


FACULTY OF **MEDICINE**
AND HEALTH SCIENCES

A prospective comparison of perioperative embolization and neuropsychological outcome in patients with carotid stenosis treated by carotid endarterectomy versus carotid stenting with distal filter protection or flow reversal

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Abbreviations

ACA = anterior cerebral artery
ACE-R = Addenbrooke's Cognitive Examination Revised
ART = Adult Reading Test
AVLT = Auditory Verbal Learning test
BMT = best medical treatment
BNT = Boston Naming Test
BSAT = Brixton Spatial Anticipation Task
BSRT = Buschke Selective Reminding Test
CAS = carotid artery stenting
CASdp = transfemoral carotid artery stenting with distal protection filters
CASfr = transcervical carotid artery stenting with dynamic flow reversal
CCA= common carotid artery
CEA = carotid endarterectomy
CFT = Complex Figure Task
CFT-R = Rey Complex Figure Task
COWAT = Controlled Oral Word Association Test
CPD = cerebral protection device
CTM = Color Trail Making Test
CVLT = California Verbal Learning Test
D-2 = d2 Test of Attention
D-KEF = Delis-Kaplan Executive Function
DS = Digit Span from the WAIS-III
DW-MRI = diffusion-weighted magnetic resonance imaging
ECA = external carotid artery
FOME = Fuld Object Memory Evaluation
FTP = fetal variant of the circle of Willis
FRT = Facial Recognition Task
GIT = Groninger Intelligence Test
GP = Grooved Pegboard
HVLT = Hopkins Verbal Learning Test
ICA = internal carotid artery
JLO = Judgement of Line Orientation
LLT = List Learning Test
MCA = Middle cerebral artery
MOCA = Montreal Cognitive Assessment
MMSE = Mini-Mental State Examination
MWT-B = Mehrfach-Wahl-Wortschatz-Test
NCT = Number Connection Test
NVLT = Non-Verbal Learning Test

PAD = peripheral arterial disease
PET = positron emission tomography
PCA = posterior cerebral artery
RAPM = Raven Advanced Progressive Matrices
RAVLT = Rey Auditory Verbal Learning Test
RBANS = Repeatable Battery for the Assessment of Neuropsychological Status
RBMT = Rivermead Behavioral Memory Test
RNGT = Random Number Generation Task
RWFT = Regensburger Word Fluency Test
SCWT = Stroop Color and Word Test
SES = socioeconomic status
SPECT = single-photon emission computed tomography
SRT = Selective Reminding Test
SS = Spatial Span from the WAIS-III
SS-C = Symbol Substitution coding task from the WAIS-III
TAP = Test Battery for Attentional Performance
TCD = transcranial Doppler ultrasonography
TIA = transient ischemic attack
TMT = Trail Making Test
TT = Token Test
WAIS-III = Wechsler Adult Intelligence Scale, third edition
WAIS-R = Wechsler Adult Intelligence Scale Revised
WMS = Wechsler Memory Scale
WMS-R = Wechsler Memory Scale Revised
WCST = Wisconsin Card Sorting Test

Chapter 1

General introduction and thesis outline

This chapter is based on the article:

Neurocognitive functioning after carotid revascularization: a systematic review

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General Introduction

Stroke is the third leading cause of death in most western countries.[1] Carotid stenosis, a narrowing of the internal carotid artery, has been identified as an important risk factor for stroke, with increasing risk depending on the severity of the stenosis.[2] Carotid stenosis occurs when an atherosclerotic plaque builds up in the internal carotid artery. This plaque is made up of fat, cholesterol, calcium, and other substances found in the blood. Over time, the plaque hardens and narrows the carotid arteries. On one hand the carotid stenosis may limit or even block the blood flow towards the brain, resulting in an ischemic stroke. On the other hand, an ischemic stroke can also occur if a piece of plaque breaks away from the stenosis. The clot can migrate to the brain and get stuck in one of the brain's smaller arteries, also causing an ischemic stroke. The prevalence of carotid stenosis increases with age in both men and women[3] and with increasing life expectancy, this problem tends to become more important. Throughout this thesis, the term stroke will be used for ischemic stroke which is defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.[4]

To reduce the risk of stroke, carotid endarterectomy (CEA), i.e. the surgical removal of the plaque, is performed and has shown to be effective in reducing stroke in patients with recent carotid territory symptoms[5] as well as in asymptomatic patients.[6] A patient with carotid artery stenosis is considered symptomatic if the patient has transient or permanent focal neurological symptoms related to the ipsilateral retina or the cerebral hemisphere such as amaurosis fugax, transient ischemic attack (TIA), or stroke.[7] Asymptomatic patients are defined as patients with a significant carotid stenosis without these carotid territory symptoms. In CEA, the inner layer of the artery, intima and part of the media is removed (Figure 1). During the removal of the plaque, the internal carotid is clamped proximally and distally. A temporary shunt can be used to ensure sufficient blood flow to the brain during the procedure. Following recent guidelines, it is considered that patients with carotid territory symptoms within the past 6 months should undergo intervention when there is a stenosis of in ipsilateral internal carotid artery of at least 50%. For asymptomatic patients it is considered reasonable to perform CEA when there is at least a 70% stenosis of the internal carotid artery.[8] Since CEA reduces the stroke risk by half in asymptomatic patients,[6] CEA is carried out

regularly, although the debate whether asymptomatic patients on appropriate medical treatment should be treated invasively is still ongoing.[9]

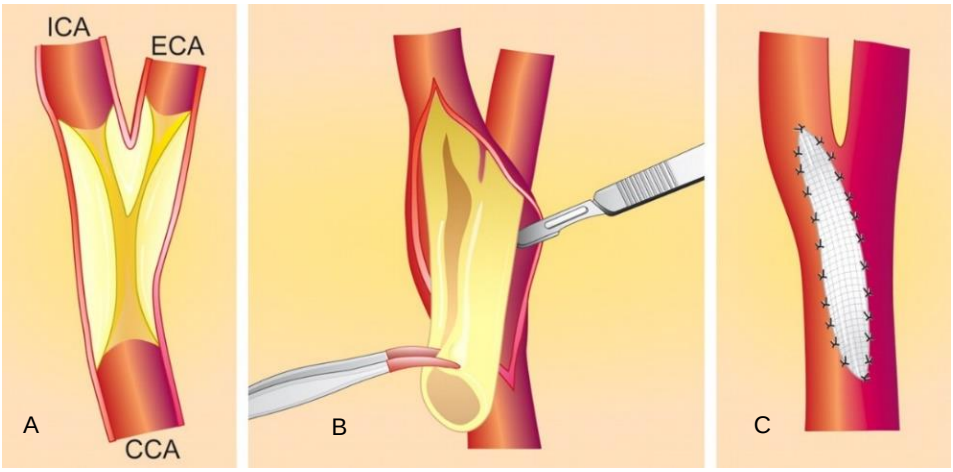

Figure 1. *Carotid endarterectomy (CEA). A) Dissection of the carotid artery. B) Removal of the atherosclerotic plaque. C) Closure of the carotid artery with a patch.*
CCA = common carotid artery; ECA = external carotid artery; ICA = internal carotid artery
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Carotid artery stenting (CAS) may be an alternative for CEA, especially in high-risk patients for surgery, reducing cranial nerve injury, wound complications and possible negative effects of general anesthesia such as myocardial infarction.[11] In CAS, a catheter is threaded up from the femoral artery into the internal carotid artery, where stenting and pre and/or post balloon dilatation is carried out (Figure 2). Distal embolic protection devices are often used to prevent cerebral embolization during CAS. Typically, a filter is deployed cranial/distal to the stenosis before angioplasty and stenting, and retrieved afterwards (Figure 3A). The use of prophylactic CEA and CAS with distal protection filters (CASdp) has been evaluated in many studies, and both methods are safe and effective options for stroke prevention in appropriately selected patients and if performed by proficient surgeons or endovascular therapists.[12-14] CASdp is nonetheless associated with an increased risk of stroke and lesions on new diffusion-weighted magnetic resonance imaging (DW-MRI), compared with CEA.[15, 16]

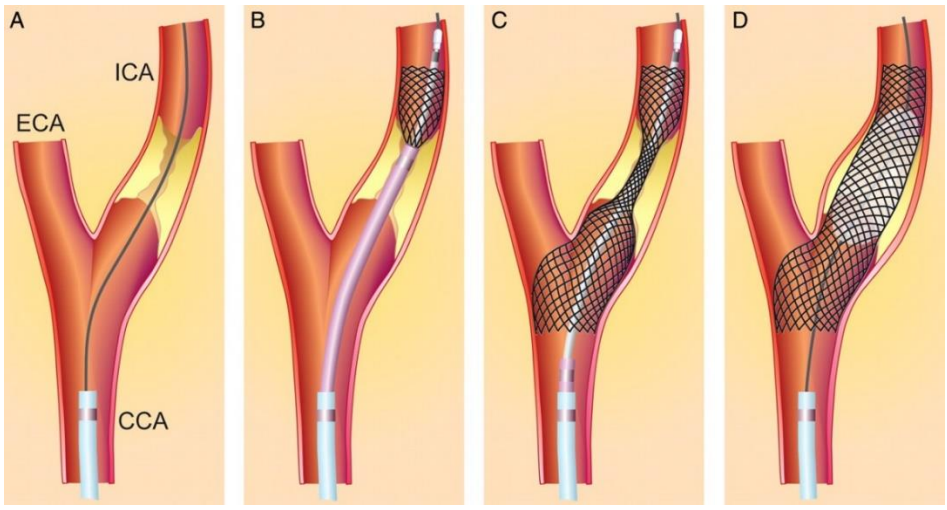

Figure 2. *Carotid stenting (CAS). A) A guidewire crosses the stenosis in the internal carotid artery. B and C) the stent is deployed. D) Balloon post dilation is performed to expand the stent.*
CCA = common carotid artery; ECA = external carotid artery; ICA = internal carotid artery
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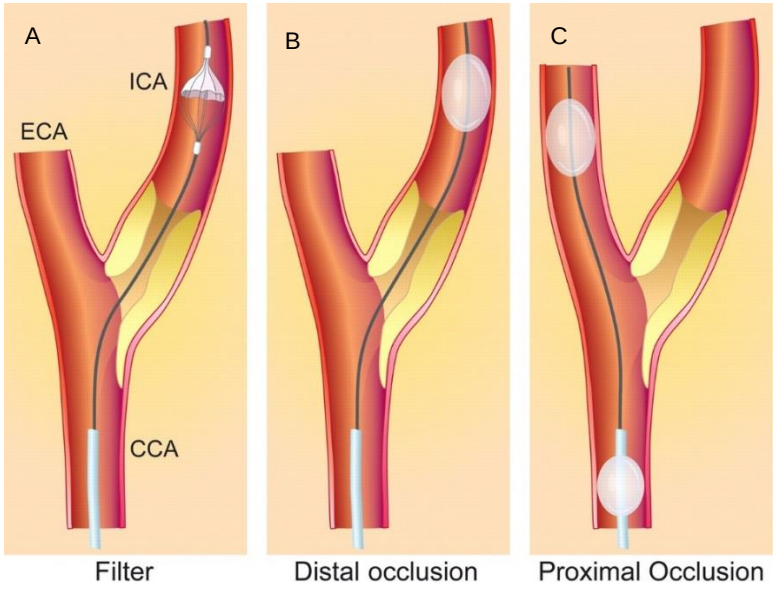

Figure 3. *Cerebral protection methods used during carotid stenting. A) Distal embolic protection filters (CASdp). B) Distal balloon occlusion. C) Proximal protection established by balloon occlusion in the proximal common carotid and external carotid.*
CCA = common carotid artery; ECA = external carotid artery; ICA = internal carotid artery
Reproduced from Roffi et al.[10] with permission of the publisher, Oxford University Press.

