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Middle cerebral artery pulsatility index and cognitive improvement after carotid endarterectomy for symptomatic stenosis

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Abstract

Object—Transcranial Doppler (TCD) is frequently used to evaluate peripheral cerebral resistance and cerebral blood flow (CBF) in the middle cerebral artery prior to and during carotid endarterectomy (CEA). Patients with symptomatic carotid artery stenosis may have reduced peripheral cerebral resistance to compensate for inadequate CBF. The authors aim to determine whether symptomatic patients with reduced peripheral cerebral resistance prior to CEA demonstrate increased CBF and cognitive improvement as early as 1 day after CEA.

Methods—Fifty-three patients with symptomatic CEA were included in this observational study. All patients underwent neuropsychometric evaluation 24 hours or less preoperatively and 1 day postoperatively. The MCA was evaluated using TCD for CBF mean velocity (MV) and pulsatility index (PI). Pulsatility index ≤ 0.80 was used as a cutoff for reduced peripheral cerebral resistance.

Results—Significantly more patients with baseline PI ≤ 0.80 exhibited cognitive improvement 1 day after CEA than those with PI > 0.80 (35.0% vs 6.1%, $p = 0.007$). Patients with cognitive improvement had a significantly greater increase in CBF MV than patients without cognitive improvement (13.4 ± 17.1 cm/sec vs 4.3 ± 9.9 cm/sec, $p = 0.03$). In multivariate regression model, a baseline PI ≤ 0.80 was significantly associated with increased odds of cognitive improvement (OR 7.32 [1.40–59.49], $p = 0.02$).

Conclusions—Symptomatic CEA patients with reduced peripheral cerebral resistance, measured as PI ≤ 0.80, are likely to have increased CBF and improved cognitive performance as early as 1 day after CEA for symptomatic carotid artery stenosis. Revascularization in this cohort

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Disclosure

Author contributions to the study and manuscript preparation include the following. Conception and design: Heyer, Connolly. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Heyer. Statistical analysis: all authors. Administrative/ technical/material support: Heyer, Mergeche. Study supervision: Heyer, Connolly.

may afford benefits beyond prevention of future stroke. Clinical trial registration no: NCT00597883 (ClinicalTrials.gov).

Keywords

carotid endarterectomy; symptomatic; transcranial Doppler; neuropsychometric; cognitive improvement; vascular disorders

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Maintenance of adequate cerebral blood flow (CBF) is achieved by a variety of cerebral autoregulatory mechanisms. These mechanisms deficient events. In the case of patients with carotid artery stenosis, cerebral autoregulatory mechanisms will often reduce peripheral (distal) cerebral resistance to compensate for the reduced CBF and use collateral circulation to adequately perfuse the ipsilateral hemisphere. However, patients with symptomatic carotid artery stenosis may lack adequate collateral circulation and experience strokes or transient ischemic attacks;[4,21,25–27] these patients rely more heavily on reducing peripheral cerebral resistance to maintain adequate perfusion of the cerebral hemispheres.[20,34,36]

Carotid endarterectomy (CEA) is a commonly performed procedure to prevent future stroke, especially in patients with symptomatic carotid artery stenosis.[3,13,28] Transcranial Doppler (TCD) ultrasonography is a useful tool that can be used prior to and during CEA to examine the middle cerebral artery (MCA). Transcranial Doppler ultrasonography collects information regarding CBF velocity using standard ultrasound technology. This tool also collects information regarding peripheral cerebral resistance via the Gosling pulsatility index (PI).[8,20,22,33] The PI is determined as the difference between the peak systolic and end-diastolic velocities divided by the mean velocity of blood flow in the MCA. [22] The PI is often documented to be ≥ 1.0 in asymptomatic CEA patients and < 1.0 in symptomatic CEA patients, indicating reduced peripheral cerebral resistance and likely a degree of cerebral autoregulatory exhaustion.[31,34,36,38] Symptomatic patients with a baseline PI < 1.0 prior to CEA often demonstrate increased CBF after plaque removal and flow restoration.[5,6,19,20,30,31,34,36–38]

