Cognitive Decline with Untreated Carotid Lesions: *Fact or Fiction?*

John Laird, MD
Adventist Heart and Vascular Institute
St. Helena, CA

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Disclosures
John R. Laird

- Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

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Consulting Fees/Honoraria	Boston Scientific, Medtronic, Abbott, Bard/Becton Dicksenson Peripheral Intervention, Philips
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Is this improved cerebral perfusion or a great example of the placebo effect?

Background

- There is a strong link between stroke and cognitive decline
- Studies have shown that many stroke survivors suffer dementia
- Controversy exists as to whether asymptomatic carotid stenosis (CS) is an independent risk factor for cognitive decline
- If asymptomatic CS is linked to cognitive decline, then early intervention (CEA or CAS) may be appropriate for prevention

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Cognitive Impairment and Decline Are Associated with Carotid Artery Disease in Patients without Clinically Evident Cerebrovascular Disease

S. Claiborne Johnston, MD, PhD; Ellen S. O'Meara, PhD; Teri A. Manolio, MD, PhD; David Lefkowitz, MD; Daniel H. O'Leary, MD; Steven Goldstein, MD†; Michelle C. Carlson, PhD; Linda P. Fried, MD, MPH; W. T. Longstreth Jr., MD, MPH

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- 4006 patients with CS and no history of stroke, TIA, or CEA
- MMSE performed at baseline and annually for 5 years
- Patients evaluated for cognitive impairment (MMSE score < 80) and cognitive decline (average decrease by 1 point annually)
- Findings: carotid stenosis ≥ 75% associated with cognitive impairment and decline

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Review

Association between asymptomatic carotid stenosis and cognitive function: A systematic review

Xue-Li Chang, Hong-Qing Zhou, Chun-Yan Lei, Bo Wu, Yan-Chao Chen, Zi-Long Hao, Wei Dong, Ming Liu *

Stroke Clinical Research Unit, Department of Neurology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China

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ABSTRACT

Background: Asymptomatic carotid stenosis (CS), traditionally considered clinically silent, may be an independent risk factor for a cognitive impairment.
Methods: To determine whether an association exists between asymptomatic CS and cognitive function, we systematically reviewed the literature in the Cochrane Library, MEDLINE, EMBASE and the China National Knowledge Infrastructure databases.
Results: A total of 8 cross-sectional studies and 2 community-based cohort studies were included, comprising 763 participants in the CS group and 6308 participants in the non-CS group. All but one study supported the association between asymptomatic CS and cognitive impairment. Pooled analysis identified older age (2 studies) and cerebral hypoperfusion (2 studies) as additional factors in patients with asymptomatic CS that may linked to cognitive decline.
Conclusions: These results suggest that rather than being clinically silent, asymptomatic CS may be associated with cognitive impairment, and this should be further investigated in high-quality studies.

