Post-carotid endarterectomy neurocognitive decline is associated with cerebral blood flow asymmetry on post-operative magnetic resonance perfusion brain scans


*Department of Neurological Surgery, †Department of Anesthesiology and ‡Department of Biomedical Informatics, Columbia University, New York, NY, USA

Objective: Up to 25% of patients experience subtle declines in post-operative neurocognitive function following, otherwise uncomplicated, carotid endarterectomy (CEA). We sought to determine if post-CEA neurocognitive deficits are associated with cerebral blood flow (CBF) abnormalities on post-operative MR perfusion brain scans.

Methods: We enrolled 22 CEA patients to undergo a battery of neuropsychometric tests pre-operatively and on post-operative day 1 (POD 1). Neurocognitive dysfunction was defined as a two standard deviation decline in performance in comparison to a similarly aged control group of lumbar laminectomy patients. All patients received MR perfusion brain scans on POD 1 that were analysed for asymmetries in CBF distribution. One patient experienced a transient ischemic attack within 24 hours before the procedure and was excluded from our analysis.

Results: Twenty-nine percent of CEA patients demonstrated neurocognitive dysfunction on POD 1. One hundred percent of those patients with cognitive deficits demonstrated CBF asymmetry, in contrast to only 27% of those patients without cognitive impairment. Post-CEA cognitive dysfunction was significantly associated with CBF abnormalities (RR = 3.75, 95% CI: 1.62–8.67, p = 0.004).

Conclusion: Post-CEA neurocognitive dysfunction is significantly associated with post-operative CBF asymmetry. These results support the hypothesis that post-CEA cognitive impairment is caused by cerebral hemodynamic changes. Further work exploring the relationship between CBF and post-CEA cognitive dysfunction is needed. [Neurol Res 2008; 30: 302–306]

Keywords: Carotid endarterectomy; neurocognitive; magnetic resonance perfusion

INTRODUCTION
Carotid endarterectomy (CEA) effectively reduces the risk of future stroke in appropriately selected patients with carotid artery stenosis1,2,4,9. Although the incidence of major perioperative stroke is low (1–2%), up to 25% of CEA patients experience subtle declines in post-operative neurocognitive function, as detected by changes in performance on a battery of neuropsychometric tests (NPMTs)6,7.

This post-CEA neurocognitive dysfunction is increasingly well documented in literature and is believed to be caused by subtle cerebral ischemia, resulting from either the dislodgement of microemboli or hemodynamic changes induced during the procedure6,7. To test the hypothesis that abnormalities in cerebral blood flow (CBF) contribute to post-CEA cognitive deficits, we utilized analysis of MR perfusion (MRP) scans to quantify the amount of CBF asymmetry in each cerebral hemisphere. We sought to determine whether post-CEA cognitive dysfunction is associated with post-operative CBF abnormalities.

METHODS
Study population
We prospectively enrolled 22 patients undergoing CEA for carotid artery stenosis who agreed to receive post-operative MRP scans in this institutional review board-approved study. All CEA patients had at least 60% stenosis of the operative carotid artery. Patients with new onset neurological deficits before the procedure were excluded. One patient was excluded based on this criterion. After written informed consent was obtained, patients were assessed with a battery of NPMTs immediately before surgery and 1 day post-operatively. All patients received MRP scans within 24 hours following surgery.
Anesthesia and surgery

No patients were pre-medicated. All patients received general anesthesia with routine hemodynamic and temperature monitoring, as previously described. For patients undergoing CEA, blood pressure was continuously monitored with a radial artery catheter and an eight-channel encephalographic monitor was utilized during the course of surgery (Neurotrac II; Moberg Medical Inc., Ambler, PA, USA). Sedation before induction consisted of fentanyl and midazolam. General anesthesia was induced with fentanyl, midazolam and either vecuronium or rocuronium, and was maintained with isoflurane. Heparin (5000 or 6000 units) was administered intravenously before vessel occlusion. All CEA patients were performed by members of either the neurovascular service or the vascular service. All patients were extubated in the operating room and recovered in a post-operative care or neurological intensive care unit.

