Neuropsychological Performance One Week After Carotid Endarterectomy Reflects Intra-Operative Ischemia

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SUMMARY Fourteen patients with severe bilateral carotid artery stenosis underwent carotid endarterectomy. Intra-operative ischemia was monitored by somatosensory evoked potentials (SSEP) bilaterally. Neuropsychological evaluations were completed within two days before operation and 4–9 days after operation. Complete loss of N1-P1 or P1-N2 components of the SSEP (seen in 4 patients) was associated with a worsening of neuropsychological abilities (p < .01). Two of these patients subsequently had strokes (7 and 35 days after operation). No other patients in the series have had strokes. Patients whose N1-P1 or P1-N2 amplitudes decreased by 50% or more performed worse after operation than patients with less severe reductions in these amplitudes (p < .02). Time since first ischemic symptoms, age, education, clamp time, pre-operative stroke, and interval from surgery to assessment were not statistically related to changes in neuropsychological abilities. Patients with ischemic events in the week prior to surgery tended to improve in neuropsychological abilities 4–9 days after operation (p < .05). Recentness of ischemic episode, however, was not related to intra-operative SSEP change. Results suggest the potential utility of intra-operative SSEP monitoring and early post-operative neuropsychological assessments both for clinical and research purposes.

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ERRI-OPERATIVE STROKE is the most significant complication attending carotid endarterectomy. Although such strokes result from a number of causes, one recognized mechanism is ischemic damage induced by clamping the internal carotid artery to insert a shunt or to perform the endarterectomy without a shunt.† A major methodological difficulty in assessing the impact of intra-operative ischemia on peri-operative stroke is the inability to isolate ischemia from other pathogenetic mechanisms and the requirement for large sample sizes because of the low frequency of frank stroke when it is used as the outcome measure. This latter difficulty requires data collection to proceed for long periods to distinguish factors predisposing to peri-operative stroke. The present study is designed to assess and correlate two more versatile outcome measures related to intra-operative ischemia: 1) early post-operative neuropsychological performance, and 2) altered intra-operative evoked cortical potentials.

Alterations in the electrical activity of the brain have frequently been demonstrated to occur in response to ischemia. The spontaneous electroencephalogram displays amplitude and mean frequency reductions in the face of ischemia measured by 133Xenon inhalation techniques during carotid endarterectomy.² ³ Intra-operative monitoring of somatosensory evoked cortical potentials appears to provide promise as an intra-operative monitoring technique,³ since a firm relationship between evoked cortical potentials and cerebral blood flow appears to exist.⁶ When cerebral perfusion falls below 22 ml g⁻¹ min⁻¹ the SSEP is dramatically altered. Conversely, a patient displaying such SSEP alterations during carotid endarterectomy has probably endured a period of flow reduction to or below the electrical threshold range of 0.2 ml g⁻¹ min⁻¹.⁸

The clinical implications of intra-operative ischemia are not always clear except when there are new post-operative neurological deficits thought to be due to ischemia. The hypothesis of this investigation is that mild, transient intra-operative ischemia may have manifestations identifiable neuropsychologically up to one week following surgery. It is not unusual to find neuropsychological impairments several days after a clinically-defined transient ischemic attack.⁴ Additionally, Savageau et al⁵ reported transient reductions in neuropsychological performance nine days after elective cardiac surgery in 28% of patients. Mild residual effects of ischemia induced by carotid clamping, therefore, may also be detectable by neuropsychological evaluation one week after operation. With intra-operative monitoring of the SSEP to demonstrate the degree of ischemia, a quantitative analysis of intra-operative ischemia and early post-operative neuropsychological functioning is possible. The purpose of this study was to determine whether greater degrees of intra-operative ischemia as measured by the SSEP may be reflected in neuropsychological performance one week after operation.

Intersubject variability in degrees of pre-existing ischemia and response to surgery may potentially conceal subtle neuropsychological changes due to intra-operative ischemia. To minimize the problem of intersubject variability, this study was based on a small subset of carotid endarterectomy candidates: patients with severe bilateral stenosis. These patients were designated "low-flow-endangered brain" by Whitten et al⁶ and are at far greater risk for the development of
peri-operative stroke. This group, therefore, provides not only homogeneity but a more frequent incidence of ischemic damage during operation.

