Identifying Patients Likely to Demonstrate Cognitive Improvement Following Carotid Endarterectomy: The Association between Cerebrovascular A utoregulation and Cognition

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A. Study Purpose and Rationale

Well over I million carotid endarterectomys (CEA) have been performed worldwide since the 1950s when the procedure was pioneered as a treatment for patients at high risk for stroke [1]. However, in the late 1980's, high rates of perioperative complications began to call into question what had largely been anecdotal evidence of benefit [2]. Subsequent large multi-center trials have unequivocally demonstrated that CEA yields a significant and durable reduction in the risk of stroke in symptomatic patients with greater than 70% stenosis [2, 3] and in asymptomatic patients with greater than 60% stenosis at centers where the perioperative morbitity and mortality is less than 3% [4, 5]. However, more sensitive measures of cognitive performance, namely a battery of neuropsychometric tests (NPMT), have shown that approximately 20% of patients show significant improvement in cognitive performance perioperatively [6] while 25% show cognitive decline relative to spinal- surgery-matched control patients [7]. These effects have both been shown to be durable one month postoperatively.

Which,patients axe-irriost likely to -cxpc6ence-these significant-changes~irj',cognitive performance, however, remains unclear. It is also unclear whether the neuropsychological benefit experienced by 20% of patients has real implications for quality of life or stroke-free survival. If either were true, predicting the cognitive improvement might impact the decision making in patients in whom the risk-benefit ratio of CEA is currently marginal.

It has been proposed that improvements in cognitive function following CEA are a result of restoration of good blood perfusion to the brain [8]. As such, one would expect greater cognitive improvements in those patients with more significant hemodynamic lesions. While cognitive improvement has been demonstrated in patients with significant flow-restrictive vascular disease following CEA relative to patients with hemodynamically-less-significant lesions [9], more recent and larger studies have demonstrated a mixture of cognitive improvement and decline within the cohort of patients with greater than 70% stenosis [7].

One reason why the degree of unilateral internal carotid artery (ICA) stenosis alone might not accurately screen for hypoperfusion of brain tissue is that Collateral supply, largely from the Circle of Willis, but also from extracranial-to-intracranial collaterals, maintains normal perfusion in many patients with carotid artery stenosis and occlusion [10]. In order to test the hemodynamic significance of a stenotic ICA, we must use a physiologic parameter. In response to flow restriction, the intracranial arterial circulation vasodilates. Its ability to ftirther dilate in response to an exogenously administered vasodilator such as C02 is therefore diminished. This decrease in responsiveness can be measured and quantified with Transcranial Doppler ultrasonography JCD). Impaired vasodilatory reserve can therefore be used to demonstrate insufficient collateral blood supply [I I].

We hypothesize, therefore, that those patients with decreased cerebrovascular reserve are most likely to show impaired performance on NPMT preoperatively and are therefore most likely to benefit cognitively from CEA. We believe this improved cognitive performance will result in improved quality of life. Therefore, patients with impaired cerebrovascular reserve will demonstrate improved quality of life following CEA.

However, predicting cognitive improvement in the immediate postoperative period is more complicated than simply identifying the patient population with the most potential for improvement. Relief of flow-restrictive vascular disease in the presence of impaired cerebrovascular autoregulation can actually cause postoperative neurologic deficit due to hyperperfusion. Hyperperfusion has been defined as an increase in ipsilateral cerebral blood flow well above the metabolic demands of the brain tissue and has been observed following CEA [12-14]. It is well accepted that hyperperfusion following CEA is associated with impaired postoperative cerebrovascular autoregulation [15, 16]. Hosada et. al. looked at 26 patients undergoing CEA and found that those who had reduced preoperative CVR had increased cerebral blood flow velocities one day postop and were more likely to develop cerebral hyperperfusion than their normal-CVR matched controls. These differences in flow velocities disappeared in one month. Case studies have documented the appearance of hyperperfusion syndrome in the presence of significantly elevated arterial flow velocities and observed as the flow velocities returned to normal with the same time course as resolution of the symptornatology over the course of 24 hours [17]. From a more theoretical standpoint, some of the for hyperperfusion are themselves physiologic rationale for impaired CVR including highgrade internal carotid artery stenosis, poor collateral blood flow, and contralateral carotid occlusion[16]. While the average time-courseto retumof normal cerebrovascular autoregulation upon relief of flow-restriction has not been studied, there is evidence that the range could include anywhere from within 20 minutes of vessel reconstruction to days after surgery [18].

