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Is Hemispheric Hypoperfusion a Treatable Cause of Cognitive Impairment?

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Abstract

Purpose of Review To review the current literature that supports the notion that cerebral hemodynamic compromise from internal carotid artery stenosis may be a cause of vascular cognitive impairment that is amenable to treatment by revascularization.

Recent Findings Converging evidence suggests that successful carotid endarterectomy and carotid artery stenting are associated with reversal of cognitive decline in many patients with severe but asymptomatic carotid artery stenosis. Most of these findings have been derived from cohort studies and comparisons with either normal or surgical controls. Failure to find treatment benefit in a number of studies appears to have been the result of patient heterogeneity or confounding from concomitant conditions independently associated with cognitive decline, such as heart failure and other cardiovascular risk factors, or failure to establish pre-procedure hemodynamic failure.

Summary Patients with severe carotid artery stenosis causing cerebral hemodynamic impairment may have a reversible cause of cognitive decline. None of the prior studies, however, were done in the context of a randomized clinical trial with large numbers of participants. The ongoing CREST-2 trial comparing revascularization with medical therapy versus medical therapy alone, and its associated CREST-H study determining whether cognitive decline is reversible among those with hemodynamic compromise may address this question.

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Introduction

Cognition is the underlying set of brain functions that allows us to communicate, to remember, and to make decisions, among other domains permitting us to negotiate in our world [1]. Threats to cognitive health degrade quality of life as well as place burdens on caregivers [2] and healthcare systems [3]. With the projected growth of elderly members of society, more individuals are expected to experience cognitive decline, whether as mild cognitive impairment or frank dementia. As yet, there are no impactful treatments for Alzheimer's disease, the most prevalent cause of cognitive decline [4], although cardiovascular risk-factor modification has shown to be of some benefit [5]. New research has begun to suggest, however, that some forms of vascular cognitive impairment, the second most common cause of cognitive dysfunction, may be amenable to intervention, particularly when due to impaired cerebral blood flow [6]. The purpose of this review is to examine the case for the reversibility of cognitive decline in the setting of cerebral hemodynamic compromise.

Carotid artery disease can be characterized as symptomatic if associated with stroke or TIA or as asymptomatic in the absence of such symptoms. Asymptomatic carotid stenosis (ACS) is commonly defined as a ≥ 50% atherosclerotic narrowing of the extracranial internal carotid artery [7, 8] in the absence of retinal or cerebral ischemia in the preceding 6 months [9]. Prevalence of moderate ACS varies from < 1 to 7.5%, whereas the prevalence of severe ACS (≥ 70% stenosis) ranges from 0 to 3.1% [7]. Risk for ACS increases with age and cigarette smoking status [10], and ACS is slightly higher in men than in women [11]. Additionally, the risk of developing carotid artery stenosis increases in individuals with a higher prevalence of cardiovascular-related diseases such as diabetes mellitus, smoking, dyslipidemia, and hypertension [12]. These conditions are also associated with increased risk for cerebrovascular events including ischemic and hemorrhagic stroke, as well as vascular dementia and Alzheimer's disease [13]. Even at sub-clinical levels, however, cardiovascular risk factors including ACS, are associated with alterations in brain structure [13–17, 18••], and neurocognitive dysfunction [19].

While alterations in brain structure have been implicated in the progression of dementia, recent evidence highlights hemodynamic impairments and hypoperfusion in cognitive dysfunction. Cerebral blood flow is closely tied to brain metabolism, and its regulation is mediated by an intricate vascular network. With severe carotid stenosis, collateral blood flow via large vessels, such as those in the Circle of Willis, and via smaller vessels at the surface, and small vessels within the brain prevent restriction of blood flow. However, when cerebral perfusion pressure (CPP) decreases, vasodilation is triggered to maintain CBF. If inadequate perfusion pressure persists, the autoregulatory threshold is surpassed and blood flow to tissue decreases. To counteract the reduction in blood flow, oxygen extraction fraction (OEF) increases to maintain oxidative brain metabolism [20]. As perfusion pressure falls further, however, ischemia ensues [21] and there is irreversible damage to underlying tissues [22].