Trying to reduce these higher stroke and DW-MRI lesions rates, proximal protection methods have become increasingly popular (Figure 3C). The Mo.MA system (Medtronic Invatec, Roncadelle, Italy), inserted via the groin, blocks the antegrade flow to the internal carotid artery by proximal balloon occlusion in the distal segment of the common carotid and in the external carotid arteries (Figure 3C).[17, 18] After dilation and stenting, the debris can be removed by active blood aspiration. Nonetheless, the beneficial effects of proximal balloon occlusion compared with distal filters are not observed universally.[19, 20]

CAS with dynamic flow reversal via a direct cervical approach (CASfr) is a novel technique that is designed to provide a shorter, more direct access via the neck to deliver the stent and balloon. In this technique, the flow in the common carotid is blocked and reversed by an arteriovenous shunt created between the common carotid artery and the femoral vein (Figure 4 and 5). This flow reversal ensures that emboli flow away instead of towards the brain.[21] CASfr gained increasing attention as manipulation in the aortic arch and the proximal common carotid artery is avoided and the lesion is not crossed until protection is in place, resulting in a reduced number of new DW-MRI lesions caused by emboli showers typically observed during stenting and dilation using distal embolic protection devices.[21-23]

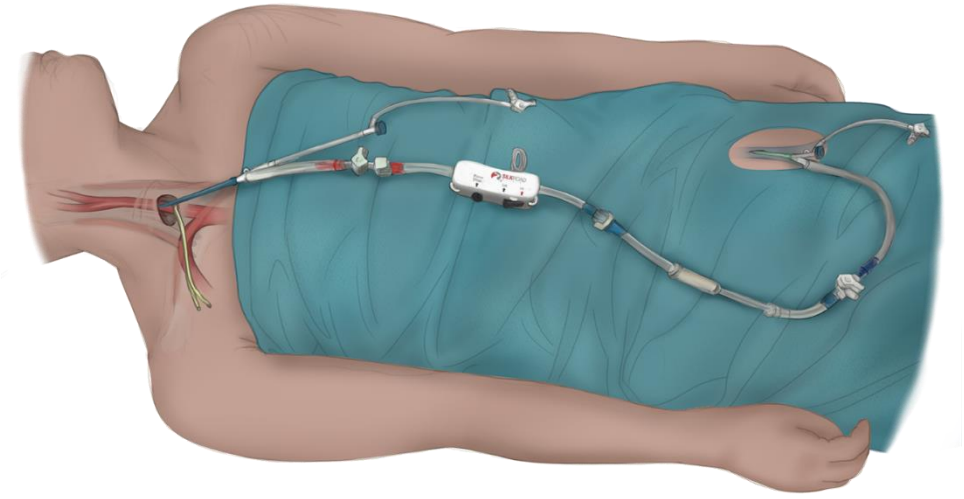

Figure 4. *CAS with dynamic flow reversal via a direct cervical approach (CASfr).*

Figure 5. *CAS with dynamic flow reversal via a direct cervical approach (CASfr).*

Carotid stenosis, carotid revascularization, and cognition

Symptomatic as well as asymptomatic carotid artery stenoses have been described to be associated with cognitive disturbances.[24, 25] Silvestrini et al.[26] demonstrated that unilateral left and right-sided asymptomatic carotid stenosis affect cognitive abilities specific to the ipsilateral hemisphere. The presence of a significant carotid stenosis in asymptomatic patients is a robust predictor of cognitive dysfunction, regardless of possible silent DW-MRI lesions[24] while no clear effect on cognition can be observed for low grade carotid stenoses (<25%).[27] Reduced blood flow to the brain or silent infarctions due to microembolization from the carotid plaque may be the cause of these cognitive deficits.[28] While it is clear that a significant carotid stenosis is associated with cognitive decline, it remains the question whether carotid revascularization can alleviate this problem.[29]

Examining the effect of carotid revascularization procedures, such as CEA and CAS, on the cognitive status of the patient is a booming research topic. Any carotid revascularization may lead to cognitive decline caused by procedural emboli, general anesthesia (CEA), or temporary flow interruption due to clamping of the carotid artery (CEA) or balloon dilatation (CAS).[29, 30] Conversely, reopening a stenotic vessel and restoring blood flow to the brain may improve cognitive dysfunction caused by chronic hypoperfusion.[29, 30] To date, it is still unclear whether these complex interactions ultimately result in a net improvement or a deterioration in the cognitive function.[31]

Several reviews about cognitive functioning after carotid revascularization have been published in 2007 and 2008.[29, 30, 32, 33] The consensus stated that it was still unclear if carotid revascularization results in cognitive decline, improvement, or no change at all and that further research is necessary to clarify the effects of CEA and CAS.

Several factors have contributed to this inconsistency. First, there is considerable variability in the demographical and clinical characteristics of patients, such as differences in symptoms (i.e. presence or absence of stroke), baseline cerebral perfusion status, age, sex, education, professional level, side and severity of stenosis, length of time between symptoms and revascularization, and medical, neurological and psychiatric histories.[33] Second, study characteristics also vary widely, in particular the susceptibility of the design to learning and practice effects, type of tests used (and their inherent difference in sensitivity), timing of assessments, and failure to implement an appropriate control group. Other factors, like underpowered studies, and variability of surgical techniques and criteria used in detecting postoperative change also flaw these cognitive studies.[29, 32]

In 2013 we performed a new review on this topic. For this review, we only included papers published since 2007 for two reasons. First, studies published before 2007 have already been discussed extensively in former reviews while no systematic overview of the recent literature has been reported since 2008. Second, because carotid treatment has continuously evolved, including evolution in medical devices (e.g. protection devices for CAS and type of stents) and drug therapy. Therefore, it is important to look at the recent papers in order to obtain a better ecological validity of the findings. Indeed, there seems to be a difference between the results of publications depending on the date of publication,[29, 33] as older studies have a higher chance of finding positive results. As De Rango et al.[29] suggested, this might be the consequence of fewer methodological biases in more recent studies.

In this systematic review, we focus on the neurocognitive consequences of carotid revascularization. We included all papers written in English focusing on the cognitive effects of carotid revascularization published between 2007 and May 2013. Searches were conducted on PubMed and Web of Science using the key word ‘carotid’ in combination with ‘cognitive’, ’cognition’, ‘neurocognition’, ‘neurocognitive’, ‘neuropsychology’, and ‘neuropsychological’. References of included papers were cross-checked for other relevant papers. Only papers

investigating the effects of carotid revascularization (CEA and CAS) on the cognitive functions were retained; reviews were excluded. Papers were included when neurocognitive testing was carried out preoperatively and at least once postoperatively more than 5 days after carotid treatment. Studies that only examined the cognitive functions on the first postoperative days were excluded because anesthesia and type of postoperative medical care may heavily influence these short-term results. Indeed, by using event-related potentials, Mracek et al.[34] found that general anesthesia had a negative effect on cognition the first postoperative day, but after 6 days no differences in cognitive functions were noted between general and local anesthesia.

To ensure that studies conducted extensive neuropsychological testing, papers that only used short cognitive screening instruments, such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MOCA), were excluded. Furthermore, to assure that the studies were sufficiently powered, studies in which less than 15 patients adhered to follow-up, were excluded. Finally, studies that solely investigated the effects of revascularization of carotid occlusions were also excluded, since it may not be possible to extrapolate these results to non-occlusive significant carotid artery stenoses.

Studies were grouped into three categories: CEA alone, CAS alone, and CEA versus CAS. Results in these three categories are reviewed for common findings; a focus is given on papers with solid methodological setups, such as studies using the reliable change indices by calculating z-scores: (individual test score – mean score of control group) / SD of control group. When simply comparing pre- and post-revascularization cognitive scores for both patient and control groups separately, results are heavily influenced by characteristics like sample size in both groups. Studies are given a superscript ‘a’ mark when they included a control group and compared the patient group(s) with this control group using statistical methods. A superscript ‘b’ mark was given when they included an adequately sized control group but did not compare the groups with each other directly. Underpowered control groups were defined as sample sizes of less than half of the patient sample size. Studies received a superscript ‘c’ mark when they did not implement a control group, or when they did but did not compare the groups directly, and when the control group contained less than half the amount of subjects in the patient group. All CEA versus CAS studies were reviewed because they have at least two groups, which allows a valid comparison between the two techniques. Of the studies only examining CEA or CAS, only studies that received a superscript ‘a’ or ‘b’ mark were reviewed in the Results section to ensure the focus is given on methodologically sound studies.

Sixty-seven studies were identified, of which 36 were included in this review. The papers excluded were 5 reviews, 5 having a too small sample size in follow-up assessments, 7 only using short screening instruments (MMSE or MOCA), 1 missing a preoperative assessment, 9 only providing follow-up data for a few days, and 2 focusing on intragroup differences and not reporting results of the whole group. Of the 38 remaining articles, 1 study[35] was also excluded because of a large variation in the timing of the postoperative assessment. Patients were tested between 4 and 41 months after intervention. Since the timing of postoperative testing can also be a confounding factor, results from this study are impossible to interpret and to compare with other studies. Another study[36] was left out of this review because it was a subgroup analysis of another paper already included.[37] So in total, 36 studies were included in this review of which 11, 3, and 22 received the superscript 'a', 'b', and 'c' mark, respectively.

Studies Comparing Neurocognitive Outcome after CEA versus CAS

Five of the 7 studies comparing CEA with CAS found no significant differences in cognitive outcome between procedures[11, 38-41] (table 1). Lal et al.[42] also found no differences in the global cognitive score, but discovered that CEA resulted in a reduction in memory performance compared with CAS, while CAS patients showed reduced psychomotor speed. Wasser et al.[37] also found no significant differences in the global difference score, but the domain verbal learning showed a small improvement for CAS compared with CEA.

Although this review contains 2 studies focusing on symptomatic, 2 on asymptomatic, and 3 on symptomatic as well as asymptomatic patients, and some studies even randomized the patients to CEA and CAS, all these studies concluded that CAS and CEA have a comparable effect on cognition in asymptomatic and symptomatic patients.

When looking at the results for CAS and CEA separately compared to healthy controls and applying the methodological criteria described previously, only 2 of the 7 studies are eligible and both used an extensive neuropsychological test battery (table 1; 2 studies with a superscript 'a' mark). Wasser et al.[37] found that both patients after CAS and after CEA deteriorated significantly over time in the domain short-term memory and in visuoconstructive functions compared to controls. Altinbas et al.[38] found for CAS, but not for CEA, a small but significant decrease in the total cognitive sum score.