Neuropsychometric evaluation

Patients were assessed before surgery and 1 day post-operatively with a battery of five NPMTs. All examinations were administered by a research assistant, trained to administer and score these NPMTs under the supervision of a neuropsychologist. Ten raw scores were generated from this battery of five NPMTs, which were chosen to represent a range of cognitive domains. The Boston Naming test was administered to evaluate patients’ ability to verbally identify objects pictured on a series of cards. Halstead–Reitan Trails parts A and B evaluated visual conceptual and visuomotor tracking by timing how long it took a subject to connect consecutively numbered circles with a single line (part A) and then connect the same number of consecutively numbered and lettered circles by alternating between the two sequences (part B). The Controlled Oral Word Association test evaluated verbal fluency and provided information on dominant hemisphere function. During this test, patients were asked to generate as many words as possible within 60 seconds that begin with a certain letter. Three separate trials were performed, one each with the letters C, F and L. The sum of all words generated over the three trials constituted the raw score. The copy portion of the Rey Complex Figure test was administered to evaluate visuospatial organization, providing information on the functioning of the non-dominant hemisphere. Patients were asked to copy the figure and a standardized scoring system was used to evaluate the presence of specific design features and the accuracy of their location.

Each pre-operative and post-operative test was scored individually for both the enrolled CEA patients and a control group of 20 contemporaneous lumbar laminectomy (LL) patients, who were matched for age and cardiovascular risk factors and received a similar anesthetic regimen as the CEA group. As previously described, the change in individual test scores were converted to z scores as follows:

\[ z = \frac{\text{change score} - \text{mean change score}_{\text{LL}}}{\text{standard deviation of change score}_{\text{LL}}} \]

z scores for each test were transformed into a point system as follows: z scores greater than or equal to −0.05: 0 points; less than −0.5 to −1.0: 1 point; less than −1.0 to −1.5: 2 points; less than −1.5 to −2.0: 3 points; less than −2.0 to −2.5: 4 points; less than −2.5 to −3.0: 5 points; less than −3.0: 6 points. The higher the test score, the greater the patient’s test performance deviated from performance of the control population in the direction of decline. These test scores were summed to generate a total deficit score (TDS), measuring a patient’s level of global cognitive decline. By definition, a CEA patient was determined to have experienced neurocognitive decline when the patient’s TDS was greater than two standard deviations above the mean total cognitive change score of the control group. Neuropsychometric outcome was expressed as a dichotomous variable (‘injured’ or ‘uninjured’).

Post-operative MRP scans and image analysis

All 21 non-excluded CEA patients received MRP brain scans within 24 hours following surgery. Additionally, for non-statistical comparison, two LL (control) patients also received MRP brain scans within 24 hours following surgery. To analyse these scans, we utilized a previously described algorithm that quantifies the degree of relative difference in CBF between corresponding regions in the ipsilateral and contralateral cerebral hemispheres. This algorithm constructs a relative difference map (RDM) representing this CBF asymmetry. The degree of relative difference in CBF between hemispheres was calculated by the intensity value on the side where the CBF reading was relatively larger (‘relatively normal hemisphere’). The resulting RDM reflects the amount of CBF asymmetry. The degree of relative CBF differences in both hemispheres was analysed and represented as a histogram, demonstrating the distribution of relative differences in CBF between one brain region and its contralateral counterpart.

RESULTS

Cohort characteristics

Demographic and intraoperative variables for the CEA patients are shown in Table 1. All 21 CEA patients completed the NPMT battery pre-operative on post-operative day 1, and received brain MRP scans within 24 hours following surgery. Thirty-eight percent of CEA patients presented with symptomatic carotid stenosis, while 62% had asymptomatic disease. On post-operative
day 1, 6 CEA patients (29%) demonstrated neurocognitive dysfunction (Table 2). The mean age of injured patients exceeded that of the uninjured cohort (72.8 ± 2.4 versus 67.5 ± 8.5, p=0.04). We detected no statistical difference between the injured and uninjured cohorts in any of the other demographic or intraoperative variables analyzed.