Methods

Patients

Fourteen patients were included in the analysis. All patients met the criteria of Whitten et al. for the low-flow-endangered brain (LFEB); that is, angiography demonstrated reduction in total cross-sectional area of the internal carotid arteries of more than 75%.

Median age was 58 years (range 52–70) and median education was 11 years (range 5–12). All patients were males who were selected for operation on the usual clinical grounds. Indications for operation were a clear history of TIA’s or a small stable stroke. No patient had developed a fixed neurological deficit more recently than six weeks prior to operation. In 8 patients, the first episode of ischemia had occurred within six months of the operation. Five patients had episodes of ischemia within one week of the operation. No patients had operation for asymptomatic carotid bruits or asymptomatic carotid stenosis.

All patients underwent four vessel angiography before the operation. Twelve of the patients had unilateral internal carotid artery occlusions with stenosis of the contralateral internal carotid artery. Two patients had severe bilateral internal carotid artery stenosis.

Operations

All operations were performed by the same surgeon using standard techniques. Two patients had external carotid reconstruction in the face of a tight lesion in that vessel and demonstrated retrograde flow in the ophthalmic artery. Ten patients had internal carotid endarterectomy on the non-occluded artery, and a Javid shunt was employed in one of these patients. The two patients with severe bilateral stenosis had bilateral operations two to three weeks apart. Only data from the first operation were included in this analysis. Anesthesia was standardized and consisted of Pentobarbital (3–5 mg/kg) for induction, positive pressure ventilation with nitrous oxide and oxygen, and varying doses of narcotics (Fentanyl) for maintenance. Care was taken to avoid further narcotic doses during ischemic clamp time.

Somatosensory Evoked Potentials (SSEP)

SSEP’s were recorded intra-operatively using a Nicolet CA-1000 clinical averager with a DC-2000 floppy disc system. The median nerve at the wrist was stimulated bilaterally using EEG needle electrodes. The stimuli were delivered by a Grass SIU-5 stimulus isolation units and two Grass S-88 stimulator and two Grass SIU-5 stimulus isolation units. The pulse duration was 200 microseconds. The rate of stimulation was 5.1/sec. The strength of the stimulus was adjusted to produce movement of the thumb. In some cases due to muscle relaxants the movement of the thumb was not visualized. In no case, however, did the intensity of the stimulus exceed 30 millivolts. Averaging was accomplished by summing 500 responses to stimulation. The analysis time was 150 milliseconds. High and low pass filters were set at 30 Hz and 3KHz respectively. The floppy disc system allowed us to analyze and store the responses obtained in a sequence of every 2.5 to 3.0 minutes.

Prior to the monitoring of long-latency somatosensory evoked potentials (LLSEP), the integrity of the ascending sensory system from the wrist was tested by recording the short-latency evoked potentials on 30 milliseconds analysis time from Erb’s point and first cervical vertebral region (fig. 1A & B). Then the LLSEP’s were recorded from the scalp using EEG disc electrodes placed at C3 and C4 and the reference electrode at Fz according to the 10–20 international system.

The LLSEP’s occurring within 150 milliseconds after the stimulus depending upon the maximum polarity were termed N1, N2, N3, P1, P2 (fig. 1C).

These potentials are cortical in origin. The N1 potential which occurs approximately at 18–20 milliseconds is believed to originate from subcortical structures, possibly thalamus. The P1 potential of 23–25 millisecond latency appears to be a sensory cortical response to stimulation. Our observations concur with the above conclusions. Since the N2 peak and the potentials thereafter reflect the activity within the cerebral cortex, supplied by the middle cerebral artery, any ischemia either spontaneous or induced by carotid clamping, theoretically should alter the amplitude of these potentials and interpeak interval of N1-N2, as demonstrated in figures 2A and 2B.

The following criteria were used to determine the abnormality in LLSEP’s during carotid clamping: 1) Suppression of N2 and the peaks thereafter; 2) Reduction of amplitude of N1-P1 or P1-N2 by more than 50% over the preclamp amplitude.

Neuropsychological Evaluations

Extensive neuropsychological evaluations were completed within the two day period prior to the operation. Tests included the Wechsler Adult Intelligence Scale, Russell’s Revised Wechsler Memory Scale, Buschke’s Selective Reminding Procedure, Trail Making Test, and Reitan Sensory-Perceptual Examination. These latter five tests were then repeated (employing alternate forms where relevant) 4–9 days after the operation.