The classic symptom triad exhibited by patients with hyperperfusion syndrome includes severe unilateral headache, face and eye pain, and seizures [16]. At its most extreme, hyperperfusion may lead to intracerebral hemorrhage, accounting for anywhere from 20%-3 5% of CEA perioperative strokes [19, 20]. However, patients likely experience less florid symptomatology from hyperperfusion more frequently [17], though no one has studied the impact of clinically silent hyperperfusion on cognition.

We hypothesize, therefore, that patients with preoperative flow-restricting disease as demonstrated by impaired CVR will show improved cognitive performance following CEA when their CVR returns to normal postoperatively. Patients with impaired CVR that does not show quick postoperative improvement will perform poorly cognitively until their CVR returns to normal. Whether their eventual cognitive performance will show the improvement that we predict in those patients in whom cerebrovascular autoregulation returns immediately remains to be seen and will be a subject of interest. This study will not only help us to develop fin-ther our model of perioperative changes in cognition following CEA, but will also identify a group of patients that could stand to benefit additionally from CEA but whose acute postoperative management could require close monitoring.

B. Study Design and Statistical Analysis

Patients coming to CPMC for carotid endarterectomy will be recruited by staff from anesthesiology, neurological surgery, and vascular surgery. No randomization will be employed. To determine whether decreased preoperative CVR predicts cognitive improvement, a sample size of 138 patients will be required by chi-square test (β=80, α=0.05) making the following assumptions:

1) 7.5% of our patient population will have reduced cerebrovascular reactivity to begin with. This is a conservative estimate based on a study by Markus et al [10] that found 43% of patients with ICA occlusion have significantly reduced CVR as do 5% of those with significant stenosis. Taking a weighted average based on our patient population that is almost exclusively stenotic patients, we get 7.5%. We feel this estimate is conservative because the Markus study looked only at patients who were asymptomatic while our patient population is largely symptomatic. While the proportion of symptomatic vs. asymptomatic patients with significantly reduced CVR has not been studied, it has been show that the average CVR in symptomatic patients is significantly lower than in asymptomatic patients [21],
2) 65% of those patients with decreased preoperative reserve will show cognitive improvement and

3) a total of 20% of the total patient population will show significant cognitive improvement [7]. Significant decrease in CVR will be defined as -5 20% increase in CBF at 8% inhaled $C0_2$ [10].

NPMT will be graded as follows: For each NPMT, the change in performance be calculated by subtracting the baseline score from the postoperative score. A normative data set for these changes will be derived from the control population for each NPMT. The mean change and standard deviation for the control population will then be used to calculate a z-score for each test: z-score = (change score - mean change $score_{spine}$/standard deviation of change $score_{spine}$. To illustrate cognitive improvement and decline, z scores for each of the 6 NPMT will be tabulated. This *test score* measures how far each CEA patient's performance deviates from the mean performance of the control group. For each patient, the total number of test *scores* will be summed to produce the *net improvement or deficit score.* This total score represents overall performance on the NPMT battery from pre- to post- op relative to spinal-surgerymatched controls. Data will then be analyzed by performing a linear regression to obtain a correlation between total z-score from the 6 NPMT and preoperative cerebrovascular reactivity measurements. Spinal surgery patients will be used as controls for NPMT and will be matched for age, race, and sex. Multiple regression analysis will be used to account for factors such as age, race, history of diabetes, hypertension, hyperlipidemia, and race.

To determine whether a preserved low reactivity correlates with poor 24 hour postoperative NPMT performance, a sample size of 468 patients will be required by t-test (β=80, α=0.05). This calculation assumes that in the patient population whose cerebrovascular reactivity quickly improves, that it will improve to the average value of the non-occluded side as given by the literature, a difference of 22.5 [21]. A conservative estimate for s.d. of 17 was used given a literature s.d. of 13.3 in the baseline for the nonoccluded side and assuming an additional 30% of variability will be introduced because we are looking at the difference in scores. Once again, we will use a conservative estimate of 7.5% for the proportion of patients with reduced cerebrovascular reactivity preoperatively. Change in CVR and cumulative test score performance will be analyzed by performing a linear regression to look for a correlation. Multiple regression analysis will be used to account for factors such as age, race, history of diabetes, hypertension, hyperlipidemia, and race.