Table 1. Studies comparing neurocognitive outcome after CEA versus CAS

Reference	Patients in follow-up	Control group	Follow-up period	Cognition after CEA versus CAS	Control for effect of previous stroke on cognition	Cognitive domains and tests
Witt et al.[11], 2007[c]	45 24 CEA vs. 21 CAS without CPD Randomized Sympt.	No	6 and 30 days	No differences between CEA and CAS at 6 or 30 days *At 6 days:* Decline in 19% of CEA vs. 21% of CAS Improvement in 25% of CEA vs. 14% of CAS in 2 or more tasks *At 30 days:* Decline in 25% of CEA vs. 24% of CAS Improvement in 29% of CEA vs. 24% of CAS in 2 or more tasks	CAS: 33% stroke CEA: 50% stroke No differences in frequency stroke between groups	Verbal memory: RAVLT Non-verbal memory: CFT-R Attention: Paced Visual Serial Addition Test, TMT (A and B), Modified Stroop Executive function: verbal fluency (phonologic and semantic), RNGT Motor skills: Purdue Pegboard Test, Finger-Tapping Test
Takaiwa et al.[39], 2009[c]	26 11 CEA vs. 15 CAS with CPD No randomization Asympt. + sympt. (45% CEA, 60% CAS)	No	1 week, 3, 6, and 12 months	No significant differences between CEA and CAS for any of the domains or MMSE Only CEA showed decrease at 1 week *At 1 week:* CEA: 36% of patients showed decrease for immediate as well as delayed memory, visuospatial construction, language, and total score CAS: 13% showed decrease for visuospatial construction and language / 36% showed improvement for immediate and delayed memory, and total score *At 3, 6, and 12 months:* Improvement in 54% of CEA vs. 67% of CAS No deterioration	No differences in frequency symptomatic status between groups	MMSE RBANS (immediate memory, visuospatial construction, language, attention, delayed memory, and total score)
Feliziani et al.[40], 2010[c]	46 22 CEA vs. 24 CAS with CPD No randomization Asympt.	No	3 and 12 months	No significant differences between the groups over time for all studied variables No changes over time for CEA or CAS, except for a slight deterioration in visuospatial construction in the CAS group	NA	MMSE Memory: Babcock Story Recall, RAVLT, semantic fluency Attention and executive functions: TMT (A and B), COWAT Visuospatial construction: Copy Drawing Test
Altinbas et al.[38], 2011[a]	119 58 CEA vs. 61 CAS (no info about CPD) Randomized Sympt.	75 healthy (historical control)	6 months	No significant differences between CEA and CAS in any of the domains No changes in any of the 6 domains for CAS or CEA A small but significant decrease in cognitive sum score for CAS, but not for CEA	CAS: 42% stroke CEA: 51% stroke No differences in frequency stroke between groups	NRT, MMSE Abstract reasoning: WAIS-III similarities, RAPM Attention: WAIS-III digit span (f), Visual Elevator of the Test of Everyday Attention Executive functioning: BSAT, letter fluency Language: TT, BNT Verbal memory: WAIS-III digit span (b), RAVLT, semantic fluency Visual memory: CFT-R Visual perception: JLO, FRT, CFT-R (copy) Neglect: Star Cancellation Test

Lal et al.[42], 2011[c]	46 25 CEA vs. 21 CAS with CPD No randomization Asympt.	No	4–6 months	No differences on composite change score for CEA and CAS. Both groups showed improvement on composite change score and each individual test Impairment only observed in CEA for working memory index and CAS for psychomotor speed. No differences between CEA and CAS on other tests	NA	TMT Processing speed index (digit symbol coding and symbol search) of WAIS-III Working memory index (letter-number sequencing and spatial span) of WAIS-III BNT COWAT HVLT
Wasser et al.[37], 2011[a]	55 31 CEA vs. 24 CAS (CPD in 9 of 24) No randomization Asympt. + sympt. (71% CAS, 39% CEA)	27 healthy Matched (age and education)	3 months	No significant differences between the groups on 5 of the 6 domains. Only verbal learning showed an improvement for CAS whereas CEA showed deterioration Both groups deteriorated significantly over time in the domain of short-term memory, and visuoconstructive functions	CEA: 16% stroke CAS: 30% stroke No differences in frequency stroke between groups	MMSE Attention: TAP (alertness and divided attention) Short-term memory: TAP (working memory), SRT, WMS-R Executive functions: RWFT, WCST, Regard's Five Point Test Verbal learning and memory: SRT, WMS-R, Non-verbal learning and memory: CFT-R (recall), lNVLT, Spatial Recall Test Visuoconstructive functions: CFT-R (copy)
Zhou et al.[41], 2012[c]	51 35 CEA vs. 16 CAS with CPD No randomization Asympt. + sympt. (54% CEA, 50% CAS)	No	1 month	No differences between the groups on test scores No statistical methods were used to evaluate cognitive impairment or improvement	CEA: 20% stroke CAS: 25% stroke No differences in frequency stroke between groups	ART MMSE Memory: RAVLT Attention and executive function: *TMT, Digit Span, color-word interference* Language: *category fluency*, *BNT*, Motor skills: *GP* *(no information about results of tests in italic)*

Author names in bold means the study was reviewed. NA = Not applicable; CPD = cerebral protection device; WAIS-III = Wechsler Adult Intelligence Scale, third edition; WMS-R = Wechsler Memory Scale Revised; CFT-R = Rey Complex Figure Test; RAVLT = Rey Auditory Verbal Learning Test; HVLT = Hopkins Verbal Learning Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; GP = Grooved Pegboard; RWFT = Regensburger Word Fluency Test; NVLT = Non-Verbal Learning Test; SRT = Selective Reminding Test; TAP = Test Battery for Attentional Performance; JLO = Judgement of Line Orientation; RNGT = Random Number Generation Task; FRT = Facial Recognition Task; RAPM = Raven Advanced Progressive Matrices; TT = Token Test; BSAT = Brixton Spatial Anticipation Task; TMT = Trail Making Test; COWAT = Controlled Oral Word Association Test; BNT = Boston Naming Test; WCST = Wisconsin Card Sorting Test; ART = Adult Reading Test.

[a] Using statistical methods to compare the patient and control group. [c] No control group, or calculating differences for the patient and control group over time separately, with a control group that contains less than half the number of the patient group.

Studies on Neurocognitive Outcome following CEA

Ten[43-52] of the 17 studies[43-59] examining the effects of CEA fulfilled our criteria (table 2; 8 studies with a superscript 'a' mark and 2 with a superscript 'b' mark). The Department of Neurosurgery of the Iwate Medical University published several papers on the cognitive consequences of CEA, all using established tests of intelligence and memory. Studies that examined cognitive deterioration found impairment in 13% of patients after CEA,[44, 47] while studies focusing on cognitive amelioration after CEA found improvement in 10% of the cases.[45, 46] One study evaluated both trends and noted improvement in 10% and impairment in another 10% of the patients in one or more cognitive domains.[43] All these studies thus found comparable results.

Other research groups found mixed results with no change,[52] or a decrease in cognitive score in 6%[50] or even 15% of patients[49].

In the studies comparing patient groups with control groups separately, Czerny et al.[51] found an improvement over time for the patient group on the Number Connection Test at 1 year but not after 5 years. At 1 month after intervention, Soinne et al.[48] observed cognitive impairment in 11% of CEA patients but in 0% of the controls.

We can summarize that in most studies, a decrease in the cognitive score over time is found in 10-15% of patients after CEA. Improvements are also often observed in about 10% of patients.

Table 2. Studies on neurocognitive outcome after CEA

Reference	Patients in follow-up	Control group	Follow-up period	Cognition after CEA	Control for effect previous stroke on cognition	Cognitive domains and tests
Bossema et al.[52] 2007[a]	45 CEA (20 lCEA and 25 rCEA) Asympt. + sympt. (lCEA: 45%, rCEA: 76%)	25 healthy (similar education, age, and hand dominance)	3 months	No interactions between time and group. Both groups improved equally No difference between patients and controls on reliable changes after CEA	No stroke included	Dichotic Listening Test Finger Tapping Test Motor Planning Test / Verbal Fluency Test (COWAT + category) Doors Test
Saito et al.[55], 2007[c]	55 CEA Asympt. + sympt. (62%)	20 patients (neck clipping through craniotomy)	1 month	Impairment: 11% in one or more cognitive domains (only impairments were assessed)	44% stroke No symptoms <1 month No significant differences between groups (impairment / no impairment) for symptomatic status	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Falkensammer et al.[59], 2008[c]	19 CEA at 7–10 days 16 CEA at 6 months Asympt.	No	7–10 days, 6 months	Overall improvement at 7–10 days and 6 months. 3 patients showed decline (1 with	NA	Fine motor coordination: GP Expressive language: COWAT, category fluency

				reliable change indices = 6%) Significant improvement in digit symbol, verbal memory. Conversely, there was a significant decline on one test assessing processing speed at 6 months (word reading in SCWT)		Verbal memory: RAVLT Mental status screen: MMSE Estimated premorbid verbal IQ: ART Processing speed/attention/executive function: Digit Span and Digit Symbol (WAIS-R), TMT (A and B), SCWT, D-KEF Sorting Test
Hirooka et al.[54], 2008[c]	158 CEA Asympt. + sympt. (70%)	No	1 month	Impairment: 11% on 1 or more of 5 domains (only impairments were assessed)	51% stroke No control for stroke or symptomatic status	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Chida et al.[44], 2009[a]	60 CEA Asympt + Sympt (62%)	44 patients (neck clipping through craniotomy; historical control)	1 month	Impairment: 13% in one or more of 5 domains (only impairments were assessed)	43% stroke No significant differences between groups (impairment / no impairment) for symptomatic status	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Soinne et al.[48], 2009[b]	44 CEA Asympt. + sympt. (48%)	22 healthy Matched (sex, age, education, and social class)	100 days	Equal improvement for CEA and controls At 100 days: Impairment: CEA, 5 patients (11%) vs. controls, 0% On the domain level: attention 48% of CEA vs. 18% of controls had impairment (significant), motor dexterity, 32% of patients vs. 18% of controls (NS)	15% minor stroke No control for stroke on cognition	Language: BNT Verbal memory and learning: RAVLT Immediate verbal memory: WAIS-R Digit Span –F and B Verbal fluency: word and category naming Visual memory: CFT-R – Visual Design Learning Test Immediate visual memory: Corsi Blocks F and B Attention: Letter Cancellation Task, TMT (A) Executive function: Stroop Test, TMT (B) Motor dexterity: Purdue Pegboard
Yocum et al.[49] 2009[a]	149 CEA Asympt. + sympt. (no percentages are given)	60 patients (lumbar spine surgery)	1 month	*At 1 month:* moderate to severe cognitive deterioration: 16% (10% severe, 6% moderate)	No information is given about symptoms	Verbal function: BNT Verbal fluency: COWAT Visuospatial construction: CFT-R (copy) Visuospatial memory: CFT-R (recall) Complex conceptual switching: TMT (B) Attention: TMT (A) Verbal learning and memory: HVLT or BSRT
Chida et al.[45], 2010[a]	79 CEA Asympt. + sympt. (59%)	70 healthy	1 month	Improvement: 9% in one or more of 5 domains (only improvements were assessed)	19% stroke No symptoms <2 weeks No significant differences between groups (improvement / no improvement) for symptomatic status or stroke	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Czerny et al.[51], 2010[b]	25 CEA Asympt. + sympt. (60%)	25 healthy Matched (age and sex)	1 and 5 years	Improvement for patient group at 1 and 5 years on the NCT No changes on MMSE	No stroke included	MMSE NCT