Peri-Operative and Post-Operative Factors

A standard regimen was followed for medications during the peri-operative and post-operative course. No patients developed intra-operative stroke. One patient (#14) had a stroke on the sixth post-operative day and died four days later. The post-operative neuropsychological evaluation in this patient was completed on Day 5, one day before the stroke. Autopsy indicated a patent operated artery and a thrombotic hemispheric and brain stem infarction. Another patient (#11) developed a gradually progressing right hemiplegia during the week following the operation. He had a pre-operative mild right hemiparesis and mild dysphasia,
and the new deficits were thought to be due to a new stroke.

Medication dispensing records were reviewed to determine the quantity and types of medications administered the day before and the day of post-operative neuropsychological evaluation.

Analysis

Changes in the N1-N2 interpeak latency and in the amplitudes of the N1-P1 and P1-N2 peaks were analyzed separately for the operated and non-operated side, employing the t-test for correlated means. Similarly, changes in raw scores on the neuropsychological tests were analyzed by t-tests for correlated means.

To determine the degree to which intra-operative SSEP changes may predict post-operative neuropsychological performance, algebraic differences between pre-operative and post-operative neuropsychological test scores were calculated for each test procedure. Ranks of difference scores were then determined for each neuropsychological test. A total of ten test scores were ranked: Buschke Total Recall, Buschke Total Long-Term Retrieval (LTR), Buschke Long-Term Storage (LTS), Buschke Consistent LTR (CLTR), Trail-Making Test Part A (time to completion), Trail-Making Test Part B (time to completion), Finger Tapping Test (total for left and right), number of tactile sensory-perceptual errors, number of visual sensory-perceptual errors, and Digit Symbol Substitution Test (DSST). For each patient, the mean rank for neuropsychological test difference scores was calculated and these mean ranks were subsequently ranked to provide an overall index of degree of neuropsychological change from the greatest improvement to greatest decrement in performance.

The Mann-Whitney procedure was employed to test the hypothesis that degree of SSEP change, probably due to ischemia, is associated with changed neuropsychological performance one week after surgery. The first analysis concerned whether patients whose SSEP changed to the point that the N1 or N2 peak could not be identified performed differently from patients whose N1 and N2 peaks are identifiable but reduced in amplitude.

Second, the reduction in amplitudes of the N1-P1 and P1-N2 peaks during carotid clamping was expressed as the percentage reduction relative to baseline (within 2 minutes before clamping). Neuropsychological performance of patients with greater than a 50% reduction in amplitude of either peak on either side was compared to that of patients with lesser reduction in amplitude.

To determine whether patients who had the greatest intra-operative SSEP changes were more impaired pri-
or to operation, the degree of SSEP change was correlated with the pre-operative Full Scale IQ (FSIQ) from the Wechsler Adult Intelligence Scale, and with the average pre-operative rank on the 10 variables that were employed to evaluate neuropsychological change.

Finally, a number of factors which may conceivably have produced misinterpretations of the data were evaluated by the Mann-Whitney Test: clamp-time, time since first symptoms of ischemia (greater or less than 6 months), time since most recent ischemic event (greater or less than 1 week), history of stroke, age, education, and number of days following surgery when the post-operative neuropsychological evaluation was done.

Results

As noted in table 1, clamping of the carotid artery produced significant increases in the N1-N2 latency and significant reductions in the amplitudes of the N1-P1 and P1-N2 peaks. These changes were noted bilaterally and are consistent with an earlier report.9

The data in table 2 indicate that there was no significant change in neuropsychological test performance when group data were considered.

As reflected in table 3, reductions in amplitudes of the late components of the SSEP to the point that the N1 or N2 peak could not be identified were associated with a decrement in post-operative neuropsychological performance (p < .01). Four patients whose late components of the SSEP disappeared on at least one side were among the five patients with the worst post-operative neuropsychological performance. Three patients had bilateral disappearance of the late components of the SSEP. The relationship between loss of the N1 or N2 peak and change in neuropsychological performance is further demonstrated in table 4. Five patients were identified as being at a more impaired level one week after the operation. Four of these patients had a complete loss of the N1 or N2 component. In none of the other patients (who performed equivalently or better than pre-operatively) did the SSEP demonstrate this degree of change (p = .005 by Fisher’s Exact Test20).

