained with Hematoxylin and Eosin. This section includes part of the somatosensory cortex. Photographic prints were made of each histological slide. Without knowledge of the post-occlusion SEP's, the left hemisphere was microscopically examined. Cortex and subcortical grey matter (basal ganglia, thalamus, hypothalamus) were classified according to the severity of ischemic neuronal alterations as previously described: normal, Grade 1, Grade 2, or Grade 3. The observations were delineated on the corresponding photograph and the percentage area of each ischemic grade was determined separately for cortical and subcortical grey matter using an HP9815A calculator and HP9864A digitizer.

Statistical Analysis

Statistical analysis was performed using an unpaired t-test or linear regression where appropriate. A p < 0.05 was regarded as statistically significant.

Results

Blood pressure, temperature and end-tidal CO₂ remained constant during the entire experimental period (blood pressure 110–130/60–90, temperature 36.5–38.5, end-tidal CO₂ 31–33). PaO₂ was greater than 200 mm Hg and an adequate depth of anesthesia was consistently maintained with inspired halothane concentrations of 0.75–1.25%.

Pre-occlusion SEP's

There were no significant differences in latency or amplitude of the left or right hemisphere SEP's before tourniquet implantation compared with the post-implantation values. During the acute experiment, the SEP's prior to arterial occlusion were similar to those recorded during the implantation procedure. Figure 1 shows examples of left hemisphere SEP's recorded before middle cerebral artery occlusion. A cortical potential with a major positive (P) and negative (N) deflection was always present. Before arterial occlusion, the left hemisphere cortical potential had a latency of 9.8 ± 1.0 milliseconds (P wave) and amplitude of 8.8 ± 4.1 microvolts, while the right hemisphere cortical potential showed a latency of 10.0 ± 1.0 milliseconds (P wave) and an amplitude of 10.0 ± 4.1 microvolts. The latencies and amplitudes are displayed in table 1. Other smaller far-field positive potentials usually preceded the major cortical potential (fig. 1) but these were not consistently observed in all cats.

Figure 1. Examples of left hemisphere somatosensory evoked potentials in 2 cats. In animal A the SEP was abolished within 10 minutes following occlusion and showed no subsequent recovery. In animal B the SEP disappeared within 10 minutes following occlusion but demonstrated recovery. P represents the major positive cortical deflection; N represents the major negative cortical deflection.
### Table 1  Somatosensory Evoked Potentials

<table>
<thead>
<tr>
<th></th>
<th>Pre Occlusion (n = 15)</th>
<th>Post Occlusion (n = 8)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Latency (msec) P</td>
<td>9.8±1.0</td>
<td>10.0±1.0</td>
</tr>
<tr>
<td>Latency (msec) N</td>
<td>13.6±1.1</td>
<td>14.1±1.5</td>
</tr>
<tr>
<td>Amplitude (µV)†</td>
<td>8.8±4.1</td>
<td>10.0±4.1</td>
</tr>
</tbody>
</table>

*Data from animals in whom SEP's were not abolished or returned after occlusion.
†Measured from P peak to N trough.
Mean ± S.D.

#### Post-occlusion SEP's

After left middle cerebral artery occlusion two general patterns of SEP's were observed (fig. 1). In seven cats the left hemisphere SEP was abolished completely within ten minutes of occlusion and showed no recovery over the subsequent six hour study period (fig. 1A). The SEP disappeared by five minutes in six cats and by ten minutes in one. In eight other cats the ipsilateral SEP was reduced in amplitude (3 cats) or abolished completely (5 cats) after left middle cerebral artery occlusion but demonstrated recovery over the six hours of study (fig. 1B). The post-occlusion SEP amplitudes at the termination of the experiment varied from 25–102% of the pre-occlusion values. In four of the cats the maximal recovery occurred before six hours post-occlusion, while in the other four animals the peak was maximal at the termination of the study.

When recovery of the SEP occurred, the latencies for P (9.1 ± 0.6 msec) and N (12.6 ± 1.0 msec) cortical deflections were not significantly different from the latencies of the pre-occlusion SEP's (see table 1). The latencies of the contralateral (right) cortical SEP did not change significantly after left middle cerebral artery occlusion (P deflection 9.1 ± 0.8 msec, N deflection 12.8 ± 1.2 msec). However, the amplitude of the contralateral cortical potentials decreased over the course of the experiment from 10.0 ± 4.1 µV to 5.7 ± 3.1 µV.

#### Ischemic Neuronal Changes and Correlation with SEP's

Ischemic neuronal alterations were found in the left cortex of all cats, primarily in the ectosylvian, suprasylvian, and sylvian gyri with relative sparing of the marginal gyrus. However, the area of ischemic changes and severity of ischemia varied considerably. The total ischemic area (Grades 1, 2 and 3) ranged between 23–85% of the entire cortical area. The ischemic changes in the subcortical grey matter were much less extensive in area and severity compared with cortical changes. Subcortical ischemia (Grades 1, 2, and 3) ranged from 1.9–4.3% of the total subcortical grey area.