Patients can demonstrate cognitive changes after CEA due to the common due to the common fluctuations in CBF during and after surgery; approximately 20%–25% demonstrate cognitive dysfunction[18,23] and approximately 10%–15% demonstrate cognitive improvement,[1,2,9,11,12,39] while approximately 60%–70% demonstrate no cognitive changes.[14,40] Current unpublished data suggest that patients with reduced CBF velocity during cross-clamping of the carotid artery are more likely to exhibit cognitive dysfunction 1 day after CEA. A previous study looked at SPECT scans to demonstrate that improvement in CBF was associated with improvement in cognitive function 1 month after CEA.[39] Another study assessed hypercapnia and cerebrovascular reserve with TCD ultrasonography and found an association between reduced preoperative cerebrovascular reserve and postoperative cognitive improvement 5 days after CEA.[9] However, no study has evaluated reduced peripheral resistance with perioperative TCD ultrasonography in the context of cognitive dysfunction as early as 1 day after CEA. Given the previous work that identifies most symptomatic patients as having reduced peripheral cerebral resistance prior to CEA followed by increased CBF after plaque removal,[5,6,19,20,30,31,34,36–38] it is reasonable to consider that these patients may be more likely to exhibit cognitive improvement.

In this study, we aim to determine whether symptomatic CEA patients with reduced peripheral cerebral resistance prior to CEA demonstrate increased CBF after plaque removal and cognitive improvement as early as 1 day after CEA. We hypothesize that symptomatic CEA patients with reduced peripheral resistance prior to CEA, in the MCA after plaque removal and cognitive improvement as early as 1 day after CEA.

Methods

Patients, Anesthesia, and Surgery

One hundred twenty-four patients were initially enrolled with written informed consent in an Institutional Review–Board approved observational single-center study at Columbia University Medical Center from 1995 to 2012 (clinical trial no: NCT00597883 [ClinicalTrials. gov]). Patients eligible for inclusion in this current study were those scheduled for elective CEA for carotid artery stenosis, English-speaking with no Axis I psychiatric disorders, with symptomatic history of stroke and/or transient ischemic attack, with complete intraoperative TCD ultrasonography records, and with complete neuropsychometric evaluation performed 24 hours or less preoperatively and 1 day postoperatively. Fifty-three patients met these criteria and were included in the current analyses.

All patients received general anesthesia with standard hemodynamic and temperature monitoring, as previously described.[14,15,18] No patient received a blood transfusion. The surgical technique, anesthesia management, and indications for CEA have remained constant at our institution. Six senior neurological and vascular surgeons performed all of the procedures. Four neurosurgical anesthesiologists administered general anesthesia; one anesthesiologist administered the anesthesia in 61.5% of cases.

Cognitive Measures

All patients underwent an extensive battery of neuropsychometric tests 24 hours or less preoperatively and 1 day postoperatively. The neuropsychometric tests evaluate 4 cognitive domains: verbal memory (Controlled Oral Word Association Test, Hopkins Verbal Learning Test, and/or Buschke Selective Reminding Test), visuospatial organization (Rey-Osterrieth Complex Figure Copy and Recall), motor function (Grooved Pegboard and/or Finger Tapping Test), and executive action (Halstead-Reitan Trials A and B).

Similar to previous studies,[14,15,17,18,24] Z-scores were generated based on a surgical reference group's performance to account for practice effect, trauma of surgery, general anesthesia, and the overnight hospital stay experience. The surgical reference group comprised 53 age- and sex-matched patients older than 60 years of age undergoing lumbar-level laminectomy or microdiscectomy on 2 levels or fewer without fusion, no tumor/cyst, or blood loss necessitating transfusion. These patients experienced similar surgical and anesthesia times as well as a similar general anesthetic. The mean difference score of the surgical reference group was subtracted from the difference score for the CEA patient and then divided by the standard deviation of the surgical reference group ([$Difference_{CEA}$ − Mean Difference $_{Reference}$]/$Standard Deviation_{Reference}$). Therefore, each test is evaluated in units of standard deviation of the surgical reference group's change in performance.

Carotid endarterectomy patient domains were evaluated to account for both focal and global/hemispheric improvements: 1) > 2 standard deviations better performance than the surgical reference group in 2 or more cognitive domains or 2) > 1.5 standard deviations better performance than the surgical reference group in all 4 cognitive domains. The details of each neuropsychometric test and their respective scoring rubrics have been described in great detail in previous work.[10,14,16,18,29] The surgical reference group was only used to generate Z-scores; therefore, the surgical reference patients were not included in any other analysis or reported otherwise in this study.

