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Reduced middle cerebral artery velocity during cross-clamp predicts cognitive dysfunction after carotid endarterectomy

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Abstract

Transcranial Doppler (TCD) is a useful monitor that can be utilized during carotid endarterectomy (CEA). Cognitive dysfunction is a subtler and more common form of neurologic injury than stroke. We aimed to determine whether reduced middle cerebral artery (MCA) mean velocity (MV) predicts cognitive dysfunction and if so, whether a threshold of increased risk of cognitive dysfunction can be identified. One hundred twenty-four CEA patients were included in this observational study and neuropsychometrically evaluated preoperatively and 24 hours postoperatively. MCA–MV was measured by TCD and percentage of baseline during cross-clamp was calculated ($MV_{\text{cross-clamp}}/MV_{\text{baseline}}$). Patients with cognitive dysfunction had significantly lower MV during cross-clamp than those without cognitive dysfunction (33.1 ± 13.7 cm/s *versus* 39.6 ± 16.0 cm/s, $p = 0.02$). In the final multivariate model, each percent reduction in MV was significantly associated with greater risk of cognitive dysfunction (odds ratio [OR]: 0.05 [95% confidence interval {CI} 0.01–0.23], $p < 0.001$) while statin use was associated with lower risk (OR: 0.33 [95% CI 0.12–0.92], $p = 0.03$). Using receiver operator characteristic curve analysis, the Youden index identified 72% of baseline MV during cross-clamp as the cutoff of maximum discrimination. Significantly more patients with MV < 72% of baseline during cross-clamp exhibited cognitive dysfunction than patients with MV $\geq$ 72% of baseline (74.1% *versus* 27.1%, $p < 0.001$). Reduced MCA–MV during cross-clamp is a predictor of cognitive dysfunction exhibited 24 hours after CEA. MCA–MV reduced to < 72% of baseline, or a $\geq$ 28% reduction from baseline, is the threshold most strongly associated with increased risk of cognitive dysfunction. These observations should be considered by all clinicians that utilize intraoperative monitoring for CEA.

Keywords

Carotid endarterectomy; Cognition; Cognitive dysfunction; Transcranial Doppler

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Conflicts of Interest/Disclosures

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1. Introduction

Transcranial Doppler (TCD) is a useful adjunct to the commonly used electroencephalographic (EEG) monitoring during carotid endarterectomy (CEA)(1-6). The incidence of perioperative stroke during CEA is very low(2, 7), but is generally attributed to either ischemia during cross-clamp of the carotid artery or emboli during reperfusion(8). EEG is commonly used to prevent ischemic stroke by detecting significant hemispheric ischemia during the cross-clamp period. Previous studies have determined that TCD assessment of cerebral blood flow mean velocity (MV) through the middle cerebral artery (MCA) can detect ischemic as well as embolic events and can further reduce the risk of stroke(4, 9, 10).

As the incidence of perioperative stroke is exceedingly rare, investigators are studying subtler forms of neurologic injury, like cognitive dysfunction, to improve the safety of this commonly performed procedure(11-15). To our knowledge, however, no studies have determined whether TCD assessment of cerebral blood flow through the MCA can detect mildly ischemic conditions that are undetected by EEG and associated with cognitive dysfunction. Though less clinically momentous than stroke, postoperative cognitive dysfunction has significant implications for quality of life and early mortality(16). Glial markers of neuronal injury are significantly elevated in CEA patients that exhibit cognitive dysfunction as early as 24 hours after CEA(17). In our previous work, we documented that approximately a quarter of CEA patients exhibit cognitive dysfunction 24 hours after CEA(18, 19). Given the common occurrence and significance of cognitive dysfunction, determining if TCD parameters can predict cognitive dysfunction is not only interesting, but it can improve the neurologic safety of this commonly performed procedure.