C. Study Procedure

Patients admitted to the Irving Clinical Research Center (CRQ will have a follow-up test on day 1. Those coming into the hospital on the day of surgery, "Same Day", will be evaluated on day 1. Subsequent follow up examination will be at I month.

Preoperative neuropsychological evaluation will be performed. The neuropsychometric tests are not intended to be diagnostic of specific neuropsychiatric disorders, but rather are designed to demonstrate general neuropsycho logical pathology. These tests can be divided into three types:

1 an evaluation of language,
2 an evaluation of speed of mental processing,
3 an evaluation of ability to learn using a list of words, and
4 an evaluation of visual perception requiring a patient to copy a complex figure.

The specific tests are as follows.

1 First, the Boston Naming Test evaluates an important component of language, the ability of a patient to name various pictures.
2 Second, the Oral Word Association Test,evaluates the ability to say a list o f words beginning with a specific letter in a limited period of time, as another component of language.
3 Third, the Reitan Trail Making Test measures the time a subject takes to connect circles numbered from "1 " to "25" (Part A). Part B is more complicated because it requires the subject to connect circles labeled with numbers or letters alternating between numbers and

letters, i.e. "1" connects to "A" connects to "2" connects to "B" et cetera. Performance on these tests is dependent on attention.

4 Fourth, the Rey Complex Figure Test measures the ability of a patient to copy a complex figure, as a nondominant parietal lobe function.

5 Fifth, the Buschke Verbal Selective Reminding Test asks a patient to learn a list of 12 words, as a verbal memory test. The number of words learned, or not learned is scored.

6 Sixth, the Grooved Pegboard test measures the time a subject takes to place twenty-five notched pegs into mirror-image holes, as a component of fine finger/hand manipulation.

Each of these tests arrives at a number that can be used to evaluate performance. These tests will require approximately one hour to administer.

A TCD examination to clinically evaluate cerebral blood flow will be performed before, during (including 10 minutes after closure of the carotid), one day, and one month after surgery. The TCD examination will be modified in order to test the ability of cerebral blood flow to respond to an increased concentration of carbon dioxide (at room air 6% and 8% C02).

The preoperative and postoperative TCD examination will be performed by attaching ultrasound probes to the patient's head with a standard elastic headband, one pr obe on each side to measure the flow in an artery on either side of the brain. Then, while the patient is reclining comfortably on his/her back on the examining table, we will place a soft rubber mouthpiece (like a snorkel mouthpiece) in the patient's mouth and place a soft nose clip on his/her nose so that he/she breaths only through his/her mouth. The mouthpiece will be connected to plastic tubing, through which room air, or a mixture of air and carbon dioxide (C02) will be delivered. This gas mixture will cause cerebral blood vessels to dilate as previously described.

D. Study Drugs and Medical Devices

Patients may experience light-headedness during TCD. There are no additional risks to the patient since no experimental drugs or procedures will be administered or performed. Only neurologic and neuropsychologic evaluations will be administered.

E. Study Subjects

Inclusion criteria include ability to speak English and age > 18.

Exclusion criteria include history of permanent neurological impairment, Axis I psychiatric diagnosis, or drug abuse.

F. Study Questionnaires

Every patient will fill our a brief questionnaire that asks about age, gender, race, handedness, smoking history, and history of hypercholesterolemia, HTN, and DM. The NPMT will be given to every patient in the study.

G. Confidentiality of the Study Data

To maintain the privacy of study subjects, each patient will be assigned a new, non-identifiable number and be refer-red to by that number throughout the data analysis. Patient identity will only be known by the primary investigators.

H. Potential Conflict of Interest

N/A

I. Location of Study

Columbia Presbyterian Medical Center.

J. Potential Risks

N/A

K. Potential Benefits

Patients stand to benefit indirectly from knowledge gained during the study.

L. Compensation/Cost to Subjects

N/A

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