Transcranial Doppler Ultrasonography

An ST-3 TCD ultrasonography machine (Spencer Technologies) was used in all 53 cases. A 2-MHz probe was applied over the thinnest portion of the squamous component of the temporal bone on the operative side of the head. The MCA was located and insonated at an approximate depth of 50 mm from the scalp. A Marc 600 headframe (Spencer Technologies) was used to hold the probe in place for the duration of the surgery. The TCD ultrasonography parameters evaluated in this study were CBF mean velocity (MV) measured in units of centimeters per second and the Gosling PI, which was determined as the difference between the peak systolic and end-diastolic velocities divided by the MV of flow in the MCA. [8,20,22,33]

Previous studies identified PI values < 1.0 indicative of reduced peripheral cerebral resistance in the context of a variety of outcomes (0.87,[36] 0.78,[6] and 0.77[34]). Based on these previous studies, baseline PI ≤ 0.80 was used as a conservative cutoff for reduced peripheral cerebral resistance prior to CEA in this study.

Prospective recordings were obtained throughout the case. Baseline TCD measurements were obtained prior to induction of general anesthesia while the patient was still awake, and the measurements were continuously recorded from the time of induction of general anesthesia until extubation at the end of each case. The 2 time points evaluated closest in this study were at baseline and 15 minutes after the plaque removal and flow restoration through the internal carotid artery. We considered the parameters at 15 minutes after plaque removal and flow restoration to allow perfusion to stabilize after flow restoration. Transcranial Doppler ultrasonography was solely used intraoperatively, and as such the 15-minute time point was the last recording before extubation. Change in CBF MV and PI were calculated from baseline to 15 minutes after plaque removal and flow restoration (that is, CBF $MV_{15\ minutes}$ − CBF $MV_{baseline}$).

Statistical Analysis

Statistical analysis was performed using JMP 10 software (SAS Institute, Inc.). For univariate analyses, the Student t-test, Wilcoxon rank sum test, the Fisher exact test, the Pearson chi-square test, and simple logistic regression were used where appropriate. A multiple logistic regression model was constructed to identify independent predictors of cognitive improvement 1 day after CEA. All factors with $p \leq 0.20$ in simple univariate logistic regression with cognitive improvement were entered into the final model. A p value ≤ 0.05 was considered significant.

Results

Patient characteristics are presented in Table 1. In the entire cohort of 53 symptomatic CEA patients, 20 patients (37.7%) had a baseline PI ≤ 0.80. There were no significant differences in patient characteristics, medication use, medical history, or baseline neuropsychometric scores between patients with baseline PI ≤ 0.80 and > 0.80.

The TCD parameters are presented in Table 2. In the entire cohort of 53 symptomatic CEA patients, the average PI was 0.88 ± 0.21 at baseline and 1.11 ± 0.22 15 minutes after plaque removal and flow restoration. Patients with baseline PI ≤ 0.80 trended toward a greater increase in CBF MV from baseline to 15 minutes after plaque removal, although this did not reach statistical significance (9.6 ± 12.1 cm/sec vs 3.7 ± 11.1 cm/sec, $p = 0.08$). The PI 15 minutes after plaque removal was not significantly different between patients with baseline PI ≤ 0.80 and > 0.80. However, the change in PI from baseline to 15 minutes after plaque removal was significantly greater in patients with baseline PI ≤ 0.80 (0.39 ± 0.05 vs 0.14 ± 0.04, $p < 0.001$).

Nine patients demonstrated cognitive improvement 1 day after CEA (17.0%). Patient characteristics and baseline neuropsychometric scores were not different between patients with and without cognitive improvement. Significantly more patients with baseline PI ≤ 0.80 had cognitive improvement than patients with baseline PI > 0.80 (35.0% vs 6.1%, $p = 0.007$). Patients with cognitive improvement had a significantly greater increase in CBF MV from baseline to 15 minutes after plaque removal than patients without cognitive improvement (13.4 ± 17.1 vs 4.3 ± 9.9 cm/sec, $p = 0.03$). Seven of the 9 patients who demonstrated cognitive improvement also had baseline PI ≤ 0.80 as well as an increase in CBF MV; 1 of the remaining 2 patients had no change in CBF MV while the other had a baseline PI of 0.9.

History of CABG, baseline PI ≤ 0.80, and CBF MV change from baseline to 15 minutes after plaque removal were included in the final multivariate regression model (Table 3). Baseline PI ≤ 0.80 was the only factor significantly associated with greater odds of cognitive improvement 1 day after CEA (OR 7.32 [1.40–59.49], $p = 0.02$).