Association Between Asymptomatic Carotid Stenosis and Cognitive Function

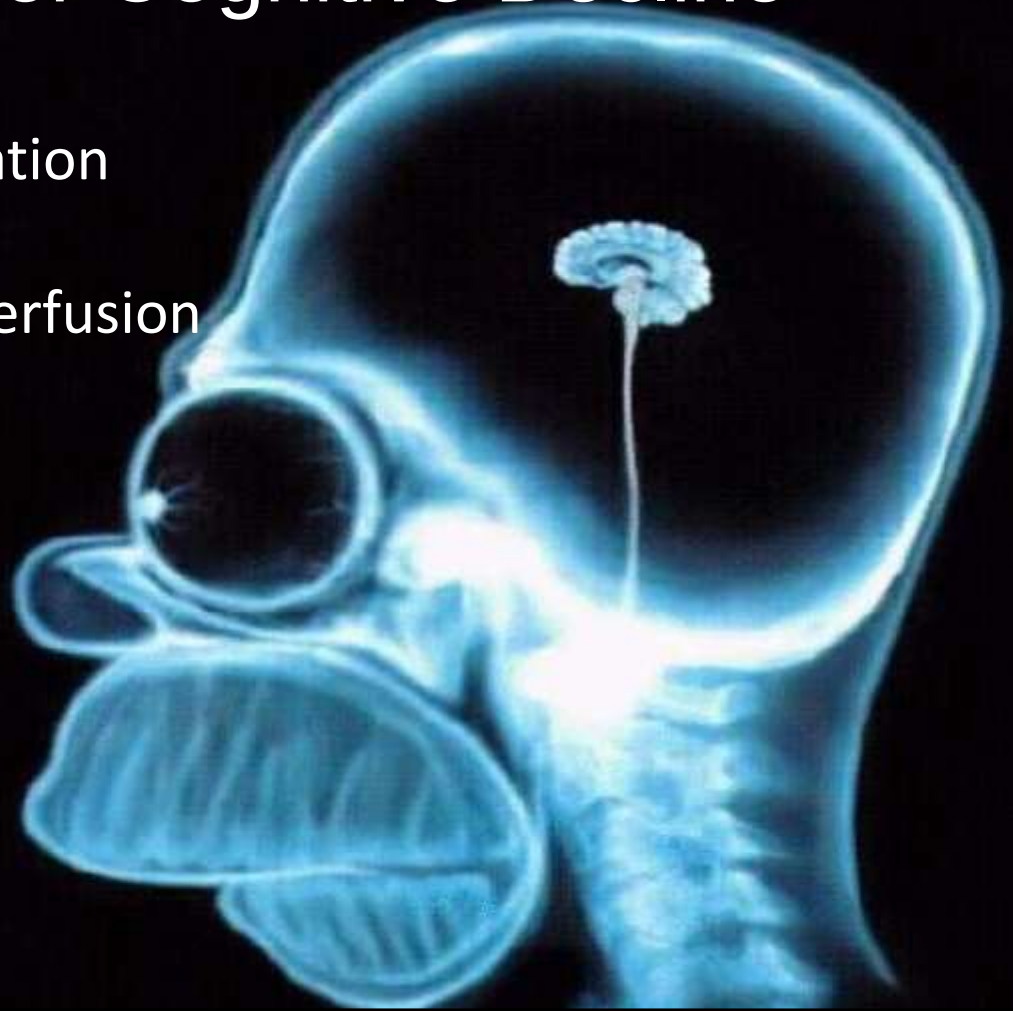
- 8 cross sectional studies and 2 community-based cohort studies included
- 763 participants in the carotid stenosis group and 6308 participants in the non-carotid stenosis group
- All but one study supported the association between asymptomatic carotid stenosis and cognitive decline
- Pooled analysis identified older age (2 studies) and cerebral hypoperfusion (2 studies) as additional risk factors

Study Limitations

- Small number and size of studies
- Heterogeneity of subjects and methods
- Cognitive function assessed with a variety of different neuropsychological test with different sensitivity and specificity (no consistent testing methodology)
- Some studies did not have blinded assessment of cognitive function

Rationale for Cognitive Decline

- Silent embolization
- Chronic hypoperfusion



Silent Embolization and Cognitive Impairment?

- White matter lesions detected by MRI in patients with CS have been associated with increased risk of cognitive decline

(Prins et al.,2004)

- Several studies found significant associations between CS and reduced cognitive function independently of the presence of brain lesions detected by MRI

(Johnston et al., 2004; Mathiesen et al., 2004; Romero et al., 2009)

- These findings support the notion that CS by itself is an independent marker of poor cognitive performance

Cerebral Hypoperfusion and Cognitive Decline?

- As CS becomes severe, patients with inadequate collateralization compensate by progressive dilatation of intracranial arteries/arterioles in the ipsilateral hemisphere.

- This maintains cerebral blood flow, but a point arises where the vessels cannot vasodilate any more: they enter a state of impaired/exhausted cerebral vascular reserve (CVR) with limited capacity to dilate further

R. Naylor

Cognitive Deterioration in Bilateral Asymptomatic Severe Carotid Stenosis

Laura Buratti, MD; Clotilde Balucani, MD; Giovanna Viticchi, MD; Lorenzo Falsetti, MD; Claudia Altamura, MD; Emma Avitabile, MD; Leandro Provinciali, MD; Fabrizio Vernieri, MD; Mauro Silvestrini, MD

Background and Purpose—This study aimed to monitor cognitive performance during a 3-year period in subjects with bilateral asymptomatic severe internal carotid artery stenosis and to explore the role of cerebral hemodynamics and atherosclerotic disease in the development of cognitive dysfunction.

