From the Society for Vascular Surgery

Volume of subclinical embolic infarct correlates to long-term cognitive changes after carotid revascularization

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ABSTRACT

Objective: Carotid intervention is safe and effective in stroke prevention in appropriately selected patients. Despite minimal neurologic complications, procedure-related subclinical microemboli are common and their cognitive effects are largely unknown. In this prospective longitudinal study, we sought to determine long-term cognitive effects of embolic infarcts.

Methods: The study recruited 119 patients including 46% symptomatic patients who underwent carotid revascularization. Neuropsychological testing was administered preoperatively and at 1 month, 6 months, and 12 months postoperatively. Rey Auditory Verbal Learning Test (RAVLT) was the primary cognitive measure with parallel forms to avoid practice effect. All patients also received 3T brain magnetic resonance imaging with a diffusion-weighted imaging (DWI) sequence preoperatively and within 48 hours postoperatively to identify procedure-related new embolic lesions. Each DWI lesion was manually traced and input into a neuroimaging program to define volume. Embolic infarct volumes were correlated with cognitive measures. Regression models were used to identify relationships between infarct volumes and cognitive measures.

Results: A total of 587 DWI lesions were identified on 3T magnetic resonance imaging in 81.7% of carotid artery stenting (CAS) and 36.4% of carotid endarterectomy patients with a total volume of 29,327 mm^3. Among them, 54 DWI lesions were found in carotid endarterectomy patients and 533 in the CAS patients. Four patients had transient postoperative neurologic symptoms and one had a stroke. CAS was an independent predictor of embolic infarction (odds ratio, 6.6 [2.1-20.4]; $P < .01$) and infarct volume ($P = .004$). Diabetes and contralateral carotid severe stenosis or occlusion had a trend of positive association with infarct volume, whereas systolic blood pressure ≥140 mm Hg had a negative association ($P = .1$, .09, and .1, respectively). There was a trend of improved RAVLT scores overall after carotid revascularization. Significantly higher infarct volumes were observed among those with RAVLT decline. Within the CAS cohort, infarct volume was negatively correlated with short- and long-term RAVLT changes ($P < .05$).

Conclusions: Cognitive assessment of procedure-related subclinical microemboli is challenging. Volumes of embolic infarct correlate with long-term cognitive changes, suggesting that microembolization should be considered a surrogate measure for carotid disease management. (J Vasc Surg 2016;■:1-9.)

Carotid revascularization procedures including carotid endarterectomy (CEA) and carotid artery stenting (CAS) have been shown to be effective in stroke prevention in appropriately selected patients with low perioperative morbidities and mortality.[1-3] Recent advancements in medical therapy spark controversies on the efficacy of carotid revascularization and intense debates on the best treatment strategies for asymptomatic patients with severe carotid occlusive disease.[4] However, the ongoing debates and most studies evaluating the effectiveness of carotid interventions focus on neurologic outcomes. Neurocognitive outcomes have not been fully considered.

With improved life expectancy and a growing aging population, cognitive dysfunction has become an important global population health concern. Cognitive impairment affects patients, families, and their social networks, representing a significant psychosocial and health economic burden. Patients with carotid occlusive diseases are known to be at the highest risk for cognitive impairment.[5,6] In recent years, cognitive effects of carotid interventions are increasingly recognized as an important outcome for carotid disease management and carotid interventions. Although revascularization procedures improve cerebral perfusion and theoretically brain

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health, procedure-related factors, such as microembolization, have been shown to adversely affect cognition after carotid interventions.[7-9]

Procedure-related subclinical embolization can be detected by transcranial Doppler ultrasound[10] and magnetic resonance imaging (MRI) with a diffusion-weighted imaging (DWI) sequence.[11,12] Subclinical microemboli are common (20%-70%) despite an absence of neurologic symptoms.[13-20] Studies that evaluated cognitive effects of microembolization have yielded mixed findings.[7,8,21,22] In an experimental animal model, dose-dependent effects of embolization on inflammation and neuronal injury have been observed, and repeated embolization is shown to lead to cognitive impairment.[23] We postulated that the inconsistency in the cognitive effects of subclinical embolization may be related to size of the emboli. To date, there is extremely limited information in the literature on quantification of volumes of procedure-related embolization after carotid revascularization procedures. How the size of emboli influences procedure-related cognitive changes is largely unknown. In this study, we aimed to evaluate the volume of procedure-related emboli in patients who undergo CEA and CAS, focusing on the effect of volume of emboli on cognitive changes in the CAS cohort.