Gigante et al.[50], 2011[a]	127 CEA Asympt. + sympt. (4%)	71 patients (lumbar laminectomy / similar age and education)	30 days	*At 30 days:* Moderate to severe deterioration: 6%	No information is given about the type of symptoms in the symptomatic patients	Verbal function: BNT Verbal fluency: COWAT Visuospatial construction: CFT-R (copy) Visuospatial memory: CFT-R (recall) Complex conceptual switching: TMT (B) Attention: TMT (A) Verbal learning and memory: HVLT or BSRT Manual dexterity: GP
Ghogawala et al.[53], 2013[c]	23 CEA (at 1 month) 20 CEA at 6 months 19 CEA at 12 months Asympt. + sympt. (21%)	No	1, 6, and 12 months	*At 1 month:* Improvement: 30% Deterioration: 30–40% on TMT (A and B) and HVLT *At 12 months:* significant improvement for all tests Improvement: 60%	No stroke included	Attention: TMT (A) Executive functioning: TMT (B) Verbal fluency: COWAT Verbal learning and memory: HVLT
Nanba et al.[47], 2012[a]	70 CEA Asympt. + sympt. (71%)	44 patients (neck clipping through craniotomy; historical control)	1 month	Deterioration: 13% in one or more of 5 domains (only impairments were assessed)	31% stroke No symptoms <2 weeks No significant differences between groups (impairment / no impairment) for symptomatic status	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Yamashita et al.[46], 2012[a]	140 CEA Asympt. + sympt. (69%)	70 healthy (historical control)	1 month	Improvement in 10% of patients in one or more of 5 domains (only improvements were assessed)	No symptoms <2 weeks No significant differences between groups (improvement / no improvement) for symptomatic status	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Yosida et al.[56], 2012[c]	213 CEA Asympt. + sympt. (65%)	40 healthy	1–2 months	Improvement: 13% Deterioration: 12%	No symptoms <2 weeks No control for stroke on cognition	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Inoue et al.[57], 2013[c]	81 CEA Asympt. + sympt. (54%)	No	6 months	Significant improvement for all scores (VIQ, PIQ, WMS-memory and WMS-attention)	No information about stroke tendency of positive effect of symptomatic status on progress	WAIS-R (verbal IQ + performance IQ) WMS (memory + attention)
Saito et al.[43], 2013[a]	100 CEA Asympt. + sympt. (64%)	40 healthy (historical control)	1 month	Improvement: 10% Impairment: 10% in one or more of the 5 cognitive scores	No symptoms <2 weeks No significant differences between groups (improvement / deterioration) for symptomatic status	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Takaiwa et al.[58], 2013[c]	15 CEA Asympt.	No	3 months	Improvements in immediate memory, attention, total scale of the RBANS, and 2 subtests of WAIS-R Improvement: 30% Deterioration: 7% in RBANS and WAIS-R subtest scores	NA	RBANS (immediate memory, visuospatial construction, language, attention, delayed memory, and total score) WAIS-R 2 subtests (information and picture completion) ART

Author names in bold means the study was reviewed. NA = Not applicable; WAIS-R = Wechsler Adult Intelligence Scale Revised; WMS = Wechsler Memory Scale; CFT-R = Rey Complex Figure Test; RAVLT = Rey Auditory Verbal Learning Test; HVLT = Hopkins Verbal Learning Test; BSRT = Buschke Selective Reminding Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; GP = Grooved Pegboard; NCT = Number Connection Test; TMT = Trail Making Test; COWAT = Controlled Oral Word Association Test; BNT = Boston Naming Test; ART = Adult Reading Test; SCWT = Stroop Color and Word Test; D-KEF = Delis-Kaplan Executive Function.

[a] Using statistical methods to compare the patient and control group. b Calculating differences for the patient and control group over time separately, the control group contains more than half the number of the patient group. c No control group, or calculating differences for the patient and control group over time separately, with a control group that contains less than half the number of the patient group.

Studies on Neurocognitive Outcome after CAS

Only 2[60, 61] of the 12[60-71] included studies examining the effects of CAS fulfilled our methodological criteria regarding control groups (table 3; 1 study with a superscript 'a' mark and 1 with a superscript 'b' mark). Xu et al.[61] implemented a relevant control group that underwent a carotid angiography to correct for practice effects. They used an extensive neuropsychological battery. Only verbal memory showed better results over time in the CAS group; no deterioration in the other tests was observed. Ishihara et al.[60] did not use a reliable change index to measure differences over time in the CAS group, but they had two different control groups. They found differential effects for right-sided CAS (improvement in performance IQ and delayed memory) and left-sided CAS (improvement in verbal IQ). The first control group undergoing neck clipping through craniotomy had minor and nonsignificant increases in the Wechsler Adult Intelligence Scale (third edition) and the Wechsler Memory Scale scores. The second control group with atherosclerotic disease displayed no cognitive changes over time, but this was a smaller group and thus had lower statistical power. Though there are only 2 studies methodologically solid enough to draw conclusions, small, but positive results are found over time for CAS patients. The problem of the lack of methodologically solid studies can also be observed in the review of De Rango et al.[29]. Only few studies have been published investigating the cognitive consequences of CAS, and even fewer have recruited a control group.

Table 3. Studies on neurocognitive outcome after CAS

Reference	Patients in follow-up	Control group	Follow-up period	Cognition after CAS	Control for effect of previous stroke on cognition	Cognitive domains and tests
Xu et al.[61], 2007[a]	51 CAS with CPD at 1 week 47 CAS with CPD at 12 weeks Asympt. + sympt. (no percentages are given)	57 patients (carotid angiography)	1 and 12 weeks	CAS patients performed better on the RAVLT at 1 as well as 12 weeks At 1 week but not at 12 weeks, CAS patients showed deterioration in BNT	No stroke <1 month Both groups had similar percentage of stroke	RAVLT CFT-R BNT Digit Span (WAIS) TMT Finger Tapping Test MMSE

Mlekusch et al.[63], 2008[c]	71 CAS with CPD Asympt. + sympt. (6%)	No	6 months	Significant improvement for TMT (A) Improvement: 45% (at least 2 tests) Deterioration: 8%	No stroke patients included	MMSE Attention: TMT (A and B) Verbal intelligence and fluency: COWAT + semantic
Turk et al.[68], 2008[c]	17 CAS (no info about CPD) Asympt. + sympt. (76%)	No	3 months	Total RBANS score, immediate memory and attention improved	35% stroke No control for stroke	MMSE RBANS TMT
Tiemann et al.[65], 2009[c]	22 CAS without CPD Asympt.	No	6 weeks	Improvement: LLT Deterioration: Digit span Tendency to improvement: phonemic verbal fluency Improvement: 36% Deterioration: 27%	NA	MWT-B, LLT, NCT, Digit Span (F and B), Spatial Span (F and B) Verbal fluency: phonological and semantical Block-Design-Test (WAIS)
Grunwald et al.[64], 2010[c]	41 CAS without CPD Asympt.	7 patients (endovascular treatment ACA aneurysms)	3 months	CAS: significant increase in cognitive speed but not memory Control group: no significant differences	NA	MMSE Cognitive speed: NCT, Labyrinth Test, Figure-Symbol Test, Color-Word Test Memory: Repeat the Numbers Test, Word List Test, Image Test, Word Pairs Test, Symbol Test, Latent Learning Test
Raabe et al.[67], 2010[c]	62 CAS with CPD (51 at 3 months, 48 at 6 months, and 51 at 12 months) Asympt. + sympt. (31%)	No	3, 6, and 12 months	*At 3 months:* 16% improvement, 82% stable, 2% decline *At 6 months:* 21% improvement, 71% stable, 8% decline *At 12 months:* 22% improvement, 78% stable, 0% decline	No major stroke 26% minor stroke No effect of symptomatic status on cognition No control for stroke	DRS-2 RAVLT TMT (B) ART MMSE
Murata et al.[69], 2011[c]	16 CAS with CPD Sympt.	16 healthy	1 month	No differences for total score RBMT. No scores for control group are provided	No info about stroke No control for stroke	RBMT
Chen et al.[62], 2012[c]	34 CAS with CPD [divided into I (n = 6): ipsilateral ischemia and failed CAS; II (n = 17): ipsilateral ischemia and successful CAS, and III (n =11): no ischemia and successful CAS] Asympt.	No	3 months	Only group II showed significant improvement in ADAS-cog, MMSE and CTM (A) No changes for CTM (B) and semantic fluency No significant changes for groups I and III	NA	MMSE Alzheimer's Disease Assessment Scale cognitive subscale CTM (A and B) Semantic fluency
Mendiz et al.[71], 2012[c]	20 CAS with CPD Asympt.	No	3 months	Improvement in set shifting (TMT B), processing speed (digit symbol coding and symbol search), and working memory (digit span backwards), verbal (RAVLT acquisition) and visual memory (CFT-R delayed score) The other tests revealed no differences	NA	MMSE ACE-R BNT Verbal fluency: phonologic and semantic RAVLT CFT-R Digit Span (F and B) TMT (A and B) WCST INECO Frontal Screening, Digit Symbol Coding (WAIS-III)

						Symbol Search (WAIS-III)
Cheng et al.[66], 2013[c]	144 CAS (no info about CPD) – all MCI patients Asympt. + sympt. (55%) No randomization	64 MCI patients (carotid stenosis on drug therapy) Asympt. + sympt. (56%)	6 months	CAS group: small but significant improvements in MMSE, MOCA, FOME and digit span. Rapid verbal retrieval showed no significant differences No significant changes for the control group	No stroke <4 weeks Both groups had similar % of stroke	MMSE MOCA FOME Rapid verbal retrieval digit span (WAIS)
Ishihara et al.[60], 2013[b]	39 (21 rCAS, 18 lCAS) with CPD Asympt. + sympt. (no percentages are given)	2 control groups: (a) 17 patients (neck clipping through craniotomy), (b) 12 patients (atherosclerotic carotid artery disease)	6 months	IQ performance and delayed memory improved after rCAS VIQ improved after lCAS Group A: slight but not significant increases in most WAIS-III and WMS scores Group B: no significant changes in the WAIS-III or WMS scores	No stroke <3 months No control for stroke on cognition	WAIS-III (verbal IQ, performance IQ, and full IQ) WMS-R (general memory, verbal memory, delayed memory, visual memory, attention, and concentration)
Ortega et al.[70], 2013[c]	33 CAS with flow reversal Asympt. + sympt. (50%)	No	6 months	Global improvement, mainly information processing speed, language, memory and visuospatial function	48% stroke Global score improved for patients with and without previous stroke	Digit Span (WAIS-III), WMS-III Mental Control (attention) BNT Token Test Verbal fluency: COWAT and Semantic Fluency CVLT GP JLO SCWT

Author names in bold means the study was reviewed. NA = Not applicable; CPD = Cerebral Protection Device. WAIS-III = Wechsler Adult Intelligence Scale, third edition; WMS = Wechsler Memory Scale; CFT-R = Rey Complex Figure Test; RAVLT = Rey Auditory Verbal Learning Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; MOCA = Montreal Cognitive Assessment; GP = Grooved Pegboard; NCT = Number Connection Test; RBMT = Rivermead Behavioral Memory Test; CVLT = California Verbal Learning Test; JLO = Judgement of Line Orientation; FOME = Fuld Object Memory Evaluation; CTM = Color Trail Making Test; ACE-R = Addenbrooke's Cognitive Examination Revised; LLT = List Learning Test; TMT = Trail Making Test; COWAT = Controlled Oral Word Association Test; BNT = Boston Naming Test; WCST = Wisconsin Card Sorting Test; ART = Adult Reading Test; SCWT = Stroop Color and Word Test; MWT-B = Mehrfach-Wahl-Wortschatz-Test; ACA = anterior cerebral artery.

[a] Using statistical methods to compare the patient and control group. [b] Calculating differences for the patient and control group over time separately, the control group contains more than half the number of the patient group. [c] No control group, or calculating differences for the patient and control group over time separately, with a control group that contains less than half the number of the patient group.

Symptomatic Status

Some papers only included asymptomatic patients, some admitted symptomatic patients without major (and minor) stroke, and others included all types of symptomatic patients. Sadly, several studies failed to provide information about the symptomatic status and type of symptoms in their patients. Furthermore, differences in timing between the symptoms and intervention can also influence the results.