Due to the persistent autoregulatory processes by which the brain works to maintain homeostatic balance, there is tantalizing evidence that restoration of anterograde blood flow can reverse hypoxia-induced changes, and restore cognitive function [6]. Accordingly, in this review, we attempt to outline the current state of knowledge regarding the efficacy of revascularization procedures in reversing cognitive impairment.

Carotid Stenosis and Cognitive Decline

The notion that carotid disease and impairments in blood flow can have consequences on cognitive functions was initially postulated in the early 1950s by Fisher [23]. Since then, several studies have identified associations between cognitive deficits and carotid occlusions, although cognitive impairment can also occur as the result of cerebral emboli, small vessel disease, and silent cerebral infarction. Studies on cognitive function in patients with symptomatic and asymptomatic carotid occlusive disease found that a great majority (78%) reported cognitive deficits [24]. The Trømso study (Mathiesen et al. [25]) compared 189 patients with carotid stenosis to 201 healthy controls. Patients with carotid disease had significantly lower scores on tests of attention, psychomotor speed, memory, and motor function than controls, with an association between degree of stenosis and cognitive dysfunction [25]. In good agreement with the Trømso findings, Romero et al. [26] identified that carotid atherosclerosis was correlated with measures of brain ischemia and cognitive impairments, and more recently shown in Lal et al., Dux [27••]. Similarly, in the Framingham Offspring Study, participants ($n = 1975$) without dementia or history of stroke were assessed with carotid ultrasound, MRI, and neuropsychological tests. Carotid stenosis was associated with reduced cognitive performance and indices of cerebral ischemia on MRI [26].

Balestrini et al. [28] showed that severe unilateral carotid stenosis was associated with increased rates of cognitive deterioration during a 3-year follow-up in 210 patients with asymptomatic carotid artery disease. At follow-up, patients with severe unilateral ACS were more likely to show cognitive deterioration compared to controls [28]. Comparably, another three-year follow-up study examined cognitive performances in 159 patients with asymptomatic bilateral carotid stenosis (70 to 99%) [29]. Patients with bilaterally impaired cerebrovascular reserve (CVR) at baseline had the most rapid cognitive decline as assessed by the change in the Mini-Mental State Examination (MMSE) at 36 months [29].

Taken together, these studies provide ample support for an association between cognitive dysfunctions and carotid stenosis. In addition, some research has been focused on identifying cognitive domains that are affected among individuals with carotid artery atherosclerosis, with available evidence suggesting that clinical as well as subclinical cardiovascular disease affect cognition along parallel domains. For instance, in a case-control study of 249 patients, clinical cardiovascular disease was associated with decreased performance on executive function tests, memory, and psychomotor speed [30]. This aggregation of affected domains was similarly manifested in patients with subclinical cardiovascular disease [31].

Mechanisms of Cognitive Decline in the Absence of Stroke

Conceptualization of any restorative approach depends on the presumed underlying pathophysiological mechanisms of the disease. To that end, we outline the mechanisms that are believed to contribute to the associations between cardiovascular disease and cognitive decline [12]. Primarily, evidence links reductions in cerebral blood flow [6, 27••, 32], white matter lesions [33, 34], intima media thickness [35], cortical thinning [18••], and degree of stenosis [25, 36] in cognitive impairments.