Methods—One hundred fifty-nine subjects with bilateral asymptomatic severe internal carotid artery stenosis were included and prospectively evaluated for a 3-year period. At entry, demographics, vascular risk profile, and pharmacological treatments were defined. Cognitive status was evaluated using the Mini-Mental State Examination at baseline and at follow-up. Cerebral hemodynamics was assessed by transcranial Doppler–based breath-holding index test. As a measure of the extent of systemic atherosclerotic disease, common carotid artery intima-media thickness was measured. A cutoff for pathological values was set at 0.69 for breath-holding index and 1.0 mm for intima-media thickness.

Results—The risk of decreasing in Mini-Mental State Examination score increased progressively from patients with bilaterally normal to those with unilaterally abnormal breath-holding index, reaching the highest probability in patients with bilaterally abnormal breath-holding index ($P<0.0001$). Pathological values of intima-media thickness did not influence the risk of Mini-Mental State Examination score change.

Conclusions—Our findings suggest that patients with asymptomatic bilateral severe internal carotid artery stenosis may be at risk of developing cognitive impairment. The evaluation of the hemodynamic status, besides providing insights about the possible mechanism behind the cognitive dysfunction present in carotid atherosclerotic disease, may be of help for the individuation of subjects deserving earlier and more aggressive treatments. (***Stroke*. 2014;45:2072-2077.**)

Key Words: carotid stenosis ■ mild cognitive impairment ■ ultrasonography

Cognitive Deterioration in Bilateral Asymptomatic Severe Carotid Stenosis

- 159 patients with bilateral 70-99% carotid stenosis
- No previous signs or symptoms of cerebrovascular disease
- Cognitive performance monitored over a 3-year period
- Cerebrovascular reactivity (CVR) as a measure of the brain hemodynamic status and carotid IMT monitored
- Cognitive function was evaluated using the Mini-Mental Status Examination (MMSE)

Cognitive Deterioration in Bilateral Asymptomatic Severe Carotid Stenosis

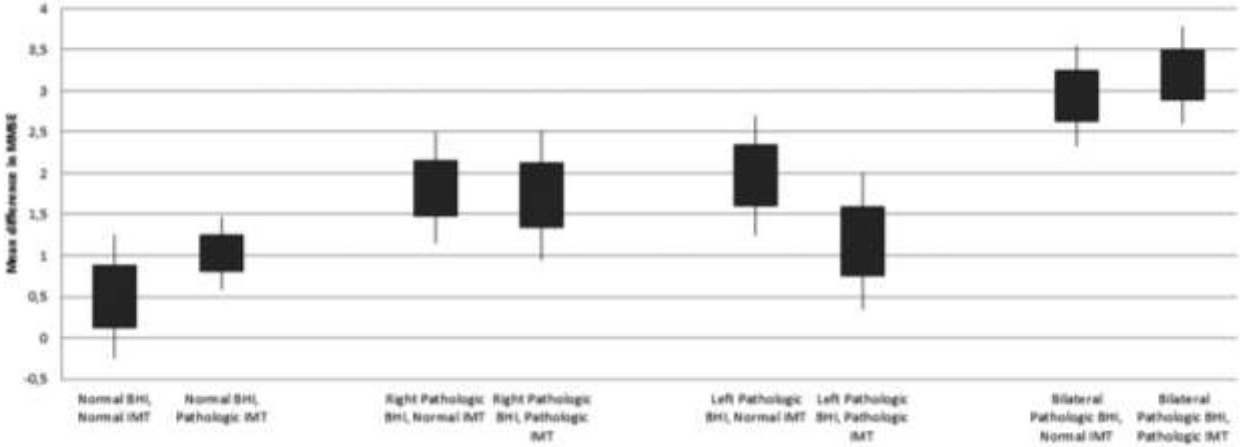


Figure. Effect of the association of breath-holding index (BHI) and common carotid artery intima-media thickness (IMT) values on Mini-Mental State Examination (MMSE) difference form entry to the end of the 3-year follow-up period.