The aim of this study was to determine whether TCD assessment of cerebral blood flow through the MCA during cross-clamp of the carotid artery can predict cognitive dysfunction 24 hours after CEA and if so, whether a threshold associated with increased risk of cognitive dysfunction can be identified. These findings could ultimately be utilized to improve the safety of this commonly performed procedure.

2. Methods

2.1. Patients, anesthesia and surgery

One hundred twenty-four patients were enrolled with written informed consent in this Institutional Review Board-approved observational single center study at Columbia University Medical Center (<http://www.ClinicalTrials.gov> NCT00597883). Patients eligible for inclusion in this observational study were those scheduled for elective CEA for high-grade carotid artery stenosis who were English-speaking, with no axis-I psychiatric disorders, with complete intraoperative TCD records, and complete neuropsychometric evaluation preoperatively and 24 hours postoperatively.

All patients received general anesthesia with standard hemodynamic and temperature monitoring, as previously described(18). No patients received blood transfusions. The surgical technique, anesthetic management, and indications for CEA have remained constant at this institution, as previously described (18-21).

2.2. Cognitive measures

All patients were examined with an extensive battery of neuropsychometric tests 24 hours preoperatively and 24 hours postoperatively. The neuropsychometric tests evaluate four cognitive domains – verbal memory (Controlled Oral Word Association Test, Hopkins Verbal Learning Test, and/or Buschke Selective Reminding Test), visuo-spatial organization

(Key-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(18-20, 22, 23), 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 was composed of 124 age- and sex-matched patients 60 years of age undergoing lumbar level laminectomy or microdiscectomy on 2 levels without fusion, no tumor/cyst, or blood loss necessitating transfusion. These patients experience similar surgical and anesthetic 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 ($[\text{Difference}_{\text{CEA}} - \text{Mean Difference}_{\text{Reference}}] / \text{Standard Deviation}_{\text{Reference}}$). Therefore, each test was evaluated in units of standard deviation (SD) of the surgical reference group's change in performance.

CEA patient domains were evaluated to account for both focal and global/hemispheric deficits: (1) 2 SD worse performance than the reference group in two or more cognitive domains or (2) 1.5 SD worse performance than the reference group in all four cognitive domains. The details of each neuropsychometric test and their respective scoring rubrics are described in great detail in previous works(18, 19, 21, 24, 25). 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.

A variety of factors affect the risk of cognitive dysfunction after CEA, but only age > 75 years, diabetes mellitus, and statin use have been previously shown to significantly and independently affect the risk(23, 26). Other factors that might also affect the risk, but have not been shown to independently do so, were evaluated as well. These included sex, years of education, body mass index, history of smoking, hypertension, extensive peripheral vascular disease, previous myocardial infarction, previous coronary bypass-grafting, symptomatic history of transient ischemic attack or stroke, operative side, and duration of cross-clamp.

2.3. EEG

All patients were monitored intraoperatively with a 16 channel XL-Tek EEG (Natus Medical Inc., San Carlos, CA, USA) bipolar "double-banana" montage(27) using the nomenclature of the International 10-20 electrode placement system with either an Electro-Cap (Electro-Cap International Inc., Eaton, OH, USA) (N=83) or microelectrodes (Rhythmlink, Columbia, SC, USA) (n = 41). Intraoperative monitoring for cerebral ischemia was performed by board certified neurologists. No patients included in this study experienced significant intraoperative ischemia detected by EEG that required shunt placement. No patients included in this study had a perioperative stroke.