In terms of blood flow, cerebral hypometabolism and perfusion measured by oxygen-15 positron emission tomography (PET O^{15}) have been associated with cognitive impairments and atrophy of corpus callosum in carotid artery disease [37]. Reductions of 40 to 50% in cerebral blood flow are sufficient to cause ischemic cell injury [38], ultimately leading to neurodegenerative processes and cognitive dysfunctions [39]. Indeed, chronic cerebral hypoperfusion has been implicated in neuronal death and reactive astrogliosis [22]. Moreover, increased OEF, and impaired CVR have been linked to cognitive impairments [27••, 28, 32, 40] and dementia [13, 21, 35, 41, 42]. In 2012, Marshall et al. showed that unilateral cerebral hypoperfusion and hemispheric hemodynamic failure with increased OEF were associated with cognitive impairments in patients with symptomatic carotid artery disease. Increased ipsilateral OEF (≥ 1.13) as measured by PET was associated with cognitive dysfunction in 43 patients with symptomatic carotid artery occlusions, compared to those who were without these PET changes. This association held even for patients who had TIA but no stroke [40]. Furthermore, Ruitenberg et al. [43] identified CBF as a risk factor that precedes atrophy of amygdala and hippocampal structures. Compared to subjects with reduced CBF, individuals with greater cerebrovascular reactivity (CVR) were more likely to have larger amygdala and hippocampal volumes and less likely to show cognitive decline over a 6.5-year follow-up period [43]. Lastly, Haratz et al. [41] tested the association between impaired CVR and cognitive scores. Hemodynamic dysfunction ipsilateral to the stenosis negatively correlated with lower global cognitive scores and poorer executive function in 98 patients with impaired CVR [41].

The critical association between hemodynamic dysfunction and cognitive impairment supports the plausibility that hypoperfusion-mediated cognitive impairments might be reversible [6, 44]. However, whether cognitive impairment could be ameliorated following protracted periods of ischemia remains an open question. Speculation regarding the reversibility of cognitive dysfunction in people with carotid stenosis became one catalyst for revascularization interventions [45–47].

Revascularization: Effects on Cognition in Symptomatic and Asymptomatic Patients

Research that compares the effect of carotid endarterectomy (CEA) and carotid artery stenting (CAS) on cognitive performance has included both symptomatic and asymptomatic patients, and yielded evidence to suggest that subclinical cognitive impairments may indeed be modifiable. However, no significant differences between procedures have emerged. Lunn et al. [47] reviewed 28 studies and found that 57% reported cognitive improvements following CEA, whereas the remaining 43% reported cognitive decline or no change. Another review on cognitive function after revascularization, which included 22 studies published before 2007, showed uncertainty regarding the efficacy of CAS vs CEA on cognition [48]. Four out of 15 CEA studies showed cognitive improvement after revascularization, while the remaining studies reported impairment or no change in cognition following CEA. Of seven studies that analyzed cognition after CAS, nearly half reported improvements in memory [48]. Lastly, Antonopoulos et al. [49] conducted a meta-analysis of 16 studies that evaluated various domains of cognitive performance before and after CAS, reporting improvements in global cognition, attention/psychomotor speed, and memory following stenting.

In combination, 66 studies that evaluated the effects of revascularization on cognition were included in the above-cited reviews. The results were mixed, making conclusions challenging. Several methodological concerns contributed to this uncertainty, including different intervals for follow-ups, the variety of cognitive tests employed, and participant age, especially because age appears to affect cognitive performance after revascularization. For instance, Wasser et al. [50] examined the cognitive effects of CEA and CAS in symptomatic and asymptomatic patients. Both CEA and CAS patients < 68 years of age maintained cognitive function following revascularization. These effects, however, did not hold for older patients. Transient cognitive decline was observed in patients ≥ 68 years old who underwent CAS, whereas persistent cognitive decline was evident for CEA patients at

3 months postoperatively [50]. These results are congruent with earlier research in which age and diabetes increased risk of cognitive decline following CEA in symptomatic and asymptomatic patients [51].

Overall, about half of the reviewed studies used a control group, which included healthy individuals along with patients with significant vascular risk factors, and surgical patients. It is therefore not surprising that while some studies reported improvements, others reported decline, or mixed findings. The degree to which the negative effects of procedure-related embolization are overcome by the countervailing positive effects of increased perfusion has yet to be elucidated. Patient heterogeneity likely contributes heavily to conflicting results within and across studies. The extent to which a stroke or TIA in symptomatic patients may have contributed to the ambiguous results on reversibility of cognitive dysfunction is especially meaningful when considering results from animal studies. In a seminal animal study on the reversibility of cerebral hypoxia without infarction, CA1 hippocampal neuronal injury with a high degree of reactive astrocytosis was successfully reversed when a de-occlusive procedure was completed within 2 weeks of occlusion. However, under chronic conditions, neuronal damage was permanent [52]. As a result, the authors concluded that neuronal cells may exist in a prolonged state of reversible ischemia, thus supporting the concept of reversible chronic ischemia in otherwise healthy subjects [52]. Substantiation of the concept of reversibility of chronic ischemia is strengthened by studies reporting improvement in cognitive function after revascularization in patients with ACS. To evaluate the effects of CAS and CEA in patients without history of stroke or infarcts, several investigators have considered revascularization effects in asymptomatic patients.