- Cognitive deterioration during a 3-year period is significantly associated with impairment in CVR
- Maximum cognitive decline with bilateral impaired CVR

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If Asymptomatic Carotid Stenosis with Cerebral Hypoperfusion Leads to Cognitive Decline, Carotid Revascularization Should Improve Things

Neurocognitive Improvement After Carotid Artery Stenting in Patients With Chronic Internal Carotid Artery Occlusion and Cerebral Ischemia

Mao-Shin Lin, MD; Ming-Jang Chiu, PhD; Yen-Wen Wu, PhD; Ching-Chang Huang, MD; Chi-Chao Chao, MD; Ying-Hsien Chen, MD; Hung-Ju Lin, MD; Hung-Yuan Li, PhD; Ya-Fang Chen, MD; Lung-Chun Lin, PhD; Yen-Bin Liu, PhD; Chia-Lun Chao, PhD; Wen-Yih Isaac Tseng, PhD; Ming-Fong Chen, PhD*; Hsien-Li Kao, MD*

Background and Purpose—Chronic cerebral hypoperfusion may lead to impairment in neurocognitive performance in patients with chronic internal carotid artery occlusion, and the effects of carotid artery stenting on neurocognitive function have been unclear.

Methods—We prospectively enrolled 20 chronic internal carotid artery occlusion patients with objective ipsilateral hemisphere ischemia, in whom carotid artery stenting was attempted. Functional assessments, including the National Institutes of Health Stroke Scale, Barthel Index, and a battery of neuropsychological tests, including the Mini-Mental State Examination, Alzheimer Disease Assessment Scale–Cognitive Subtest, verbal fluency, and Color Trail Making A and B, were administered before and 3 months after intervention.

Results—Successful recanalization was achieved in 12 of 20 patients (60%). There was no procedural or new cerebral ischemic event, except for 1 intracranial hemorrhage, which occurred during the procedure and had neurologic sequelae; this case was excluded from analysis. The demographics and baseline cognitive performance were similar between the group with a successful outcome (group 1, n=12) and patients who did not (group 2, n=7). Ten of 12 patients in group 1 had improvement in ipsilateral brain perfusion after the procedure, but none in group 2 had improvement. Significant improvement in the scores on the Alzheimer Disease Assessment Scale–Cognitive Subtest (before, 7.7±8.9 versus after, 5.7±7.1; $P=0.024$), Mini-Mental State Examination (before, 25.8±3.8 versus after, 27.7±2.7; $P=0.015$), and Color Trail Making A (before, 123.2±68.6 versus after, 99.3±51.5; $P=0.017$) were found in group 1 but not in group 2.

Conclusions—Successful carotid artery stenting improves global cognitive function as well as attention and psychomotor processing speed in patients with chronic internal carotid artery occlusion. **(*Stroke*. 2011;42:2850-2854.)**

Key Words: carotid occlusion ■ carotid stenting ■ brain perfusion ■ neurocognitive function

Association of the Recovery of Objective Abnormal Cerebral Perfusion With Neurocognitive Improvement After Carotid Revascularization

Ching-Chang Huang, MD,* Ying-Hsien Chen, MD,* Mao-Shin Lin, MD,*† Cheng-Hsin Lin, MD,†‡
Hung-Yuan Li, MD, PhD,* Ming-Jang Chiu, MD, PhD,§‖ Chi-Chao Chao, MD,§
Yen-Wen Wu, MD, PhD,*¶# Ya-Fang Chen, MD,†† Jen-Kuang Lee, MD,‡‡
Ming-Jiuh Wang, MD, PhD,§§ Ming-Fong Chen, MD, PhD,* Hsien-Li Kao, MD*
Taipei and New Taipei City, Taiwan

Objectives This study sought to report the effect of carotid artery stenting (CS) on neurocognitive function (NCF) in patients with severe carotid artery occlusive disease, depending on baseline brain perfusion status.

Background The effect of CS on NCF has been controversial.

Methods We prospectively enrolled 61 patients with carotid artery disease (22 with occlusion, 39 with severe stenosis) in whom CS was attempted. Computed tomography perfusion and NCF assessments including Mini-Mental State Examination (MMSE), Alzheimer Disease Assessment Scale–Cognitive subscale (ADAS-Cog), verbal fluency, and Color Trails Test Parts 1 and 2 were applied before and 3 months after intervention.