2.4. Transcranial Doppler

An ST-3 TCD machine (Spencer Technologies, Seattle, WA, USA) was used for all patients. 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 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 primary TCD parameter evaluated in this study was MCA-MV measured in units of cm/s. Pulsatility index (PI) was also recorded to document a surrogate marker of cerebrovascular distal resistance. Prospective recordings were obtained at baseline, pre-clamp, clamp, 30 seconds post-clamp, pre-release, release, 5 minutes post-release, and 15 minutes post-release. Patients had baseline MV and PI values recorded prior to incision. During cross-clamp of the carotid

artery, MV and PI were recorded at several time points, but the values utilized in this study are the values recorded after perfusion stabilized and remained constant during the cross-clamp period; immediately after cross-clamp, the MV often takes seconds to minutes to stabilize as cerebrovascular distal resistance, reflected as PI, decreases to compensate for the reduced blood flow (Fig. 1). The stabilized MV during cross-clamp was then divided by the MV at baseline ($MV_{\text{cross-clamp}}/MV_{\text{baseline}}$) to provide the percentage of remaining MCA blood flow velocity and presumptive blood flow. TCD records were also evaluated for high-intensity transient signals (HITS) to account for potential embolic or micro-embolic events during reperfusion(28).

2.5. Statistical analysis

Statistical analysis was performed using R environment for statistical computing (R Development Core Team, Vienna, Austria). Multivariate imputation by chained equations (mice) with fully conditional specification was used in the event of missing data.(29) Five imputations were performed, with predictive mean matching for continuous variables and logistic regression for categorical variables. The R package mice (R Development Core Team)(30) was used to perform the imputation and pooled analyses.

For univariate analyses, Student's *t*-test, Wilcoxon rank sums test, Fisher's exact test, Pearson's χ^2 test and simple logistic regression were used where appropriate. A multiple logistic regression model was constructed to identify independent predictors of cognitive dysfunction within 24 hours. All factors with $p < 0.20$ in simple univariate logistic regression were entered into the final model. Model fit and calibration were confirmed with the likelihood ratio test, Hosmer–Lemeshow goodness-of-fit test, and receiver operating characteristic analysis. $p = 0.05$ was considered significant.

To determine the reduced MV during cross-clamp cutoff of maximal discrimination between patients with and without cognitive dysfunction, receiver operating curve (ROC) analysis and maximum Youden index was used. This was performed using the R package pROC (R Development Core Team)(31).

3. Results

Patient characteristics of the entire cohort of 124 CEA patients are presented in Table 1. Fifty-nine patients exhibited cognitive dysfunction 24 hours after CEA. Significantly fewer patients with cognitive dysfunction were taking statins at the time of CEA (69.5% *versus* 84.6%, $p = 0.04$), consistent with previous findings(23). Patients with cognitive dysfunction had significantly lower MCA–MV during cross-clamp than those without cognitive dysfunction (33.1 ± 13.7 cm/s *versus* 39.6 ± 16.0 cm/s, $p = 0.02$) (Fig. 2). There were no significant differences in MCA–PI between patients with and without cognitive dysfunction (Fig. 3). TCD records positive for HITS during reperfusion were similar between patients with and without cognitive dysfunction (57.6% *versus* 55.4%, $p = 0.80$).

Education, statin use, diabetes mellitus, hypertension, cross-clamp duration, and MV reduction during cross-clamp met criteria for inclusion in the multivariate regression model predicting cognitive dysfunction. In the final multivariate model, each percent reduction of MV from baseline during cross-clamp was significantly associated with increased risk of cognitive dysfunction (odds ratio [OR]: 0.05 [95% confidence interval {CI} 0.01–0.23], $p < 0.001$) while statin use was associated with lower risk of cognitive dysfunction (OR: 0.33 [95% CI 0.12–0.92], $p = 0.03$) (Table 2).

Using ROC analysis to determine a threshold of MV reduction most predictive of cognitive dysfunction, the area under the curve was 0.74 (95% CI 0.66–0.83). The maximum Youden

index identified 72% of baseline MV as the cutoff of maximum discrimination for cognitive dysfunction (Fig. 4); this corresponds to a 28% reduction in MV from baseline to cross-clamp. Patient characteristics were not different between those whose MV was reduced to < 72% of baseline MV during cross-clamp and those ≥ 72% of baseline MV (Table 3). Significantly more patients with an MV reduced to < 72% of baseline MV during cross-clamp exhibited cognitive dysfunction than patients with an MV ≥ 72% of baseline MV (74.1% versus 27.1%, $p < 0.001$).