Asymptomatic Patients: Cognition Following Revascularization

Increasingly, research has been aimed at exploring whether asymptomatic carotid disease increases the risk for cognitive decline. The preponderance of the evidence supports associations between unilateral carotid atherosclerotic stenosis or occlusion and cognitive decline in the absence of physical signs and symptoms. Twelve studies were identified and are summarized below.

Bossema et al. [53] compared 56 patients with severe ACS scheduled for CEA, with 46 healthy control subjects, and 23 patients scheduled to undergo endarterectomy of the superficial femoral artery (remote endarterectomy) (REA). Baseline cognitive assessments indicated reduced performance on attention, verbal and visual memory, planning of motor behavior and psychomotor skills, and executive functions for CEA and REA patients compared to the healthy controls. Both patient groups were reassessed again at 3 and 12 months.

Significant improvements were reported for verbal memory, executive functioning, and planning speed for CEA and REA patients, with no significant differences between procedures [53]. Given that REA did not involve alterations to brain perfusion, the authors concluded that cognitive improvements in CEA could not be attributed to removal of stenosis, but rather to relief from psychological stress related to surgery in both groups.

To determine whether post-procedural hyperperfusion was associated with cognitive impairment, Ogasawara et al. [54] studied 92 carotid stenosis patients who underwent cognitive testing, and measures of CBF were assessed at baseline and again after revascularization. At follow-up, mean cognitive scores improved from baseline, but cognitive dysfunction was found in 11 patients who had experienced perioperative complications such as hyperperfusion or cerebral ischemia. A logistic-regression analysis identified that perioperative hyperperfusion alone predicted post-operative cognitive impairment. Cerebral hyperperfusion is now a rare postoperative complication that may manifest following CEA or CAS secondary to alterations in the autoregulatory response, which ultimately can lead to cognitive decline [54], capillary injury, necrosis, and intracerebral hemorrhage [55]. Ogasawara's findings lend support to earlier research that highlighted the effect of cerebrovascular reserve on cognition in symptomatic patients. For instance, Fearn et al. [44] used ultrasonography to measure CVR in 159 symptomatic CEA patients. Cognitive tests were administered before and after revascularization. At 2 months postoperatively, memory, attention, and accuracy had improved in CEA patients, with the greatest improvements found in patients with impaired CVR at baseline.

Borroni et al. [56] evaluated 78 patients with severe carotid stenosis who underwent CEA. Uniquely, the authors divided participants into two groups based on baseline cognitive results: those with no cognitive impairment (CON), and a group who showed mild vascular cognitive impairment (mVCI). Cognitive testing was conducted 1 week before and 3 months after revascularization. At the 90-day follow-up, it was found that 100% of the mVCI group maintained (40%) or improved cognitive function (60%). [56]. An important feature of this study was the inclusion of patients with heart failure and rhythm abnormalities, which independently can affect cognition.

Tiemann et al. [57] found that preoperative cognitive performance improved significantly in 22 patients with ACS after CAS. Baseline group means of cognitive z-scores (i.e., statistical comparisons to a normative population with a normal distribution) did not reveal cognitive deficits; however, single-subject cognitive deficits were recorded for 81% of patients in one or more cognitive domains. Mean z-scores at 6-week follow-up revealed significant improvements in verbal memory, and verbal memory span.