As previously stated, symptomatic status does not seem to have an influence on the cognitive differences or similarities found between CAS and CEA. Many studies reported no differences

related to symptomatic status or history of stroke between groups improving or deteriorating after CEA[43-47, 55]. In contrast, Inoue et al.[57] reported a (nonsignificant) tendency of a positive effect of symptomatic status on cognition after CEA. For CAS, symptomatic status also does not seem to influence cognitive results.[67] Furthermore, Ortega et al.[70] found an improvement in global cognitive score for patients with, as well as without, previous stroke. It appears that symptomatic status does not have a clear impact on cognition after carotid revascularization.

Side of Intervention

For CEA, the side of carotid intervention does not have an influence on cognitive function. By using neuropsychological instruments sensitive to hemispheric specialization, Bossema et al.[52] demonstrated convincingly that changes in cognition occurred irrespective of the side of intervention. Furthermore, many studies found no difference in the side of intervention between groups improving or groups deteriorating postoperatively.[45, 46, 55, 57]

In CAS, results are less consistent. Grunwald et al.[64] and Turk et al.[68] found no correlation between the cognitive results and the side of the intervention. On the other hand, Ishihara et al.[60] and Ortega et al.[70] found differential effects for left and right sided CAS. Ishihara et al.[60] noted that the performance IQ improved after CAS in patients with severe right-sided carotid artery stenosis while the verbal IQ rose after endovascular treatment of the left carotid artery. Ortega et al.[70] found a significant increase in the global cognitive score, more specifically in language, visuospatial function, and information processing for left CAS, while patients with right CAS only presented a (nonsignificant) trend toward global cognitive improvement.

Age

In large studies and systematic reviews, age has been shown to be a predictor of postoperative cognitive dysfunction after noncardiac surgery.[72, 73] For CAS and CEA, it was also shown that increasing age may raise the risk of cognitive decline,[67, 74] though not all studies found a clear effect of age on the evolution of cognition after CAS.[63, 64, 68, 70]

Wasser et al.[36] found that older patients seem to be particularly vulnerable to cognitive decline after CEA, while CAS seems to have better results at follow-up. Feliziani et al.[40], however, did not find these differences between CEA and CAS in elderly patients. In addition, increased neurological complications occur in the elderly after CAS in comparison to CEA, hence a patient-tailored approach seems mandatory to reduce stroke and death risk in this high-risk group.[12, 75]

New Brain Lesions after Revascularization

As Schnaudigel et al.[15] showed in their systematic review, CAS is more frequently associated with new DWI lesions compared with CEA (37 vs. 10%). These findings were supported by several recent studies[37, 38, 41, 76]. In a randomized trial, Bonati et al.[16] also found that three times more patients in the CAS group than in the CEA group had new ischemic lesions (DW-MRI) on post-treatment scans. Schnaudigel et al.[15] concluded that the use of cerebral protection devices (33 vs. 45% without) and closed-cell designed stents during CAS (31 vs. 51% with open-cell stents), as well as selective versus routine shunt usage during CEA (6 vs. 16%, respectively) significantly reduced the incidence of new ipsilateral DW-MRI lesions.

Remarkably, numerous studies have failed to find an association between the incidence, the number, and the volume of new DW-MRI lesions and changes in cognition for CAS as well as CEA.[37, 48, 54, 57, 60, 64, 65, 67] It seems that DW-MRI does not capture all damage that may evoke cognitive deterioration, and some DW-MRI lesions may have little functional impact.

Perioperative embolization

TCD is a noninvasive technique in which an ultrasonic beam is aimed at the cerebral arteries via natural openings or 'windows' of the skull. Ultrasound echoes generated by moving blood cells are recorded by the probe for offline analysis.[77] By altering the depth of the sample volume and the direction of the beam, the middle cerebral artery (MCA) can be identified.[77] TCD has been shown to be an effective tool when studying perioperative embolization during carotid revascularization.[78] In agreement with a higher prevalence of new DW-MRI lesions, CASdp has consistently been associated with a greater embolic load than CEA as detected by TCD, despite the use of distal protection devices.[79-81] Although it has been shown that CASfr is capable of reducing the embolic showers that are typically observed in embologenic phases in CASdp such as stenting and balloon dilation,[82] a direct comparison between CASfr and the other common revascularization procedures regarding their effect on perioperative embolization has not been published yet.

The effect of perioperative embolization on postoperative cognitive functioning is unclear. Crawley et al.[81] for example, found no correlation between the amount of emboli during CAS and CEA with neuropsychological outcomes. Martin et al.[83] concluded in their systematic review that

the effect of perioperative embolization on cognition remains undecided. This may be the consequence of the variability in type (gaseous vs. particulate) and size of emboli. A few particulate emboli can be more damaging than several gaseous emboli.[92] Therefore, differentiation between emboli may be valuable, but this is not easy as even the EmboDop which was designed to differentiate between gaseous and particulate emboli seems unreliable.[84, 85]

S-100β

S-100β is a neuroprotein that is present in the cytosol or on the membrane of astroglial cells.[86] When the central nervous system is damaged, the serum concentration of S-100β increases as it leaks from the injured cells into the cerebrospinal fluid and subsequently across the impaired blood-brain barrier into the systemic circulation.[87, 88] Hence, S-100β is a sensitive marker of cerebral injury and blood–brain barrier dysfunction.[89-91] S-100β shows maximum levels within 24 hours after cardiac surgery,[92] has a biological half-life of approximately 25 minutes, and is rapidly excreted by the kidney.[93] Because of the short half-life, most researchers tend to measure S-100β serum levels before, during, and several times within 12 to 24 hours after intervention.[91, 94-96] It has been shown that elevated S-100β concentrations are associated with ischemic brain damage,[92] especially persisting elevated levels of S-100β 6 hours post intervention were related to neurological disturbances.[94, 97, 98] Moreover, increased S-100B levels are correlated with symptomatic status.[99] Transitory increases in S-100β serum levels appear, on the other hand, related to impairments in the blood-brain barrier without any neurological consequences.[94, 95, 97, 98] S-100β rises in patients with focal brain damage after ischemic territorial MCA infarction,[89] which makes this biomarker especially relevant to study cerebral damage after carotid revascularization because the MCA arises from the internal carotid. S-100β has therefore been studied in many carotid revascularization studies, but studies connecting S-100β to perioperative embolization assessed by TCD have reported conflicting results.[96, 100]

Several studies have investigated the relation between S-100β concentrations and postoperative cognition.[11, 59, 99, 101] Witt et al.[11] found no elevated levels of S-100β early after carotid intervention, and thus no link between these levels and cognition after one month. Although Sahlein et al.[101] did find higher S-100β concentrations due carotid intervention, no association was found with cognition one day postoperatively. Falkensammer et al.[59] also failed to find an association between S-100β and cognition, but one of their twenty included patients showed neurological and cognitive disturbances postoperatively as well as persisting higher S-100β

concentrations after surgery. Connolly et al.[86] detected a significant correlation between S-100β and cognition after one day, even in the absence of overt ischemic strokes. Based on the current literature, the relationship between increased S-100β levels during or early after carotid revascularization and postoperative cognition remains unclear.[11, 59, 99, 101] Methodological issues such as only testing the patient one day postoperatively,[86, 101] only using short cognitive screening instruments,[91] or not assessing intra-operative S-100β levels[11] make it difficult to compare the different studies.

Other Findings Related to Postoperative Changes

Using computed tomography perfusion, Cheng et al.[66] found a close relation between perfusion changes and changes in cognitive performance. Patients undergoing CAS with baseline impairment of MCA blood flow were more likely to experience improvement in flow after revascularization. This MCA blood flow improvement was associated with greater cognitive improvement in attention and executive functioning.[53] Repair of a presurgical low relative cerebral blood flow in the ipsilateral cerebral hemisphere has been shown to significantly improve postoperative cognitive function in patients undergoing CEA.[45, 46]

Postoperative cognitive deterioration on the contrary seems significantly associated with postoperative hyperperfusion regardless of any new lesions on MRI.[44, 47, 54] Similarly, cerebral hyperperfusion after CEA results in postoperative cerebral white matter damage (detected by diffusion tensor imaging), that is related to postoperative cognitive impairment.[47] The available data show a link between cognition and postoperative perfusion changes for CAS as well as CEA.

General remarks

Several methodological issues arise from our review. In future research, we recommend to include a control group, preferably patients with asymptomatic carotid stenosis not undergoing revascularization. Although several researchers[53, 58] correctly claim that different forms of material (i.e. different sets of the same test) reduce practice effects, patients become 'test wise'. This can also result in significantly increased test scores over time.[102] To increase the validity of the results by correcting for 'test learning effects', control groups are deemed necessary.[103]

Furthermore, future research papers should be clear about the type of cerebral protection which was used and characteristics that are essential to interpret the results, such as symptomatic status. It

is for example important to reveal if symptomatic stroke patients are included since on the one hand, stroke patients may show better cognitive improvement due to neural reorganization that has nothing to do with revascularization. On the other hand, stroke patients could have fewer benefits of revascularization due to more permanent brain damage that is not alleviated by restored perfusion. When researchers decide to include stroke patients, it is essential to check whether stroke has an influence on the postoperative changes in order to rule out the fact that these changes are the result of stroke instead of the revascularization. Moreover, some researchers use changes in total scores to compare different groups while others employ scores in various domains. The latter is advised because some domains may improve while others may deteriorate, and a global cognitive score may not pick up these subtle differences. We recommend to report the percentage of patients in whom cognition improves and in whom cognition deteriorates. Finally, in order to reduce the high dropouts of patients during follow-up, we advise future researchers to test patients at home or to reduce the frequency and duration of the assessments. In the research projects proposed in this thesis, a special focus will be given to these issues to avoid similar methodological problems.

In this review, we were not able to be strict on features like the type of control group. Healthy controls might not be an ideal comparison for patients with carotid artery disease, since these two groups are likely to differ on cardiovascular risk factors and general medical condition. Comparing carotid interventions to other interventions is a better alternative but still leaves the risk of confounding factors being responsible for the difference in results. An ideal comparison is that of patients with significant carotid stenosis undergoing revascularization and similar patients on best medical treatment, though for researchers advocating the usefulness of revascularization in asymptomatic patients, this may be difficult ethically.

In comparison with former reviews, we focused on methodological criteria when interpreting the results, such as the use of a control group, comprehensive psychometric evaluation (not solely short screening instruments), and assessments beyond the early postoperative stage. From the review, it appears that CEA and CAS have a comparable effect on cognition. The inconsistency of the various studies has been explained throughout this review article with cognitive deterioration in 10-15% of CEA patients, while an improvement of 10% of patients was also found regularly. Though there are limited methodologically solid studies examining the effects of CAS on cognitive

function, the studies provided show similar results. Nonetheless, there remains a need for larger, controlled prospective studies assessing cognition after carotid revascularization.

Although cognition following intervention for carotid stenosis remains a matter for debate, it is an important outcome measure when comparing different treatments. As stated by Siddiqui and Hopkins[104] and Huang et al.[105], postoperative testing should be performed beyond 3 months to show lasting effects. Especially patients with baseline impaired cerebral perfusion could be a vulnerable cohort in which revascularization might enhance cognition.