Discussion

Carotid endarterectomy is a commonly performed procedure to prevent future stroke in patients with symptomatic carotid artery stenosis.[3,13,28] Previous TCD studies have demonstrated that symptomatic CEA patients exhibit reduced peripheral cerebral resistance prior to CEA as measured by the Gosling PI of the MCA.[5,6,19,20,30,31,34,36–38] Symptomatic patients rely more heavily on reducing peripheral cerebral resistance to maintain sufficient perfusion of the hemispheres, likely due to lack of adequate collateral circulation in conjunction with carotid artery stenosis. Because of a baseline degree of exhausted cerebral

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autoregulation,[4,19–21,25–27,30,31,34,36,38] symptomatic CEA patients also tend to demonstrate increased CBF after plaque removal and flow restoration. [5,6,19,30,36–38]

Cerebral blood flow and TCD ultrasonography have been previously studied in the context of cognitive improvement.[9,39] However, cognitive improvement was evaluated at 5 days and 1 month after CEA. This study is the first to demonstrate that symptomatic CEA patients with reduced peripheral resistance measured as PI ≤ 0.80 prior to CEA are likely to have a greater increase in CBF velocity after plaque removal and are significantly more likely to exhibit cognitive improvement as early as 1 day after CEA than patients with PI > 0.80. These findings have important implications for patients with symptomatic carotid artery stenosis and reduced peripheral cerebral resistance.

Prior to CEA, patients with symptomatic carotid artery stenosis are likely to have reduced peripheral cerebral resistance to compensate for a lack of sufficient collateral circulation in conjunction with carotid artery stenosis;[5,6,19,20,30,31,34,36–38] the patients likely have a degree of cerebral autoregulatory exhaustion. Although these cerebral autoregulatory mechanisms are actively trying to compensate for the stenosis and lack of collaterals, the manifestation of stroke and/or transient ischemic attack indicates that the CBF is still less than is required to adequately perfuse the brain. Therefore, it is reasonable to consider that after plaque removal and flow restoration during CEA, CBF increases and is potentially manifested as cognitive improvement as early as 1 day after surgery.

The findings in this study demonstrate that prior to CEA and after plaque removal, the absolute CBF velocities are comparable between patients with baseline PI ≤ 0.80 and those with PI > 0.80. However, the change in CBF velocity from before CEA to after plaque removal are notably different. The patients with baseline PI ≤ 0.80 experience an almost 3-fold increase in CBF velocity compared with patients with baseline PI > 0.80. The patients with baseline PI ≤ 0.80 demonstrated an incidence in cognitive improvement almost 6-fold that of the patients with baseline PI > 0.80. Of the 9 patients who demonstrated cognitive improvement, 8 had an increase in CBF MV while 1 had no change, and 8 had a baseline PI ≤ 0.80 while 1 had a baseline PI of 0.9. These observations suggest that patients with reduced peripheral cerebral resistance measured by baseline PI ≤ 0.80 are very likely to have increased CBF and cognitive improvement after CEA for symptomatic carotid artery stenosis. These findings suggest that carotid artery revascularization in this cohort may afford benefits beyond prevention of future stroke.

We acknowledge limitations of this study. This study is a single-center observational trial in a relatively small cohort of patients; the findings of this study cannot be generalized to the greater population without more extensive study. Transcranial Doppler ultrasonography has limitations as it provides indirect measurements of CBF and cerebrovascular reserve; the measurements of PI and MV are parameters partially dependent on a variety of factors that include depth of anesthesia, blood pressure, end-tidal CO_2, and ventilatory rate. Although these factors were not prospectively recorded for every patient, the anesthetic technique and maintenance remained consistent through-out the study. Patients with symptomatic carotid artery stenosis may experience embolic or ischemic events prior to CEA;[7,27,32,35] the etiology of the patients' symptoms were not known in this study. It is unclear whether designating patients with embolic or ischemic symptoms differently could have influenced the findings of this study. Additionally, we acknowledge that the time point of our cognitive improvement is limited to 1 day; ideally, in future studies we would like to follow up with patients at further time points to see if the cognitive improvement is sustained after it is documented at 1 day. However, based on previous studies evaluating similar outcomes, cognitive improvement is evident in patients who have undergone CEA at 5 days, 8 weeks, and 1 month.[9,39]

Conclusions

This study demonstrates that symptomatic CEA patients with reduced peripheral cerebral resistance prior to CEA, measured by baseline PI ≤ 0.80 on TCD ultrasonography, are likely to have increased CBF after plaque removal and improved cognitive performance as early as 1 day after CEA for symptomatic carotid artery stenosis. Carotid artery revascularization may produce benefits beyond those of future stroke prevention in this cohort.