In their study, Feliziani et al. [58] enrolled 46 severe ACS patients ≥ 65 years of age. Twenty-four patients received CAS

and 22 received CEA, based on clinical characteristics. Cognitive function was assessed prior to revascularization, at 90 days, and again 12 months after intervention. Cognitive assessments included: the MMSE, Babcock story recall, and the Rey Auditory Verbal Learning Test (Rey AVLT: immediate and delayed recall), a category naming test, Trail Making A and B, the Controlled Oral Association Test (COWAT), and copy drawing test. Compared to the CAS group, the CEA group had better albeit non-significant scores on the TMT-A at baseline. However, this trend was reversed at both follow-up assessments, so that performance on the TMT-A in the CEA group was poorer at follow-up compared to CAS patients. For all other cognitive assessments, no significant differences were observed between groups at any time point. Cognitive performance over time did not differ between groups, and similar results were reported for performance over time within groups. Except for visuospatial and constructional abilities, mean cognitive scores at 90 and 360 days did not change significantly for CAS or CEA; however, slight deterioration in visuospatial and constructional scores was observed in the CAS group only. The authors concluded that carotid revascularization, regardless of procedure, does not alter cognitive functions acutely or chronically in either CEA or CAS patient groups.

Grunwald et al. [59] compared 41 patients with ACS, and a group of seven patients with anterior communicating artery aneurysms who underwent endovascular treatment. Both groups underwent cognitive testing (cognitive speed and memory function tests) 1 day pre- and 3 months post-intervention. At follow-up, a significant improvement in cognitive speed, but not memory function, was observed in the CAS group, whereas no difference in either domain was found in the endovascular treatment group [59]. Similar to other studies, the authors included patients ($n = 10$) with unspecified cardiac diseases.

In a non-randomized prospective study with patients with severe ACS undergoing CEA ($n = 25$) or CAS ($n = 21$), individuals underwent cognitive testing 1 to 3 days before revascularization, and again at 4 to 6 months [60]. Cognitive tests included TMT-A & -B, Processing Speed Index, Boston Naming Test, Working Memory Index, Controlled Oral Word Association Test, and Hopkins Verbal Learning Test. A composite score was generated for each patient at baseline and follow-up, and change scores between the two time points were used as the primary outcome. A secondary analysis compared change scores for each individual test. Results showed overall improvements in cognitive functions. Compared to baseline, composite change scores improved for both CEA and CAS groups at follow-up; however, non-significant differences emerged between the two groups. In addition, scores for the individual cognitive function domains improved for each test except for Working Memory Index, which was decreased in 80% of CEA patients, but showed improvement in

the CAS group. Conversely, improvements were reported for each cognitive test except for Processing Speed Index, which decreased in 18/21 CAS patients.

Chen et al. (2012) compared 34 patients with severe ACS, who underwent CT perfusion scans to measure CBV, CBF, and a cognitive assessment at baseline and 3 months post-procedurally. Following stenting, patients were subdivided into three groups: Group 1 (G1), 6 patients, included those with ipsilateral ischemia and failed stenting procedure; Group 2 (G2), 17 patients, included those with ipsilateral ischemia and successful CAS; while Group 3 (G3), 11 patients, included those with no ischemia (as indicated by CT perfusion) and successful CAS. Ischemia was reversed in 94% of patients in G2 in contrast to patients in G1 or G3 in which there were no perfusion changes. Furthermore, cognitive changes were reported for patients only in G2. Specifically, scores on ADAS Cog Alzheimer's measure, MMSE, and Color Trail Making A were all improved after revascularization. Additionally, there was a trend toward improvement in Color Trail Making B. No significant changes across any test parameters were observed in G1 or G3. Overall, the results from this study provided a strong demonstration of improved cognition following CAS related to the improvement in cerebral hemodynamics.

In their study, Baracchini et al. [61] found that cognitive performance improved significantly in symptomatic patients ($n = 75$) following CEA, whereas postoperative mean cognitive scores for asymptomatic patients with $\leq 69\%$ occlusion ($n = 70$) remained unchanged.