Following the former review, we have postulated several research questions that will form the basis of this thesis:

1. Do CEA and CASdp result in similar cognitive outcomes? ***(Chapter 2)***
2. Does the newer stenting technique CASfr provide similar cognitive results as the established carotid revascularization therapies? ***(Chapter 2)***
3. Is there a measurable impact of carotid revascularization on cognition? ***(Chapter 2)***
4. Is it possible to predict cognitive outcome in order to detect patients at risk for cognitive decline or susceptible for cognitive improvement? ***(Chapter 3)***
5. Is S-100β a useful biomarker to differentiate between carotid revascularization therapies and predict cognitive outcome? ***(Chapter 3)***
6. Can perioperative embolization as recorded by TCD be used to differentiate between carotid revascularization therapies and predict cognitive outcome? ***(Chapter 3 and 4)***
7. Is CASfr able to reduce the higher embolic load observed in CASdp? ***(Chapter 4)***
8. Which procedural phases are at higher risk for perioperative embolization in the three treatment modalities? ***(Chapter 4)***

Thesis Outline

As reported above, the jury is still out there if CEA and CASdp have a similar impact on cognition.[29, 106, 107]. Both cognitive improvement and deterioration have been reported after either technique in 10 to 15% of patients.[106] The impact of transcervical CAS with dynamic flow reversal on cognition is unclear. Ortega et al.[70, 108] have shown promising results i.e. higher postoperative cognitive test scores after CASfr, but in the first study, there was no control group while in the second study normative data were used as a control group to assess cognitive changes after CASfr. Despite the fact that normative data are a good way to evaluate a cognitive performance at one point, they will not diminish the effect of possible confounders such as practice effects.

To follow up on these outstanding questions, and taking the methodological limitations of previous studies into consideration, we investigated the effects of these three revascularization therapies on postoperative ***cognition***. In particular, we aimed to avoid some methodological issues that arose in the literature by using a comprehensive neuropsychological test battery and by including a control group of patients with known peripheral arterial disease instead of healthy subjects. This study will be described in **Chapter 2**.

In addition, perioperative ***embolization*** and levels of the biomarker ***S-100β*** will be studied in CEA, CASdp and CASfr procedures in patients with high-grade asymptomatic carotid artery stenosis or symptomatic lesions that have caused a TIA such as amaurosis fugax. Since some patients may experience cognitive improvement while others may have cognitive decline after carotid revascularization, it is important to identify those patients as this may influence the decision to intervene, especially in asymptomatic patients. Because of their ability to evaluate the differences between techniques in vivo or early after intervention, we will investigate whether embolization as detected by TCD and S-100β measures are able to predict postoperative cognition. This study will be described in **Chapter 3**.

Finally, embolic showers may be reduced by novel techniques such as transcervical CAS with flow reversal.[82] Because direct comparisons between CASfr, CASdp and CEA are currently lacking, **Chapter 4** will describe a detailed analysis of the transcranial Doppler recordings during

these three revascularization techniques. The ***perioperative embolic load*** will be divided into three phases; before, during, and after cerebral protection to study the specific embologenic risk inherent to every phase during carotid revascularization.

In **Chapter 5** the results of this thesis will be summarized, compared to the literature and discussed. Limitations inherent to our research and future perspectives for research in this field will be explored.

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Chapter 2

Prospective comparison of cognitive effects of carotid endarterectomy versus carotid stenting with flow reversal or distal filters

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Abstract

Objective: It is unclear whether carotid revascularization can improve the cognitive problems often observed in patients with carotid stenosis. We examined the presence of preoperative disturbances and the effects of different types of carotid revascularization on cognition.

Method: Forty-six patients treated for significant carotid stenosis [26 carotid endarterectomy (CEA), 10 transfemoral carotid stenting with distal filters (CASdp), and 10 transcervical stenting with flow reversal (CASfr)] as well as a matched control group of 26 vascular patients without carotid stenosis were included. Patients and controls were tested 1 day preoperatively and 1, 6, and 12 months after surgery on 18 neuropsychological variables.

Results: A significant amount of carotid patients as well as vascular controls showed cognitive defects at preoperative testing. None of the neuropsychological variables showed significant group differences between CEA, CASdp, CASfr, and controls, and only 1 revealed interaction between type of revascularization and improvements over time, though this effect dissolved when two outliers were excluded. Thirteen of 18 variables showed improved scores over time, regardless of the group. Compared with controls, about 10% of patients showed improvements, while 20% showed cognitive deterioration 6 months after revascularization.

Conclusions: Results show similar effects for CEA, CASdp, and CASfr on cognition. Large practice effects due to repeated testing confirm the importance of using control groups in prospective cognition studies. Because of the small sample size, this study should be regarded as an exploratory study, larger studies on the cognitive consequences of carotid revascularization remain warranted.

Introduction

Carotid artery stenosis has been identified as an important risk factor for stroke, with increasing risk depending on the severity of the stenosis [1]. Furthermore, symptomatic as well as asymptomatic carotid stenoses have been described to be associated with cognitive disturbances.[2, 3] Silvestrini et al.[4] demonstrated that unilateral left and right-sided asymptomatic carotid stenosis affects cognitive abilities specific to the ipsilateral hemisphere. Reduced blood flow to the brain or silent infarctions due to microembolization from the carotid plaque may be factors linking the carotid stenosis to cognitive deficits.[5]

To reduce the risk of stroke, carotid endarterectomy (CEA) - that is, the surgical removal of the plaque - is classically performed and is shown to be effective in reducing stroke risk in patients with recent carotid territory symptoms[6] as well as in asymptomatic patients.[7] Since CEA reduces stroke risk by half in asymptomatic patients,[7] CEA is carried out regularly in this population, although the debate whether asymptomatic patients on appropriate medical treatment should also be treated surgically is still ongoing.[8] Transfemoral carotid stenting with distal filter protection (CASdp) has been suggested as an alternative for CEA, especially in high-risk patients, reducing cranial nerve injury, wound complications, and possible negative effects of general anesthesia such as myocardial infraction.[9] In CASdp, a catheter is threaded up from the femoral vein to the carotid, where stenting and possible balloon dilatation can be performed. Although some studies have supported that CAS and CEA are both safe and effective methods of stroke prevention in appropriately selected patients and if treated by proficient surgeons or endovascular therapists,[10-12] CASdp is associated with an increased risk of new lesions on diffusion-weighted magnetic resonance imaging, compared with CEA.[13, 14]

CAS with flow reversal (CASfr) via a direct cervical approach is a novel technique that is designed to provide a shorter, more direct access via the neck to deliver the stent and balloon. The blood flow is reversed in the treated carotid as a protective measure to ensure that emboli flow away instead of towards the brain.[15] CASfr gained a lot of attention because manipulation in the aortic arch and common carotid artery is avoided and because of a reduced number of new diffusion-weighted magnetic resonance imaging lesions caused by emboli showers typically observed during stenting and dilation using distal embolic protection.[15]

Whether carotid revascularization in general has a positive, negative or no effect on cognition is still under discussion.[16] Publications are often contradictory due to differences in demographics (educational level of the patient) and clinical presentation – for example, stroke versus transient ischemic attack (TIA), affected side and severity of the stenosis.[17] Studies evaluating the cognitive changes after carotid treatment often have no (matched) control group, and the timing of assessments and type of tests used vary widely, which also plays an important role in the sometimes conflicting findings.[17] Without an appropriate control group, the impact of practice effects cannot be estimated adequately. Even if there is no underlying change accomplished by the intervention, improved test scores may occur, since the mere familiarity with testing material may enhance performance. The more the control group represents the patients group, the better the practice effects can be estimated. Since carotid stenosis is related to cognitive problems, these cognitive problems could for example limit the practice effect that carotid patients can experience due to limited learning abilities. Alternatively, lower baseline scores may allow larger increases in cognitive scores. When using a control group, it is therefore important that patient and control group have similar baseline cognitive abilities.

Revascularization could improve cognition by restoring the blood flow to the brain. On the other hand, perioperative microembolization and hypoperfusion with or without postoperative hyperperfusion could inflict cerebral damage and impair cognitive functions.[16, 18] Furthermore, the jury is still out there as to whether CEA or CASdp have a similar impact on a cognitive level.[16, 17, 19] Both cognitive improvement and deterioration have been reported after either technique in 10 to 15% of patients.[17]

Studies on the cognitive outcome of CASfr by Ortega et al.[20, 21] have shown promising cognitive results - that is, higher postoperative test scores - but in the first study there was no control group, while in the second study normative data were used as a control group to assess cognitive changes after CASfr. Despite the fact that normative data are a good way to evaluate a cognitive performance at one point, they will not lighten the problem of possible confounders such as practice effects.

In this study we compare the neurocognitive consequences after CEA, CASdp, CASfr according to a strict follow up schedule. A matched control group, comprising vascular patients without significant carotid stenosis (< 50%) was selected.

Method

Patients and controls

Forty-six patients with significant internal carotid artery stenosis without ostial common carotid artery lesions or tandem lesions (≥ 80% for asymptomatic and 60% for symptomatic cases on duplex ultrasound) were included. Twenty-six were treated with CEA, 10 underwent CASdp, and 10 CASfr. Exclusion criteria were history of previous carotid interventions, coronary artery bypass grafting, or stroke within the past 2 years, age >80 years, psychiatric or neurological disorders, alcohol abuse, and a Mini Mental State Examination (MMSE) score lower than 24. Following Plessers et al.,[17] to avoid any influence of recent brain damage on the possible cognitive changes evoked by revascularization, symptomatic patients were also excluded if they suffered from a recent ischemic stroke. Consequently, only symptomatic patients that had experienced a TIA such as amaurosis fugax were included. Twenty-six patients with peripheral arterial disease (PAD) were selected from the outpatient's clinic as a matched control group using the same exclusion criteria. Controls were matched for sex, age, and socioeconomic status (SES). We used the Hollingshead's index,[22] a computed score based on education and occupation level, as a measurement of SES. All controls had less than 50% carotid stenosis on duplex ultrasound. The Ghent University Hospital ethical committee approved this prospective study and all participants gave written informed consent.

Carotid revascularization procedures

CEA or CAS was chosen as technique for revascularization based upon the anatomical characteristics and comorbidities of the patient but also taking the surgeon's preference and expertise into account.

CEA was carried out under general anesthesia using selective shunting and patch plasty. CAS was carried out under local anesthesia with selective predilation, mandatory stenting, and

selective postdilation. All CAS patients received dual antiplatelet therapy. In the transfemoral CAS embolic protection devices were always used, while in CAS via the neck flow reversal was created between the common carotid artery and contralateral common femoral vein using the ENROUTE™ Neuroprotection System (Silkroad Medical, Sunnyvale, CA, USA).

Neuropsychological assessment

Besides the MMSE as a dementia screening test, an extensive neuropsychological test battery consisting of 13 tests was used, of which 18 variables were derived (Table 1). Neuropsychological examinations were administered 1 day before and 1, 6, and 12 months after surgery and took approximately 90 to 120 min to complete. The same time intervals were used for the control group.

Neurological evaluation

All patients received a preoperative (1 day before surgery) and postoperative (after 1 month) clinical neurological evaluation.

Statistical analyses

To determine preoperative cognitive difficulties, the test scores of the patients and controls on the first examination were compared to normative data of healthy people. These normative data were subdivided according to age, sex, and sometimes education level. We considered that at least 10% of the variables should show a clinically significant impairment, so when on two of the 18 variables a patient scored more than 2 standard deviations from his norm, or on three of the 18 variables she or he scored more than 1.5 standard deviations, the patient was categorized as having a cognitive deficiency.

Table 1

Cognitive domains and neuropsychological tests.