4. Discussion

TCD is a useful adjunct to the commonly used intraoperative EEG monitoring for CEA and may, in fact, be a better predictor of cognitive dysfunction 24 hours after surgery than EEG. Previous studies have identified TCD parameters predictive of stroke(4, 9, 10), but, to our knowledge, this study is the first to use TCD to predict subtler neurologic injury in the context of cognitive dysfunction as early as 24 hours after surgery. The observations of this study have implications for anesthesiologists, surgeons, neurologists, and electrophysiologists that utilize intraoperative TCD during CEA.

The data suggest that a reduction of MCA-MV to < 72% of baseline, or a ≥ 28% reduction from baseline, is the threshold most strongly associated with increased risk of cognitive dysfunction. These parameters are most appropriately describing conditions that are mildly ischemic. The ischemic threshold to detect significant EEG changes is ~18 mL/100 g/minute, which is approximately a 60% reduction from normal baseline cerebral blood flow at ~50 mL/100 g/minute(32). Reductions 30–60% below baseline that are often undetected by EEG, but can be detected by TCD and provide information regarding risk of cognitive dysfunction due to these mildly ischemic conditions.

Interestingly, the data also demonstrate statin use is associated with lower risk of cognitive dysfunction in the context of these mildly ischemic conditions. This finding is consistent with our previous work in asymptomatic CEA patients(23) and ischemia-reperfusion models(33-37). Statins are implicated to be neuroprotective against the neurologic injury of ischemia both in human(33, 34) and animal stroke models(35-37). Therefore, it is reasonable to consider the neuroprotection of statins in the setting of subtler ischemic injuries like cognitive dysfunction; statins improve vascular function by regulating nitric oxide production(38, 39) and can reduce inflammatory cytokines associated with ischemia-reperfusion(34, 40-43).

Previous work has demonstrated that patients with cognitive dysfunction have significantly elevated markers of neuronal injury(17), reduced quality of life, and early mortality(16) following surgery. Therefore, TCD assessment of MCA-MV during CEA may be an appropriate approach to reducing the risk of cognitive dysfunction after surgery and further improving the safety of CEA. MCA-MV evaluation can be used in conjunction with the standard methods of neurological monitoring when making decisions about optimizing collateral blood flow during cross-clamp of the carotid artery by mean arterial pressure augmentation or shunt placement.

There are some limitations of this study. This is a single-center observational study and therefore, our sample size is relatively small. The findings of this study should be replicated and explored further in other populations. Previous work identifies age > 75 years and diabetes mellitus to be risk factors and predictors of cognitive dysfunction after CEA(26). Additionally, previous work found approximately 25% of CEA patients exhibit cognitive dysfunction(18, 19). This current study, however, did not replicate those findings; age > 75 years and diabetes mellitus were not significantly predictive in our multivariate model and

the incidence of cognitive dysfunction was almost double that found in previous works. These findings were unexpected, but we offer our speculation as to why these findings are different from that of previous works. The cohort analyzed in this study is a sub-set of the general CEA population operated on and studied at our institution. In order to be included in this particular study of TCD and cognitive dysfunction, the patients needed complete intraoperative TCD records as well as the complete neuropsychometric evaluation available for review. Not all patients undergoing CEA have adequate temporal windows permitting for accurate and reliable intraoperative TCD assessment of MCA blood flow. The limited, non-randomized selection of patients may account for these discrepancies and is a limitation of this study. Lastly, we do not have data available for evaluation of cognitive dysfunction at later time points such as 6 months or 1 year.