In a small study of 22 patients (CEA, $n = 10$) and (CAS, $n = 12$) with ACS, Picchetto et al. [62] assessed the effect of revascularization on cognition. Cognitive assessments were conducted 1 to 3 days before, and 3 months after CEA or CAS, and included: Wisconsin Card Sorting Test, and the Mental Deterioration Battery (Rey AVLT immediate and delayed recall, copying drawings, phonological verbal fluency). Post-intervention performance was significantly improved on the Rey AVLT immediate recall ($F = 9.348$; $P < 0.007$) and phonological verbal fluency ($F = 7.949$; $P = 0.01$). CEA or CAS of the left carotid correlated with improved performance on verbal fluency, prompting the authors to conclude that the side of occlusion accounted for most of the observed improvements in these two domains, especially because the two tests are measures of highly lateralized verbal abilities. Additionally, vasoreactivity was assessed in a subset of patients ($n = 8$), all of whom showed improved vasodilatory capacity following intervention [62]. The small number of participants and the inclusion of two patients with a history of cardiac failure in this small sample study complicate interpretation of these results.

Ortega et al. [63] conducted a prospective study with 25 patients with ACS scheduled to undergo CAS with flow reversal. Cognitive function was assessed immediately prior to CAS, and again 6 months after surgery. Mean overall

cognitive scores were reduced in several domains at baseline. Post-procedurally, significant improvements in mean global cognitive scores ($p = .002$) and information processing ($p = .018$) were observed. Mild but insignificant improvements in visuospatial function, memory, executive functions, language, and attention were reported. In addition, compared with their older counterparts (32%), patients < 80 years of age showed better post-procedural improvement in global cognitive scores ($p = .004$) [63]. Despite positive findings, the results from this study are complicated by the fact that although the authors identified their patient sample as asymptomatic, out of 25 participants, 3 patients had a history of stroke in the preceding 180 days prior to the CAS, 5 had atrial fibrillation, and 12 suffered from ischemic heart disease.

A study by Kougias et al. [64] replicated previous findings. Fifty-five ACS patients, 28 (CEA), and 27 (CAS), with underlying cardiovascular risk factors (coronary artery disease or congestive heart failure was present in 78% of CEA patients and 51% of CAS patients, respectively) underwent domain-specific cognitive testing (memory, processing speed, executive functioning, visual spatial skills, attention) at baseline, 6 weeks, and again at 6 months. Compared with CEA, cognitive processing speed (Stroop Color test: 9.0 vs 7.3, $p = .04$; and Stroop Word test: 9.0 vs 7.4, $p = .05$) was superior in the CAS group at 6 weeks. Executive functioning (phonemic verbal fluency: 10.6 vs 8.4, $p = .043$) and motor function (Grooved Pegboard of nondominant extremity motor skills: 45.7 vs 38.9, $p = .022$) were also superior in the CAS group at 6 months. Tests of attention, memory, and visual-spatial skills were similar between CAS and CEA patients at 6 weeks and 6 months [64]. While this study showed recovery of cognitive function, the improvements were mainly limited to the CAS group. However, given the high rate of cardiovascular risk factors in this sample, it is not clear how these underlying conditions (coronary and congestive heart disease) affected improvements.

Discussion and Conclusions

Taken together, these studies provide converging evidence supporting revascularization as a way to reverse of cognitive decline in many patients with ACS. This conclusion is concordant with evidence from exercise studies in which exercise in older individuals was related to increases in CBF [65], gray volume [66], and ultimately, cognitive improvements [67].

The evidence provides additional support for the hypothesis that restoration of cerebral blood flow is sufficient to facilitate cognitive recovery. Overall, most revascularization studies we reviewed confirm cognitive changes after revascularization, while two studies reported no effect [58, 61]. Unfortunately, despite the generally positive results, a number of studies suffered from methodological weaknesses (see Table 1), chief among these being patient heterogeneity. For example, several investigations included patients with underlying cardiovascular diseases such as chronic heart failure and atrial fibrillation, which are known to affect cognitive functions [30, 31] even without other risk factors. Particularly for patients with known risk factors, the progression of underlying cardiovascular events creates a remarkable confounding variable in relation to cognition.