Several other patients demonstrated marked reduction in the N1-P1 or P1-N2 amplitudes. As demonstrated in table 3, an amplitude reduction of greater than 50% of either peak over either hemisphere was associated with a reduction in neuropsychological performance (p < .02). Three patients, however, had greater than 50% reduction in amplitude but demonstrated excellent post-operative neuropsychological improvements.
There was no significant relationship between neuropsychological change and any of the following: time since first ischemic symptoms, age, education, clamp time, pre-operative stroke, or number of days following surgery when the post-operative neuropsychological evaluation was performed (all comparisons involved the Mann-Whitney Test, with $\alpha = .05$).

Recentness of ischemic events was significantly associated with greater neuropsychological improvements ($p \leq .05$), as reflected in table 3. When patients were ranked in terms of degree of reduction in amplitude of the N1-P1 and P1-N2 components (by ranking the mean amplitude reduction for each patient), no significant relationship to recentness of ischemic events was found. Reductions in these amplitudes and recentness of ischemia, therefore, apparently make independent contributions to post-operative neuropsychological functioning.

The FSIQ obtained prior to operation was not related to the degree of reduction in amplitude of the SSEP (Spearman Rho = 0.05, $p > .10$). Similarly, there was no significant relationship between the average pre-operative rank on the ten neuropsychological variables and degree of reduction in the SSEP (Rho = 0.19, $p > .10$).

As reflected in table 5, pre-operative performance on the Wechsler Adult Intelligence Scale was not related to post-operative change ($U = 21, p > .10$). Additionally, the baseline rank of performance on the 10 neuropsychological tests was not related to change in performance on these tests ($U = 29.5, p > .10$).

### Discussion

Intra-operative ischemia is well recognized among the causes of peri-operative stroke after carotid endarterectomy. The SSEP provides a reliable quantification of intra-operative ischemia during that operation. There is currently no accepted method for identifying the residual effects of ischemia early in the post-operative period.

### Table 3: Mann-Whitney Tests

<table>
<thead>
<tr>
<th>Neuropsychological Rankings</th>
<th>Days of post-op evaluation</th>
<th>N1-P1 P1-N2 Not identified</th>
<th>&gt;50% Amplitude change</th>
<th>Medication Within 48 Hours of Post-Op Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most improved</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>+</td>
<td>+</td>
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<td></td>
<td>5</td>
<td>+</td>
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<td>7</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Least improved</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>0.01</td>
<td>0.02</td>
<td></td>
<td></td>
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</tbody>
</table>

### Table 4: Analysis of SSEP Changes and Worsening of Neuropsychological Performance

<table>
<thead>
<tr>
<th>N1-P1 or P1-N2 not identifiable</th>
<th>Unchanged or improved</th>
<th>Worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>N1-P1 or P1-N2 identifiable</td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

$p = 0.005$ by Fisher's exact test.
post-operative course unless the patient has an unequivocal stroke. Data from the present study suggest that neuropsychological functioning one week post-operatively may reflect residual (usually transient) effects of intra-operative ischemia. Patients who had the most remarkable reductions in the N1-P1 and P1-N2 amplitudes during carotid clamping tended to perform more poorly on neuropsychological tests one week after the operation. The reduction in neuropsychological performance, however, was not related to age, education, time since first ischemic episode, pre-operative stroke, or post-operative medications. Since not all patients were evaluated on the same post-operative day (because of weekends and holidays and staffing limitations), the potential influence of this factor on post-operative performance was evaluated separately. There was no significant relationship between days post-operation and neuropsychological change.

Patients who had ischemic episodes within one week of the operation tended to perform better on neuropsychological tests post-operatively. These results are independent of the relationship between neuropsychological changes and SSEP changes, as recentness of ischemic events was not significantly related to intra-operative SSEP changes. These results do suggest, however, that patients who have ischemic episodes within one week of operation may be recovering from the ischemia at the time of the post-operative evaluation.