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Abbreviations used in this paper

CABG	coronary artery bypass graft
CBF	cerebral blood flow
CEA	carotid endarterectomy
MCA	middle cerebral artery
MV	mean velocity
PI	pulsatility index
TCD	transcranial Doppler

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TABLE 1

Patient characteristics*

Characteristic	All Patients (n = 53)	Baseline PI† ≤0.80 (n = 20)	Baseline PI† >0.80 (n = 33)	p Value‡
age, yrs	72.3 ± 8.1	71.4 ± 8.0	72.8 ± 8.3	0.54
sex, male	36 (67.9)	16 (80.0)	20 (60.6)	0.13
education, yrs	14.1 ± 2.8	13.7 ± 2.0	14.4 ± 3.1	0.40
BMI in kg/m^2	26.7 ± 4.5	27.3 ± 4.8	26.3 ± 4.3	0.42
history of smoking	41 (77.4)	16 (80.0)	25 (75.8)	0.72
aspirin use	46 (86.8)	17 (85.0)	29 (87.9)	0.77
statin use	43 (81.1)	16 (80.0)	27 (81.8)	0.87
diabetes mellitus	9 (17.0)	4 (20.0)	5 (15.2)	0.65
hypertension	35 (66.0)	14 (70.0)	21 (63.6)	0.63
PVD	16 (32.0)	6 (33.3)	10 (31.3)	0.88
history of MI	13 (24.5)	5 (25.0)	8 (24.2)	0.95
history of CABG	5 (9.4)	2 (10.0)	3 (9.1)	0.91
op side, rt	30 (56.6)	13 (65.0)	17 (51.5)	0.34

*Non–p values are the number of patients (%) unless indicated otherwise. Mean values are ± SD. BMI = body mass index; MI = myocardial infarction; PVD = peripheral vascular disease.

†The time point prior to induction of general anesthesia.

‡P values reported of comparative analyses between patients with baseline PI ≤0.80 and >0.80.

TABLE 2

Transcranial Doppler ultrasonography parameters

Parameter	All Patients (n = 53)	Baseline PI ≤0.80 (n = 20)	Baseline PI >0.80 (n = 33)	p Value*
baseline CBF MV (cm/sec)	45.9 ± 14.1	43.7 ± 13.7	47.3 ± 14.4	0.37
baseline PI	0.88 ± 0.21	0.68 ± 0.11	1.00 ± 0.16	<0.001
15-min CBF MV (cm/sec)†	51.8 ± 13.7	53.2 ± 17.4	50.9 ± 11.1	0.57
15-min PI†	1.11 ± 0.22	1.06 ± 0.23	1.15 ± 0.22	0.19
CBF MV change (cm/sec)‡	5.9 ± 11.7	9.6 ± 12.1	3.7 ± 11.1	0.08
PI change‡	0.23 ± 0.24	0.39 ± 0.05	0.14 ± 0.04	<0.001

*P values reported of comparative analyses between patients with baseline PI ≤0.80 and >0.80.

†Thetimepoint15minutesafterplaqueremovaland restoration.

‡Change from baseline to 15 minutes after plaque removal and flow restoration.

TABLE 3

Univariate and multivariate logistic regression model: cognitive improvement

Characteristic	Univariate OR (95% CI)	p Value	Multivariate OR (95% CI)	p Value
age, per yr	0.95 (0.86–1.04)	0.29		
sex, male	1.07 (0.20–4.72)	0.93		
education, per yr	0.93 (0.72–1.22)	0.60		
BMI, per kg/m^2	1.03 (0.88–1.24)	0.75		
history of smoking	0.38 (0.02–2.40)	0.33		
aspirin use	1.14 (0.45–1.46)	0.29		
statin use	1.29 (0.17–6.64)	0.78		
diabetes mellitus	1.78 (0.27–35.4)	0.59		
hypertension	0.50 (0.07–2.37)	0.40		
PVD	0.40 (0.08–1.94)	0.25		
history of MI	0.59 (0.13–3.17)	0.51		
history of CABG	0.26 (0.04–2.20)	0.20	0.30 (0.02–4.94)	0.37
op side, rt	0.60 (0.12–2.59)	0.50		
baseline PI ≤0.80	8.35 (1.75–61.31)	0.007	7.32 (1.40–59.49)	0.02
CBF MV change (cm/sec)*	0.94 (0.87–1.00)	0.04	0.96 (0.87–1.03)	0.23

*Change from baseline to 15 minutes after plaque removal and restoration.