Cognitive Domain	*Neuropsychological Test*
Long-term memory	AVLT, Sum
	AVLT, delayed recall
	CFT, delayed recall
Attention	SS (forwards)
	DS (forwards)
	SS-C
	D-2
	TMT-A
Executive functioning	SS (backwards)
	DS (backwards)
	SCWT
	Phonological verbal fluency, COWAT
	Semantic verbal Fluency from the GIT
	TMT-B
Fine Motor Abilities	Grooved Pegboard Left
	Grooved Pegboard Right
Spatial Functioning	Judgement of Line Orientation
	Line Bisection Task

Note. AVLT = Auditory Verbal Learning test; CFT = Complex Figure Task; SS = Spatial Span from the Wechsler Memory Scale-III (WAIS-III); DS = Digit Span from the WAIS-III; SS-C = Symbol Substitution coding task from the WAIS-III; D-2 = d2 Test of Attention; TMT = Trail Making Test (Parts A and B); SCWT = inference factor of the Stroop Color and Word Test; COWAT = Controlled Oral Word Association Test (letters NAK); GIT = Groninger Intelligence Test.

To detect significant cognitive changes over time, we used two approaches that have shown to be complementary.[23] First, we compared the mean performance of the different revascularization groups and the control group over time by using mixed models analysis, allowing us to identify main effects of time, group, and the interaction between them for each variable. Second, we assessed the incidence of improvements or deteriorations over time on a subject level. Raw scores were rescaled so that higher scores represent better cognitive results. Next, difference scores were calculated for every subject: difference score = test score (after 1, 6, or 12 months) – preoperative

test score. Like several other studies,[24, 25] *z* scores were calculated using the difference scores of the control group as a test-retest measurement error by the following formula: *z* = [(difference score patient) – (mean difference score control group)]/(standard deviation difference score control group). This way, the *z* scores represent deviations from the expected test-retest effects. The larger the absolute *z* score, the more the subject deviates from what is expected as a normal test-retest difference. When the *z* score on at least two of the 18 variables was more than 2, or on at least three of the 18 variables the *z* score was more than 1.5, the patient was categorized as either improved or impaired over time. Chi-square tests were performed to compare categorical variables such as clinical symptoms in cross tables and one-way analysis of variance (ANOVA) was used to compare continuous variables. Residuals for every variable showed a normal distribution.

Results

Demographic characteristics are displayed in Table 2. No dropouts occurred at the 1-month follow-up visit but due to severe illness, one CASdp was lost 6 months postoperatively. A subgroup consisting of 18 CEA, 5 CASdp, 4 CASfr, and 13 controls was tested at a 1-year follow-up.
All revascularization groups and the control group had similar preoperative MMSE scores, $F(3, 71)= 0.80$, $p = .50$. None of the patients showed new neurological symptoms except for one CEA patient who had cranial nerve injury and one CASdp patient who had a minor stroke in hospital. No deaths or myocardial infarcts occurred.

Preoperative cognition

There was no difference between patients and controls in the prevalence of cognitive defects, $\chi^2(1) = 0.45$, $p = .50$. Compared with normative data of healthy persons of the same sex, age, and education level, 54% and 46% of carotid patients and controls showed (preoperative) cognitive problems at the first testing. Within the group of carotid patients, 52% and 58% of patients with left or right-sided stenosis, respectively, showed preoperative cognitive defects. Thus, no significant influence of having left-sided stenosis or right-sided stenosis on the presence of preoperative cognitive abnormalities could be detected, $\chi^2(1) = 0.12$, $p = .73$ and $\chi^2(1) = 0.53$, $p = .47$.

Table 2

Demographic characteristics.

	CEA (n = 26)	CASdp (n = 10)	CASfr (n = 10)	Control (n = 26)	*p*
Age	68.2 (6.7)	64.8 (9.2)	70.5 (7.0)	67.3 (7.1)	.36
Sex (Male)	15 (58%)	7 (70%)	6 (60%)	17 (65%)	.89
Socioeconomic status	29.5 (14.6)	33.1 (13.2)	28 (11.3)	29.6 (12.7)	.85
Symptomatic lesion	12 (46%)	4 (40%)	2 (20%)	-	.35
# Days between symptoms & surgery	40.7 (39.7)	19.3 (15.2)	60.0 (42.4)	-	.42
Left sided surgery	10 (38%)	6 (60%)	5 (50%)	-	.49
Contralateral carotid artery stenosis (>50%)	10 (38%)	5 (50%)	7 (70%)	-	.23
Diabetes Mellitus	8 (31%)	4 (40%)	4 (40%)	6 (23%)	.68
Antihypertensive treatment	19 (73%)	3 (30%)	5 (50%)	17 (65%)	.095
Anticholesterol treatment (statins)	24 (92%)	7 (70%)	9 (90%)	23 (88%)	.33
Familial vascular risk factors	20 (77%)	7 (70%)	8 (80%)	16 (62%)	.33

Values are in Mean (SD) or n (%).

Outcome after carotid revascularization

Mixed models analysis shows no significant group differences for any of the 18 variables. No interactions between time and group are observed except for one variable (the D-2 test for attention), $F(9, 166.74) = 2.36$, $p = .016$. When two outliers are excluded, however, this effect dissolves $F(9, 161.69) = 1.74$, $p = .085$. Conversely, time was an independent predictor of better scores for 13 out of 18 variables, regardless of the group; results are listed in Table 3. All patient groups (CEA, CASdp, and CASfr) and the control group showed a similar increase on these variables over time.

We acknowledge that the statistical power of our analysis is rather limited due to low sample size and that, as a result, it would be difficult to detect a significant group difference in our sample. At

the same time it can be estimated from the limited differences observed in our results that we would for example need 386 carotid patients as well as controls to reach 80% power to find a significant difference ($p<.05$) for audio-verbal memory. Although this observation does not exclude the existence of a group difference when these conditions are met, it does suggest that these eventual differences are likely to be modest.

Table 3

Main effect of the factor time for each variable.

Neuropsychological Test	*F*	*Df(1)*	*Df(2)*	*p*
TMT-A	4.59	3	169.24	.004**
TMT-B	1.79	3	102.29	.15
SS Forwards	.82	3	174.05	.48
SS Backwards	1.56	3	171.04	.20
DS Forwards	1.49	3	172.55	.22
DS Backwards	4.28	3	171.71	.006**
SCWT	7.03	3	171.61	<.001**
Judgement of Line Orientation	3.09	3	171.74	.028*
SS-C	5.20	3	170.60	.002**
AVLT, Sum	13.31	3	172.62	<.001**
AVLT, Delayed Recall	17.18	3	172.11	<.001**
Phonological verbal fluency	6.32	3	171.27	<.001**
Semantic verbal fluency	8.41	3	171.58	<.001**
CFT, Delayed Recall	8.19	3	172.90	<.001**
D-2	21.91	3	166.79	<.001**
Grooved Pegboard Right	2.68	3	168.91	.049*
Grooved Pegboard Left	3.14	3	165.11	.027*
Line Bisection Task	1.31	3	173.94	.27

Note. TMT = Trail Making Test (Parts A and B); SS = Spatial Span; DS = Digit Span; SCWT = inference factor of the Stroop Color and Word Test; SS-C = Symbol Substitution coding task; AVLT = Auditory Verbal Learning test; CFT = Complex Figure Task; D-2 = d2 Test of Attention.

* $p<.05$; ** $p<.01$. Mixed-models analysis

On a subject level at 1 month, five patients (11%) and three controls (12%) showed cognitive deterioration while two patients (4%) and five controls (19%) showed improvement.

These differences were not significant $\chi^2(2) = 4.30$, $p = .12$. At 6 months, 10 patients (22%) and one control (4%) showed deterioration while four patients (9%) and one control (4%) showed improvement. This difference, however, failed to reach significance, $\chi^2(2) = 5.15$, $p = .076$. The subgroup of carotid patients and controls who received cognitive testing at 12 months showed similar improvements and impairments with the testing at 6 months.

Discussion

Preoperative cognition

Symptomatic and asymptomatic carotid stenosis may be associated with existing cognitive impairments.[2, 3] Our results show that not only patients with significant carotid artery stenosis, but also patients with PAD appear to have cognitive deficits at baseline.

This may reflect that patients with similar risk factors such as diabetes, hypertension, hypercholesterolemia, current smoking, and so on, and proven PAD but without carotid artery disease may suffer from similar cognitive deficits.[3]

Outcome after carotid revascularization

Our study unveils no clear influence of the type of carotid revascularization on postoperative cognitive functioning. None of the 18 variables showed a significant group difference, and only one showed a small interaction effect. The fact that CEA and CASdp have similar effects on cognition is in agreement with previous research.[17, 19] We now showed that also direct access using flow reversal does not lead to any significant cognitive changes compared with other techniques.

Because all groups, even the control group, scored significantly better on 13 of 18 variables over time, our results demonstrate a clear practice effect due to repeated neurocognitive testing. Even though, where applicable, alternative test versions were used, patients as well as controls became test wise. This shows the necessity of including a control group to take these practice effects into account. Repeatedly testing participants can result in higher cognitive scores, regardless of underlying cognitive changes.

Since the different types of revascularization do not yield clear cognitive differences, decisions on whether to perform one of the types of carotid revascularization seem to be better

based on primary endpoints like stroke, myocardial infarct, and other secondary endpoints, rather than on cognitive functioning. Although it is clear that CASdp is associated with higher perioperative embolization and magnetic resonance imaging lesions,[26, 27] these measures seem not be linked to worse cognitive outcome.[17, 28]

Based on our findings, advocating surgery for asymptomatic carotid stenosis solely to alleviate existing cognitive difficulties seems not justified, as patient groups do not appear to benefit from surgery when compared to vascular controls. This is in contradiction with a recent study showing that untreated patients with significant carotid stenosis have worse cognitive scores over time than treated patients,[29] so further research is certainly warranted. On a subject level, at 1 month, there are no clear differences between patients and controls, but after 6 months, a marginally significant difference seems to be present. Of the patients who received carotid revascularization, 9% and 22% showed cognitive improvements or impairments respectively, which is in good agreement with other studies.[9, 17, 28] It appears that carotid revascularization is beneficial for some patients while others do not seem to benefit from it in the long term. Previous research showed that the cognitive improvements that small groups of patients gain from revascularization seem associated with the recovery of abnormal cerebral perfusion.[30, 31] Cognitive deterioration has, on the contrary, been linked to postoperative hyperperfusion.[32, 33]

The inclusion of a control group allowed us to take practice effects into account. Moreover, our control group consisted of patients with PAD, who are more comparable to patients with carotid artery disease than healthy controls. A longer follow-up period was implemented to discriminate between short-term and long-term effects. We encourage researchers to include a long-term follow-up when evaluating cognitive changes after carotid revascularization, because the long-term results are more clinically relevant for the patients. While the measurement at 1 month and 6 months differed, the 12-month measurement was comparable to the testing at 6 months. We do not believe that differences in local versus general anesthesia had an effect on any of our results, since previous research[34] showed there is an effect of general anesthesia on cognition on the first postoperative day, but after six days this difference between local and general anesthesia already dissolves. Furthermore we used a comprehensive neuropsychological test battery. The study did not rely on

short screenings instruments such as the MMSE which are considered insufficient.[3, 17] Finally, we had a very low dropout at 1 and 6 months, preventing possible subgroup confounders.

Limitations of our study are the small sample size in the stenting groups and the nonrandomized design. Two recent systematic reviews concluded that most studies comparing CEA and CASdp do not show cognitive differences.[17, 19] Our finding that CASfr shows no cognitive differences compared to the other revascularization types corroborates with these findings. It is, however, possible that larger studies may be able to find small cognitive differences, therefore our study should be considered as an exploratory study. To further elucidate the influence of revascularization on cognition, a larger study comparing different types of revascularization with a control group consisting of asymptomatic carotid patients on best medical treatment is recommended. This would allow us to study the long-term effects on a cognitive level of intervention versus medical treatment only. Further elucidating the relationship between cognitive changes and changes in cerebral perfusion using single-photon emission computed tomography (SPECT) is also a promising research topic. Ideally, deciding on advising revascularization could also depend on the expected cognitive effects for each patient.