Results Successful recanalization was achieved in 14 of 22 occlusion patients (64%) and in all 39 severe stenosis patients. Two cases were excluded due to procedural cerebral complications. The patients were divided into 3 groups: group 1 (n = 8) consisted of patients with abnormal baseline ipsilateral cerebral perfusion in whom CS failed; group 2 (n = 33) consisted of patients with abnormal baseline ipsilateral cerebral perfusion in whom CS was successful; and group 3 (n = 19) consisted of patients without abnormal baseline ipsilateral cerebral perfusion in whom CS was successful. The demographics and baseline NCF were similar among groups. Only in group 2 was there significant improvement in ADAS-Cog (pre-procedure median [interquartile range]: 6 [4 to 9] vs. post-procedure: 5 [3 to 7], p = 0.002), MMSE (pre-procedure: 27 [25 to 28] vs. post-procedure: 28 [25 to 29], p = 0.004) and Color Trails Test Part 1 (pre-procedure: 100 [78.5 to 136.5] s vs. post-procedure: 97 [60 to 128.5] s, p = 0.003) after CS. Significant difference in changes from baseline was observed only in the Color Trails Test Part 1 among groups (group 1 vs. 2 vs. 3: 1.5 [−14 to 11.5] vs. −12.5 [−36.5 to 0.5] vs. −0.5 [−11 to 27], p = 0.0159). Significant correlation between the change of ipsilateral brain perfusion and MMSE (r = −0.33, p = 0.01) was also identified.

Conclusions Successful CS for severe carotid stenosis/occlusion improves NCF, but only in patients with objective baseline abnormal cerebral perfusion. (J Am Coll Cardiol 2013;61:2503–9)

JACC 2013;61:2503-9

Neurocognitive Improvement After Carotid Revascularization

- 61 patients with internal carotid artery occlusion (22) or severe stenosis (39) in whom carotid stenting was attempted
- CT perfusion with Diamox stress and a battery of neuropsychological tests performed before and 3 months after carotid intervention
    - MMSE, Alzheimer Disease Assessment Scale-Cognitive subscale (ADAS-Cog), verbal fluency, and Color Trails Parts 1 and 2
- Patients divided into 3 Groups:
    - Group 1: (n=8) abnormal baseline CP in whom CS failed
    - Group 2: (n=33) abnormal baseline CP in whom CS was successful
    - Group 3: (n=19) normal baseline CP in whom CS was successful

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JACC 2013;61:2503-9

Results

- Carotid stenting successful in 14 of 22 occlusion patients (64%) and in all 39 severe stenosis patients
- Baseline demographics and NCF similar between groups
- Only in group 2 (abnormal baseline CP in whom CS was successful) was there significant improvement in ADAS-Cog, MMSE, and Color Trails Test Part1.
- Significant correlation between ipsilateral brain perfusion and MMSE also identified

JACC 2013;61:2503-9

EDITORIAL COMMENT

Asymptomatic Carotid Stenosis: The Not-So-Silent Disease

Changing Perspectives From Thromboembolism to Cognition*

Adnan H. Siddiqui, MD, PhD,†‡§
L. Nelson Hopkins, MD†‡§‖

Buffalo, New York

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JACC 2013;61:2510-3

Impact of Carotid Revascularization

- Numerous studies showing cognitive improvement following CS and CEA
- Other studies demonstrating the deleterious effects of periprocedural embolic events detected on post-procedure MRI imaging following CS and CEA
- Literature review of 22 studies evaluating cognition:
  - 8 demonstrated improvements
  - 11 had mixed results
  - 3 noted declines post revascularization

JACC 2013;61:2510-3

Factors Contributing to Inconsistent Results

- Diversity of the patient population
- Differences in baseline cerebral perfusion status
- Variability of surgical and endovascular techniques (type of anesthesia)
- Differences in neuropsychological testing methodology
- Possible learning effect on repeated tests
- Placebo effect
- Procedural emboli, temporary flow interruption
- Timing of repeat neuropsychological testing

Conclusions

- There is strong evidence to support the notion that asymptomatic severe carotid stenosis can lead to cognitive decline
- The most important factor appears to be cerebral hypoperfusion (severely impaired CVR) rather than silent embolic events
- There is inconsistent data regarding the benefits of carotid revascularization for reversal or prevention of cognitive decline (Class III, Level C recommendation in Guidelines)
- The benefits of revascularization need to outweigh the detrimental effects of the procedure, including periprocedural embolic events

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John Laird, MD
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