METHODS

Patient selection. The study was approved by the Stanford Institutional Review Board and VA Palo Alto Health Care System Research and Development Committee. Patients who underwent carotid revascularization procedures for occlusive disease under the standard clinical practice guideline were prospectively recruited. Carotid revascularization was offered to patients with >80% asymptomatic carotid stenosis and >60% symptomatic stenosis based on duplex ultrasound velocity criteria. The degree of stenosis was further confirmed with magnetic resonance angiography or time-of-flight MRI of the neck. For those who underwent CAS, additional contrast angiography was performed before stenting. The decision to perform a CAS procedure was made by a consensus of vascular surgeons, patients, and families; CAS was reserved for patients who were deemed at high surgical or medical risk for CEA. Inclusion criteria for this study also required the patients to be 40 years of age or older, to have absence of psychiatric disorder or medical condition affecting cognitive function, to voluntarily participate in the study, to be able to sign an Institutional Review Board-approved informed consent, to be able to undergo MRI, and to be available for follow-up neuropsychological testing. Demographics and clinical risk factors were documented. Patients were considered to be symptomatic (prior symptoms) if they had experienced transient ischemic attack, amaurosis fugax, or stroke within 6 months leading to their referral for carotid revascularization evaluation.

ARTICLE HIGHLIGHTS

- **Significance:** This study evaluates subclinical embolization due to carotid revascularization, focusing on correlations between volumes of procedure-related infarct and cognitive outcomes.
- **Type of Research:** Prospective nonrandomized single-center analytical study
- **Take Home Message:** Carotid artery stenting was an independent predictor of embolic infarct and infarct volume, and there was negative correlation between infarct volume and cognitive decline.
- **Recommendation:** Volumes of embolic infarcts correlate with cognitive changes, and microembolization should be considered a surrogate measure for carotid disease management.
- **Strength of Recommendation:** 1. Strong
- **Level of Evidence:** C. Low or very low

Carotid intervention. All procedures were performed by experienced vascular surgeons who are proficient in CEA and CAS. All patients received intra-arterial blood pressure monitoring during the procedures. Anesthesiologists were present during the entire CEA and the critical portion of CAS procedures. CEAs were performed under general anesthesia in an operating room with cerebral oximetry monitoring. Shunts and patch were routinely used. The choices of shunt or patch were at the discretion of the operating surgeons. All CAS procedures were performed in an endovascular suite under local anesthesia with conscious sedation. Arch angiography was not routinely performed to avoid unnecessary arch manipulation, and common carotid artery cannulation was based on information from preoperative magnetic resonance angiography using a telescope technique. All patients received a distal embolic protection device before stent placement. Poststent dilation was performed for >30% residual stenosis. After CEA and CAS, all patients were monitored in the surgical intensive care unit overnight. The majority of the patients were discharged home the following day.

Imaging evaluations. Preoperative and postoperative 3T MRI scans (GE Medical Systems, Milwaukee, Wisc) with DWI sequence were performed to identify periprocedural embolic infarcts. MRI studies were performed within 1 to 2 weeks before carotid revascularization and within 24 to 48 hours postoperatively before discharge. Postoperative DWI sequence images and apparent diffusion coefficient maps were compared with the corresponding preoperative images to identify interval, periprocedural embolic infarcts. Each individual embolic infarct was manually traced on individual MRI slices using MRIcron neuroimaging software,[24] which then