An association was found between the post-occlusion ipsilateral SEP's and cortical histological ischemia. The seven cats with no recovery of cortical SEP had ischemic neuronal changes (Grades 1, 2, and 3) in a mean of 73% of the cortex, with a range of 60–85%. In contrast, the eight animals with some recovery in SEP amplitude had only a mean area of ischemia of 34% with a range from 23–60% of the total cortical area (fig. 2). The difference in ischemic cortical area between these groups was statistically significant (p < 0.001). When the area of moderate-severe (Grade 2 + 3) ischemic change only was plotted against post-occlusion cortical SEP's a more striking correlation was noted (fig. 3). The group of cats with no recovery of SEP showed 39 ± 14% (mean ± S.D.) (range 21–64%) Grade 2 + 3 cortical ischemia while the group with SEP recovery had a 9 ± 3% area of cortical ischemia (range 4–14%). There was no overlap between groups. The difference in moderate–severe ischemia between cats with recovery of SEP versus no recovery was statistically significant (p < 0.001).

Among the cats showing recovery of cortical SEP, neither six hour post-occlusion SEP amplitude nor maximal post-occlusion SEP amplitude correlated with the area of Grade 2 + 3 cortical ischemia (p > 0.10). There was no correlation between recovery of SEP and subcortical grey ischemic changes.

#### Discussion

Previous studies have used various histological criteria as measures of focal cerebral ischemia. These include light microscopic or electron microscopic neuronal alterations,9,11-16 nonstaining with India ink

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**Figure 2.** The relationship between left hemisphere ischemic neuronal changes and recovery of somatosensory evoked potential. Grade 0 = normal. Grades 1, 2 and 3 = mild, moderate and severe ischemia respectively.
or leakage of intravascular vital dyes and histological techniques. Correlations have been demonstrated between histological changes and decreased regional cerebral blood flow with histological infarction occurring at flows less than 10-12 ml/100 gm/min. Neurological deficits have also been correlated with morphological ischemia after middle cerebral artery occlusion.

SEP's have been utilized to monitor focal cerebral ischemia in several species. Experimental studies have shown that the SEP is abolished when local cortical blood flow drops below 15-16 ml/100 gm/min. However, there has been little effort to directly correlate a change in SEP with histological evidence of ischemia. In one study, Meyer and her colleagues demonstrated that cats with severe infarcts (>70%) in the mid suprasylvian and posterior ectosylvian gyri had significantly longer latencies of the major negative cortical deflection compared with cats having smaller infarcts in the same region. Furthermore, extension of infarct into the thalamus was associated with prolongation of the latency of an early far-field potential (P1 component). However, the extent of the ischemia was not graded histologically and the size of infarct was equated with the area that was not perfused with India ink infused at the time of sacrifice.

The present study shows that persistent absence of the SEP six hours after middle cerebral artery occlusion predicts a substantial area of moderate-severe (Grades 2 + 3) ischemia comprising 21-64% of the ipsilateral cortex at a coronal level which includes the somatosensory region. The partial or complete recovery of SEP after arterial occlusion does not necessarily imply that this cortical peak (PN) is generated over a wide cortical field. It is possible that extensive regions of infarct or severe ischemia may increase impedance and interfere with volume conduction of a more focally generated potential.

In the group of cats with measureable SEP's after arterial occlusion, we did not find a correlation between amplitude or latency of the cortical SEP and cortical ischemic changes. This may be due to the relatively small sample size or the variability in the SEP over time in this group. Alternatively, the cortical SEP's may not be a sensitive measure of small areas of infarction.

The progressive reduction in amplitude of the SEP of the contralateral hemisphere is of interest. This did not occur during the three to four hours of anesthesia and operation for the implantation. We do not therefore think that anesthesia per se or decay in the animal preparation were factors. Gross cerebral edema, mid-
line shift or herniation were not noted when the brains were carefully removed after in situ fixation suggesting that gross contralateral ischemia was not a factor. A more likely explanation is diaschisis. This is the depression of function in remote, often transhemispheric, areas of the brain after a focal neurological injury and has been described in this cat model, in other animal models and in humans. 29

SEP’s in the cat and in humans have been previously characterized. 6, 8, 30-32 Several short latency far-field components (designated I–IV in cat, N12–N14 in man) are presumed to originate in peripheral nerve, spinal cord, brainstem and possibly cerebellum. 30-32 These peaks were not consistently identified in our cats or in other studies. 6, 8 Early near-field peaks are postulated to originate in the thalamus or thalamocortical projections (P1 in cats, P15 in humans), somatosensory cortex (P2 or V in cats, N20 or P20 in humans) and associated cortex (P3, P4 in cats). 30, 32 We found the most reliable peak to be the primary cortical potential composed of a major positive (P) and major negative (N) deflection. This cortical peak has also been consistently observed by others to have a similar latency (9 to 13 milliseconds for P deflection). It corresponds to the early near-field potential previously designated P2-N2, P2-MN, or V and is thought to be generated in somatosensory cortical areas. 6, 8, 30, 32 The comparable SEP in humans is probably the N20 or P20 potential. 30

In our study, the duration of SEP recording (20 milliseconds) was not long enough to observe later cortical peaks reported in the literature. 6, 8

This study, using the cat middle cerebral arterial occlusion model, suggests that SEP’s provide a reliable indicator of severe focal cerebral ischemia. The disappearance of the SEP and failure to recover correlate with the extent and severity of neuronal ischemic alterations. SEP’s appear to be a useful electrophysiological measure of cerebral ischemia.

Editor’s Note: In accordance with Stroke policy, this article was guest edited by Dr. J.P. Mohr.

References
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