Observational studies raise the question as to the underlying mechanism of possible cognitive decline in the setting of unilateral, severe carotid stenosis. Under normal circumstances, loss of cerebral perfusion in one carotid artery results in compensatory collateral flow across the circle of Willis, with supply from the contralateral ICA and/or posterior circulation, or retrograde over the convexity from adjacent cerebral vessels. When these systems provide insufficient flow, there are additional sources of perfusion to the affected brain region, such as extracranial supply by means of an anastomosis via the external carotid artery or flow from cerebral arteries across border zones. The characterization of the compensatory failure in which there is inadequate perfusion to maintain cognition when there are no physical signs and symptoms has yet to be defined.

In addition to the limitations noted above, none of the prior studies were done in the context of a randomized clinical trial. To address this latter limitation, CREST-2 is a randomized clinical trial comparing the effectiveness of revascularization (CAS or CEA) plus intensive medical therapy (IMT) vs IMT alone in ACS patients with high-grade stenosis [69]. As an ancillary study to CREST-2, CREST-H study is then determining whether revascularization in CREST-2 patients will improve cognition among those with image-verified cerebral hemodynamic compromise and baseline mild cognitive impairment, compared to those only receiving IMT [70].

Additionally, inconsistencies across studies with respect to study designs, timelines of post-procedural cognitive assessments, use of control groups, as well as variability of neuropsychological measures employed in each study weaken these generally encouraging results. The absence of control groups in half of the studies introduces another limitation. Control groups can serve to compare pre- and post-procedural variances; however, even when studies included control groups, diversity in selection emerged, with some studies including surgical controls, while others enrolled healthy, medical treatment groups, or those with failed surgical revascularization. Moreover, many reports excluded crucial details, such as side of carotid stenosis. An unresolved matter is the likely but difficult to establish influence of stenosis duration. As discussed previously, prior studies have yielded important insights into the effects of duration on reversibility of

Table 1   Asymptomatic carotid artery disease studies with revascularization

Study	Year	# of patients	Control group	Cognitive measures	Comorbidities	Results
Borroni et al., [56]	2004	78	None	MMSE; SET Test; Digit Span; ROCF (copy); Rey figure recall; Babcock Story Recall Test; COWA; TMT (A): Grooved PB	Heart failure; rhythm abnormalities	Global improvement Reversal of cognitive impairment in mVCI at baseline
Bossema et al., [53]	2005	60	$(n = 23)^1$ $(n = 46)^2$	Digit Span; R-AVLT; Doors Test; verbal fluency; TMT A & B; Motor Planning Test; Finger Tapping Test	None reported	No differences between surgical groups; improvement in word learning; Trail Making B; Motor Planning Test
Ogasawara et al., [54]	2005	92	None	WAIS-R, WMS, ROCF	TIA; TIA & Stroke; stroke alone	Improvements in mean cognitive scores. Cognitive dysfunction was found in 11 patients with perioperative hyperperfusion or cerebral ischemia
Tiemann et al., [57]	2009	22	None	MWT-B; LLT; NCT; Spatial Span (WMS); Digit Span; Number Connecting Test; verbal fluency; (phonological and semantic); Block Design (WAIS)	None reported	Improved verbal memory and verbal memory span
Feliziani et al., [58]	2010	46	None	MMSE; Babcock Story Recall; Rey AVLT (immediate and delayed recall); Category Naming Test; TMT A & B; COWAT; copy drawing test	Atrial fibrillation	No improvements
Grunwald et al., (Grunwald et al. [59])	2010	41	$(n = 7)^1$	Repeat Numbers Test; Image Test; Word Pairs; Symbol Test; Singer Symbol Test; Latent Learning Test; Number Connection Test; Labyrinth Test; Color-Word Test	Cardiac disease	Significant improvement in cognitive speed in CAS. No differences in control group
Lal et al., [60]	2011	46	None	TMT A&B; Processing Speed Index (WAIS-III; BNT; Working Memory Index (WMS-III); COWAT; HVLT	None reported	Composite change score improved for entire test battery
Chen et al., [68]	2012	34	$(n = 6)$	MMSE; ADAS-Cog; semantic fluency; color TMT A & B	Myocardial infarction	Successful CAS improved cognitive function
Baracchini et al., [61]	2012	70	$(n = 68)^1$	MMSE; MoCA	Atrial fibrillation	No cognitive change
Picchetto et al., [62]	2013	22	None	WCST; Mental Deterioration Test; Rey AVLT (immediate and delayed recall) ROCF (copying); phonological verbal fluency	Heart failure	Left carotid revascularization was correlated with improved verbal fluency
Ortega et al., [63]	2014	25	$(n = 250)^2$	Token Test; COWAT; semantic fluency; CVLT; Stroop Color-Word; Grooved PB; Judgment of Line Orientation; Digit Symbol (WAIS-III); Mental Control (WMS-III)	None reported	Significant improvement in mean global cognitive score; information processing. Patients < 80 years of age showed better improvement than older patients
Kougias et al., [64]	2015	55	None	Digit Span, Letter-Number Sequencing, Digit Symbol, Symbol Search (WAIS); TMT-A; TMT-B; Stroop Color-Word Test; Judgment of Line Orientation; Brief Visuospatial Memory Test; R-AVLT, Category and Letter Fluency	Congestive heart failure; coronary artery disease	Improvements in cognitive processing; executive function; motor function in CAS. Improved attention; memory; visual spatial skills