Table 1: Demographic and intraoperative parameters of carotid endarterectomy patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CEA patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td>21</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.1 ± 7.6</td>
</tr>
<tr>
<td>Male (%)</td>
<td>16 (76%)</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>16 (76%)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>17 (81%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>18 (86%)</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>Symptomatic (%)</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>Previous contralateral CEA (%)</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>Right operative side (%)</td>
<td>12 (57%)</td>
</tr>
<tr>
<td>Duration of surgery (minute)</td>
<td>198.5 (65)</td>
</tr>
<tr>
<td>Cross-clamp time (minute)</td>
<td>49.4 (18)</td>
</tr>
<tr>
<td>Shunt placement</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Fentanyl (µg/kg)</td>
<td>2.44 (0.6)</td>
</tr>
<tr>
<td>Midazolam (mg/kg)</td>
<td>0.039 (0.01)</td>
</tr>
</tbody>
</table>

Hypertension is defined as systolic blood pressure>140 mmHg or use of antihypertensive medication; hypercholesterolemia is defined as blood cholesterol>200 mmHg or use of anti-cholesterol medication. Continuous data are expressed as mean ± standard deviation. CEA=carotid endarterectomy; MI=myocardial infarction.

DISCUSSION

In recent years, neurocognitive dysfunction following CEA has been increasingly recognized. Works now suggest that up to 25% of CEA patients experience declines in post-operative NPMT performance. Our previous work identifies a number of risk factors for post-CEA cognitive deficits on post-operative day 1, including advanced age, elevated pre-operative monocyte counts, and the APOE ε4 polymorphism. This is the first study to demonstrate an association between post-CEA neurocognitive dysfunction and post-operative CBF abnormalities detected on MRP brain scans.

Although the incidence of post-CEA cognitive decline is well established, the precise mechanism underlying this phenomenon is uncertain. Impaired NPMT performance following CEA is believed to be ischemic in nature, either due to microemboli dislodged or cerebral
hemodynamic changes induced during the procedure\(^6\). This ischemic hypothesis is supported by elevated postoperative levels of serum S100b, a marker of glial cell death, in patients experiencing declines in post-operative NPMT performance\(^5\). Our current findings suggest that hemodynamic dysregulation plays a role in post-CEA cognitive dysfunction. Patients with impaired cerebral autoregulation may be particularly vulnerable to hemodynamic shifts during the period of carotid artery cross-clamping\(^14\). Such CBF changes may cause subtle ischemic injury and cognitive decline.

While conventional MRP scan analysis relies on the averaging of CBF values over predetermined regions of interest, our algorithm compares a neighborhood of voxels with its contralateral counterpart over a reflexional axis of symmetry\(^10\). This method offers more sensitivity in detecting subtle CBF asymmetry, and has shown promise in several clinical applications, including the detection of CBF abnormalities following subarachnoid hemorrhage that predict delayed cerebral vasospasm\(^10\).

In this study, 29% of CEA patients experienced post-operative cognitive dysfunction, consistent with rates of post-CEA cognitive impairment determined in previous works\(^5,7\). Using a previously described algorithm, we demonstrate that CBF abnormalities are associated with post-CEA cognitive dysfunction on post-operative day 1 (RR=3.75, \(p=0.004\)). Our analysis of CBF asymmetry identified post-CEA cognitive dysfunction with a sensitivity of 100% and a specificity of 73%. While all CEA patients with post-operative cognitive decline demonstrated CBF asymmetry, of the 15 CEA patients without cognitive deficits, four also demonstrated CBF abnormalities. These four cases of MRP abnormalities without cognitive decline may be explained by slight hemodynamic changes that failed to manifest in impaired performance on the NPMT battery, or could represent inherent limitations in our technique. We obtained MRP brain scans on two of our control patients, which both showed CBF symmetry. While our true comparison was between injured and non-injured CEA patients, it would also have been helpful to obtain MRP brain scans on more of these control patients to establish a baseline rate of post-operative CBF asymmetry.

The association between post-operative CBF asymmetry and post-CEA cognitive dysfunction is robust. However, our study remains limited by its small sample size. Furthermore, while our analysis of post-operative MRP brain scans sheds light on the mechanisms underlying post-operative cognitive impairment, a study including pre-operative scans would be beneficial in determining whether the CBF abnormalities are induced by the procedure or whether a subset of high-risk patients displays baseline CBF asymmetry. Owing to the design of this study, we can only show an association between neurocognitive decline and asymmetric post-operative CBF, and further work is necessary to determine if a causal relationship exists. With over 100,000 CEAs performed annually, many for borderline indications\(^5\), our findings call for continued investigations into the relationship between CBF and post-CEA cognitive dysfunction.

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REFERENCES