Evidence of the sensitivity of neuropsychological tests to brief periods of ischemia has been published previously. It is not surprising, therefore, to find reductions in neuropsychological performance one week after carotid endarterectomy in patients with severe bilateral carotid artery disease. Although some reduction in neuropsychological abilities may be expected following operations which do not produce ischemia, the standardized anesthetic regimen employed in the present study, the similarities in post-operative medications, and the fact that all operations were performed by the same surgeon support the conclusion that post-operative performance was significantly related to the degree of intra-operative ischemia.

The precise relationship between early post-operative neuropsychological deficits and stroke will be difficult to determine because of the infrequent occurrence of peri-operative stroke. It appears likely, however, that reductions in neuropsychological functioning in the peri-operative period may signal an increased risk for stroke. In the present series, four patients had clearly declined from pre-operative levels of performance. Two of these patients had strokes and two returned to baseline levels or higher (one and six months post-operatively).

As noted in table 1, SSEP changes during carotid endarterectomy tended to be bilateral. Our more recent data indicate bilateral changes in the SSEP during carotid clamping even in cases of mild unilateral carotid artery disease. In view of this tendency toward bilateral SSEP changes, an investigation of lateralized SSEP amplitude reductions and neuropsychological changes referable to lateralized cerebral ischemia was not undertaken.

The reproducibility of the reductions in amplitudes of the N1-P1 and P1-N2 SSEP components are of critical importance. Because of variability in the length of the clamp time, a systematic analysis of reliability could not be undertaken. For each case in which multiple observations were possible during carotid clamping (10 of the 14 cases), the classification of the amplitude reduction (50% or greater/less than 50%) was reproduced in at least two observations.

Table 2 indicates no change in neuropsychological test scores in the first 4-9 days following the operation. Individual cases, however, were quite variable in their response to surgery. As we reported earlier, these patients with severe carotid artery disease tend to have greater improvements in cognitive abilities following carotid endarterectomy than do patients with unilateral carotid artery lesions if they are followed for several months.

These results from a homogeneous group of patients with severe bilateral carotid artery disease support the clinical application of early post-operative neuropsychological assessments following carotid endarterectomy or other operations in which brain ischemia may occur. Reductions in post-operative performance on neuropsychological tests may help to draw attention to some patients who are at increased risk for stroke. As a research tool, the combination of intra-operative SSEP measurements to quantify ischemia and early post-operative neuropsychological changes to detect residual effects of ischemia may provide a useful model for studying the early phases of ischemic stroke and potential pharmacological strategies to reduce or mitigate the effects of ischemia.

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Hemolysate-Induced Contraction in Smooth Muscle Cells of the Guinea Pig Basilar Artery

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SUMMARY The hemolysate (10^{-5}–10^{-2} times dilution; original hemoglobin concentration was 0.83 ± 0.10 × 10^{-3}M) evoked the contraction in a dose dependent manner, and this contraction was composed of low and high sensitive responses as estimated from the Eadie-Hofstee's plot. Indomethacin (10^{-5}–10^{-3}M) inhibited the latter component in the hemolysate-induced contraction. The membrane potential of smooth muscle cells was −50 mV and the cell was electrically quiescent. The hemolysate (>10^{-2} times dilution) depolarized the membrane and increased the ionic conductance of membrane. In rare occasions, the spike potential was triggered on the hemolysate-induced depolarization. The hemolysate (10^{-3}–10^{-2} times dilution) produced the contraction without change in the membrane property. Carbocyclic thromboxane A_{2} (cTXA_{2}; 2.8 × 10^{-10}M) produced the contraction without depolarization of the membrane, yet the TXA_{2} synthesis inhibitor, OKY-1581 (10^{-6}M), had no effect on the hemolysate-induced contraction. PGE_{1}, PGE_{2} and PGF_{2α} (2.8 × 10^{-10}M) produced the contraction with no change in the membrane property. The contraction evoked by 2.8 × 10^{-8}M PGF_{2α} corresponded well with that evoked by 3 × 10^{-10} times dilution of the hemolysate. Removal of the endothelium by mechanical rubbing modified the hemolysate-induced contraction. Under the assumption that OKY-1581 is a selective inhibitor for TXA_{2} synthesis, the major part of the contraction (the indomethacin sensitive component) of the basilar artery is postulated to be due to synthesis of the primary PG rather than TXA_{2} by the hemolysate, yet the hemolysate itself, has to some extent a direct action in evoking the small contraction.

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