Control Groups: 1 = other surgical group; 2 = healthy controls; 3 = medical treatment; 4 = failed CAS

ADAS-Cog Alzheimer's Disease Assessment Scale-Cognitive, *BNT* Boston Naming Test, *COWA* Controlled Word Association Test, *CVLT* California Verbal Learning Test, *Grooved PB* Grooved Pegboard, *HVLT* Hopkins Verbal Learning Test, *LLT* Location Learning Test, *MMSE* Mini Mental State Exam, *MoCA* Montreal Cognitive Assessment, *MWT-B* Multiple Choice Word Test, *NCT* Neurocognitive Test, *Rey-AVLT* Rey Auditory Verbal Learning Test, *TMT-A & -B* trail making part A & B, *WAIS* Wechsler Adult Intelligence Scale, *WCST* Wisconsin Card Sorting Test, *WLT* Word Learning Test, *WMS* Wechsler Memory Scale, *ROCF* Rey-Osterrieth Complex Figure

hypoperfusion-mediated neuronal and cognitive damage [52]. These findings are supported by later research that found that ischemic and hypoxic brain injury stimulated neurogenesis in the dentate gyrus of the hippocampus within 8 days of injury in young mice whereas the neurogenic effects of hypoperfusion were lost under chronic states of low CBF (75 days). In older mice, the hypoxia-induced neurogenic effects were not observed. In fact, after 8 days of hypoxia, older mice showed hippocampal lesions, cell loss, and astrogliosis [71]. While it is generally acknowledged that increasing age is correlated with increased carotid stenosis [11], evidence from revascularization studies confirms the role of age in cognitive recovery. For instance, Ortega et al. [63] reported significant improvement in mean global cognitive scores and information processing, with younger patients having better improvement than older patients. Age effects were also reported by Wasser et al. [50] and Mocco et al. [51].

Lastly, despite the differences in the measurement, design, analysis, and patient selection in these studies, the convergence of findings suggests that reversal of carotid occlusion appears to be effective in the restoration of hemodynamically-induced cognitive impairment. Overall, these reports raise noteworthy questions with respect to the role of hemodynamics in cognitive function, and especially in terms of reversibility of cognitive dysfunctions with revascularization. Future studies should aim for standardization in cognitive measures, timelines for assessments, more detailed information on patient characteristics, ascertaining presence or absence of hemodynamic failure, and careful patient selection.

Compliance with Ethical Standards

Conflict of Interest Amani M. Norling, Randolph S. Marshall, Marykay A. Pavol, George Howard, Virginia Howard, John Huston, III, Brajesh K. Lal, Thomas G. Brott, and Ronald M. Lazar declare that they have no conflict of interest.

David Liebeskind reports being a consultant as Imaging Core Lab for Stryker and Medtronic.

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Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

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