In conclusion, reduced MCA–MV during cross-clamp of the carotid artery is a predictor of early cognitive dysfunction exhibited 24 hours after CEA. MCA–MV reduced to < 72% of baseline, or a 28% reduction from baseline, is the threshold most strongly associated with increased risk of cognitive dysfunction. Our study suggests TCD can be used in conjunction with standard methods of neurological monitoring to predict mildly ischemic conditions that are undetected by EEG and that may lead to cognitive dysfunction. These observations should be considered by anesthesiologists, surgeons, neurologists, and electrophysiologists that utilize intraoperative monitoring for CEA.

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Fig. 1.

Line graph example of a patient's middle cerebral artery–mean velocity (MV) (black) and pulsatility index (PI) (grey) assessment during carotid endarterectomy (CEA). The x-axis is the time scale of a patient's CEA: A = baseline (pre-incision), B = induction of anesthesia, C = clamp (immediately after the clamp is placed on the carotid artery), D = 30 seconds post-clamp (as the MV and PI stabilize for the rest of the cross-clamp period), E = pre-release, F = release (immediately after the clamp is released from the carotid artery), G = 30 seconds post-release (as the MV and PI begin to stabilize), H = 5 minutes post-release, and I = 25 minutes post-release. The right y-axis is the scale of PI, which is a unitless ratio (peak systolic – end diastolic velocities/mean flow velocity). The graph demonstrates that often a period of seconds or minutes is necessary to allow the cerebrovascular distal resistance to stabilize during cross-clamp and clamp release. Here the MV decreases while PI requires extra seconds to decrease. The MV and PI remain fairly stable until clamp release.

Fig. 2.

Bar graph of average middle cerebral artery–mean velocity (MCA–MV) of all patients with cognitive dysfunction (black, $n = 59$) and all without cognitive dysfunction (grey, $n = 65$) during carotid endarterectomy (CEA). The x-axis is the time scale of CEA. Error bars are standard deviation. Patients with cognitive dysfunction had significantly lower stabilized MCA–MV than those without cognitive dysfunction (33.1 ± 13.7 cm/s *versus* 39.6 ± 16.0 cm/s, $p = 0.02$), indicated by * in graph. No other time points had significant differences between those with and without cognitive dysfunction.

Fig. 3.

Bar graph of average middle cerebral artery pulsatility index (MCA-PI) of all patients with cognitive dysfunction (black, n = 59) and all patients without cognitive dysfunction (grey, n = 65) during carotid endarterectomy (CEA). The y-axis is the scale of PI, which is a unitless ratio (peak systolic – end diastolic velocities/mean flow velocity). Error bars are standard deviation. There were no significant differences between patients with and without cognitive dysfunction at any time points.

Fig. 4.

Receiving operator characteristic curve analysis of the middle cerebral artery mean velocity during cross-clamp showing the area under the curve was 0.74 (95% CI 0.66–0.83). The point specified on the graph is the Youden index representing the cutoff of maximal discrimination, followed by, respectively, the specificity and sensitivity associated with that cutoff in parentheses.

Table 1

Characteristics of patients who underwent transcranial Doppler during carotid endarterectomy by cognitive dysfunction

	All patients n = 124	Cognitive dysfunction n = 59	No cognitive dysfunction n = 65	p value [†]
Age > 75 years	30.7	32.2	29.2	0.72
Sex, male	63.7	66.1	61.5	0.60
Education, years	14.4 ± 3.0	13.9 ± 2.9	14.8 ± 3.0	0.11
BMI, kg/m ²	26.4 ± 4.5	26.4 ± 4.6	26.4 ± 4.4	0.93
History of smoking	75.8	72.9	78.5	0.47
Statin use	77.4	69.5	84.6	0.04
Diabetes mellitus	13.7	18.6	9.2	0.13
Hypertension	58.1	50.9	64.6	0.12
PVD	33.9	38.6	29.7	0.30
Previous MI	24.2	28.8	20.0	0.25
Previous CABG	14.2	11.9	16.4	0.48
Symptomatic status	42.7	44.1	41.5	0.78
Operative side, right	51.6	48.4	51.6	0.84
Cross-clamp duration, minutes	43.6 ± 17.1	41.2 ± 14.2	46.1 ± 19.4	0.13

Data are presented as mean ± standard deviation or percentage.

[†] Student's *t*-test, χ^2 between patients with and without cognitive dysfunction.

BMI = body mass index, CABG = coronary artery bypass-grafting, MI = myocardial infarction, PVD = peripheral vascular disease.

Table 2

Univariate and multivariate logistic regression model

	Univariate odds ratio	p value	Multivariate odds ratio	p value
Age > 75 years	1.15 (0.53–2.48)	0.52		
Sex, male	1.22 (0.59–2.56)	0.60		
Education, per year	0.90 (0.80–1.02)	0.10	0.90 (0.79–1.04)	0.15
BMI, per kg/m ²	1.00 (0.93–1.09)	0.92		
History of smoking	0.74 (0.32–1.68)	0.47		
Statin use	0.41 (0.17–0.97)	0.05	0.33 (0.12–0.92)	0.03
Diabetes mellitus	2.25 (0.80–6.96)	0.14	1.96 (0.60–6.45)	0.26
Hypertension	0.57 (0.27–1.16)	0.12	0.83 (0.35–1.93)	0.66
PVD	1.46 (0.683.15)	0.33		
Previous MI	1.62 (0.71–3.76)	0.25		
Previous CABG	0.71 (0.25–2.02)	0.52		
Symptomatic status	1.11 (0.54–2.27)	0.78		
Operative side, right	1.07 (0.53–2.18)	0.84		
Cross-clamp duration, per minute	0.98 (0.96–1.01)	0.16	0.99 (0.97–1.03)	0.81
MV, per % reduction from baseline	0.08 (0.02–0.28)	<0.001	0.05 (0.01–0.23)	<0.001

Data are presented as odds ratio (95% confidence interval).

BMI = body mass index, CABG = coronary artery bypass-grafting, MI = myocardial infarction, MV = mean velocity, PVD = peripheral vascular disease.

Table 3

Patient characteristics who underwent transcranial Doppler during carotid endarterectomy by middle cerebral artery mean velocity $\geq 72\%$ versus mean velocity $< 72\%$

	All patients n = 124	MV $\geq 72\%$ n = 70	MV $< 72\%$ n = 54	p value [†]
Age > 75 years	30.7	27.1	35.2	0.34
Sex, male	63.7	64.3	63.0	0.88
Education, years	14.4 $\pm$ 3.0	14.7 $\pm$ 3.0	13.9 $\pm$ 3.0	0.13
BMI, kg/m ²	26.4 $\pm$ 4.5	26.3 $\pm$ 4.7	26.5 $\pm$ 4.2	0.87
History of smoking	75.8	74.3	77.8	0.65
Statin use	77.4	77.1	77.8	0.93
Diabetes mellitus	13.7	12.9	14.8	0.75
Hypertension	58.1	65.7	48.2	0.08
PVD	33.9	33.8	34.0	0.99
Previous MI	24.2	22.9	25.9	0.69
Previous CABG	14.2	16.7	11.1	0.38
Symptomatic status	42.7	42.9	42.6	0.98
Operative side, right	51.6	52.9	50.0	0.75
Cross-clamp duration, minutes	43.6 $\pm$ 17.1	46.1 $\pm$ 19.0	40.6 $\pm$ 14.0	0.09
Cognitive dysfunction	47.6	27.1	74.1	< 0.001

Data are presented as mean $\pm$ standard deviation or percentage.

[†] Student's *t*-test, χ^2 between patients with MV $< 72\%$ and MV $\geq 72\%$.

BMI = body mass index, CABG = coronary artery bypass-grafting, MI = myocardial infarction, MV = mean velocity, PVD = peripheral vascular disease.