In conclusion, we did not find significant differences between CEA, CASdp, and CASfr on cognition. All groups, including the control group, showed similar increases in test scores over time, attributable to practice effects. One month after surgery, results are mixed, but in the long term, around 10% of patients seem to benefit from revascularization, while around 20% show significantly lower scores. Larger studies comparing the different types of carotid revascularization remain warranted.

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Chapter 3

Perioperative embolization load and S-100B do not predict cognitive outcome after carotid revascularization

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Abstract

Background: Cognitive changes after carotid revascularization have been reported in 10-20% of patients. The aetiology of cognitive impairments remains largely unknown. This study evaluates the predictive value of S-100β serum values and perioperative micro-embolization on cognition after carotid revascularization.

Methods: Forty-six patients with significant carotid stenosis underwent carotid endarterectomy (CEA, n=26), transfemoral carotid artery stenting with distal protection (CASdp, n=10) or transcervical carotid stenting with dynamic flow reversal (CASfr, n=10). Twenty-six matched vascular patients without carotid stenosis were recruited as controls. All patients underwent comprehensive cognitive testing on the day before and one month after carotid revascularization. S-100β analysis was performed in 31 cases pre-, peri-, and 2, 6, and 24 hours after carotid surgery, and in 25 patients transcranial Doppler (TCD) monitoring was done during surgery.

Results: In the three treatment groups similar transient increases in S-100β values were observed. CASdp was associated with a higher embolic load than CEA and CASfr, while CEA was also associated with less micro-embolization than CASfr. Cognitive improvement or deterioration could not be predicted by S-100β or perioperative embolic load for any of the investigated cognitive domains.

Conclusions: Cognitive deterioration could not be predicted using perioperative embolic load and S-100β changes. A similar inverted u-curve of the S-100β levels was observed in the three groups and may be caused by impairment in the blood-brain barrier during intervention, and not due to cerebral infarction. Distal protection CAS is associated with a higher embolic load than transcervical CAS using dynamic flow reversal and CEA, but the long-term impact of this higher embolic load is yet unknown. Perfusion related measures seem promising in their ability to predict cognitive decline.

Introduction

To reduce the stroke risk in patients with significant carotid artery stenosis, carotid endarterectomy (CEA) and carotid artery stenting (CAS) are performed.[1, 2] Many studies have shown that CAS with distal protection filters (CASdp) is associated with higher stroke rates and incidence of postoperative lesions on diffusion-weighted magnetic resonance imaging (DW-MRI).[3] In an effort to reduce these higher stroke and new DW-MRI lesion rates, proximal protection is increasingly used.[4, 5] Transcervical CAS with dynamic flow reversal (CASfr) has been shown to be safe with a low stroke, death, and myocardial infarction rate.[6, 7] Furthermore it is associated with a reduced number of new DW-MRI lesions compared to transfemoral CAS with distal protection devices (CASdp).[6, 7] Manipulation in the aortic arch and origin of the common carotid is avoided and ideally during flow reversal emboli should theoretically not be able to damage the brain.[7]

Besides a focus on stroke and other primary outcome measures, as Siddiqui and Hopkins[8] stated, it is important to assess the cognitive effects of carotid revascularization, as even asymptomatic patients may sometimes benefit from revascularization. Indeed, recent studies[9-11] reported improvements for some patients, while other patients showed cognitive declines. On the one hand, carotid revascularization may improve the blood flow to the brain and hence result in cognitive improvement. On the other hand, perioperative micro-embolization and hypoperfusion, and postoperative hyperperfusion may cause cognitive decline.[11, 12] To date, it is unclear how these factors interact. In this study, we will focus on possible factors predicting negative cognitive outcome, such as perioperative embolization load and indicators of ischemic brain damage.

To study perioperative embolization during carotid revascularization, transcranial Doppler ultrasonography (TCD) is an effective tool.[13] Larger embolic loads for CASdp have been observed in comparison with CEA.[14-16] Although Ribo et al.[17] revealed that CASfr is able to reduce emboli showers typically observed during stent deployment, direct comparisons of transcervical CASfr with CASdp and CEA have not been published. It is important to examine perioperative embolization as it has shown to be linked with new DW-MRI lesions post intervention.[18]

A sensitive marker of cerebral injury and blood–brain barrier dysfunction[19-21] is the neuroprotein S-100β. S-100β rises in patients with focal brain damage after ischemic territorial MCA infarction,[19] which makes this biomarker especially relevant to study cerebral damage after carotid revascularization because the MCA arises from the internal carotid. Studies connecting S-100β to perioperative embolization assessed by TCD reported conflicting results.[22, 23] S-100β shows maximum levels most often within 24 hours after cardiac surgery,[24] has a biological half-life of approximately 25 minutes, and is rapidly excreted by the kidney.[25]

The factors that may lead to cognitive deterioration after carotid treatment have not been clearly identified. This study will directly compare perioperative embolization load and S-100β levels after CEA, CASdp, or CASfr. Furthermore, the effect of perioperative embolic load and S-100β serum level changes on cognitive changes will be investigated.

Material and Methods

Patients and controls

Between February 2011 and January 2014, 46 patients with significant internal carotid artery stenosis without ostial common carotid artery lesions or tandem lesions (≥ 80% for asymptomatic and ≥ 60% for symptomatic lesions on duplex ultrasound) were included of which 26 underwent CEA, 10 CASdp, and 10 CASfr. Exclusion criteria were history of previous carotid interventions, CABG, or stroke within the past 2 years, age >80 years, psychiatric or neurological disorders, alcohol abuse, and a Mini Mental State Examination (MMSE) score lower than 24.

To avoid any influence of recent brain damage on the possible cognitive changes evoked by revascularization, symptomatic patients were also excluded if they suffered from a recent acute stroke.[9] So only symptomatic patients who experienced a transient ischemic attack (TIA) such as amaurosis fugax were included. Twenty-six patients with peripheral arterial disease (PAD) were selected from the vascular outpatient's clinic as a matched control group using the same exclusion criteria. Controls were matched for sex, age, and socio-economic status (SES). The Hollingshead's index,[26] a computed score based on education and occupation level, was used as a measurement of SES. All controls had less than 50% carotid stenosis on duplex ultrasound. All 46 carotid patients participated in the cognitive study. Of these, only 31 patients had S-100β evaluation, and 25 patients received TCD monitoring due to logistical reasons or a poor transtemporal insonation

window for TCD in some patients.[27] Twenty-one carotid patients had S-100β, TCD monitoring as well as the cognitive assessment. The control group solely underwent cognitive testing. The Ghent University Hospital ethical committee approved this prospective study and all participants gave written informed consent.

Carotid revascularization procedures

The choice between CEA or CAS was based on the individual and anatomical characteristics, comorbidities of the patient, and the patient's preference. The decision was made by a multi-disciplinary team taking into account the international guidelines.[28] CEA was routinely carried out under general anesthesia using selective shunting and Dacron patch plasty. CAS was carried out under local anesthesia with selective predilation, mandatory stenting and selective postdilation. All CAS patients received dual antiplatelet therapy (aspirin and clopidogrel). In transfemoral CAS distal filter embolic protection was always used, while in transcervical CAS dynamic flow reversal was created between the common carotid artery and contralateral common femoral vein using the ENROUTE™ Neuroprotection System (Silkroad medical, Sunnyvale, CA, USA).

Neuropsychological assessment

Besides the MMSE as a dementia-screening test, a neuropsychological test battery consisting of 13 tests was used out of which 18 variables were derived. These variables were allocated to their respective cognitive domain: attention, long-term memory, executive functioning, fine motor abilities, or visuospatial functioning (see Table II in Plessers et al.[10] for more information about the specific neuropsychological tests). Neuropsychological examinations were performed by M.P. 1 day before and 1 month after surgery and took approximately 90 to 120 minutes to complete. Identical time intervals were used for the control group.

Transcranial Doppler

Perioperative TCD monitoring was performed unilaterally using a commercially available TCD system (DWL Doppler-Box^{TM}, Compumedics Germany GmbH, Germany). A 2-MHz transducer was placed over the ipsilateral temporal skull window before the start of the carotid surgery and recordings of the intervention were made from incision until closure.

Emboli were counted manually according to consensus statements.[13] Only unidirectional High-Intensity Transient Signals (HITS - less than 300 ms) at least 7dB higher than that of the background signal with a distinctive 'chirp', 'snap' or 'moan' sound were recorded as emboli.[13, 22] Because fluid-filled syringes always contains small air bubbles, even after thorough desufflation[29] and these small air bubbles are of low clinical value, embolic signals directly related to the injection of contrast fluid were discarded. A global TCD-score with one second of emboli showers or curtains counting as 10 separate emboli was computed as done previously by Brightwell et al.[22] As such, we obtained a mean global embolic score that is comparable for the three types of surgery.

Serum S-100β biomarker

Blood samples were collected immediately before carotid surgery, after declamping or retrieval of the embolic protection device, and 2, 6, and 24 hours post intervention. Blood samples were centrifuged at 1500 rpm for 15 minutes at 20°C. The resulting serum was stored in in multiple aliquots at -25°C. Serum levels of S-100β were determined using an automatic electrochemiluminescence assay (S100 Cobas®) with a measuring range of 0.005 – 39 µg/L. The median value and 95th percentile for healthy adults is 0.046 and 0.105 µg/L respectively. The biochemist responsible for carrying out these analyses was blinded to the revascularization group and TCD data.

Neurological evaluation

All patients received a preoperative (1 day before surgery) and postoperative (after 1 month) clinical neurological evaluation by one of the authors (D.H.).

Statistical analyses

Raw cognitive scores were rescaled so that higher scores represent better cognitive results. Next, difference scores were calculated for every subject: difference score = test score after 1 month – preoperative test score. Like several other studies,[30, 31] z-scores were calculated using the difference scores of the control group as a test-retest measurement error by the following formula: "z-score = (difference score patient – mean difference score control group) / standard deviation difference score control group". This way, the z-scores represent deviations from the expected test-retest effects. The larger the absolute z-score, the more the subject deviates from what is expected

as a normal test-retest difference. Thus, the control group data were used to estimate the practice effect. Domain z-scores were the calculated mean of the relevant variables and represent the mean change of a cognitive domain when compared with the mean change of the control group.

Linear regression analysis was used to assess the predictive value of S-100β and TCD perioperative embolization on the five cognitive domain scores for all carotid patients. Chi-square tests were performed to compare categorical variables such as clinical symptoms in cross tables and one-way ANOVA was used to compare continuous variables, such as embolic load. Changes over time and between patient groups for S-100β was examined with repeated measures ANOVA with Huyn-Feldt correction. Residuals for every variable showed a normal distribution.

Results

Demographic characteristics are displayed in Table I. All revascularization groups and the control group had similar preoperative MMSE scores, $F(3,71)=.80$, $p=.50$. Most patients experienced no neurological symptoms post intervention except for one CEA patient who had a cranial nerve injury and one CASdp patient who suffered from a minor stroke in-hospital. No death or myocardial infarct occurred and no patients were lost for follow up.

Since S-100β levels showed the highest mean peak value 2 hours after surgery, this value was used in further analysis. None of the cognitive changes in long-term memory, attention, executive functioning, fine motor abilities, and visuospatial functioning could be predicted using S-100β or the TCD micro-embolic load for the whole group of carotid patients (Table II).

Table I. Demographic characteristics.

	CEA (n = 26)	CASdp (n = 10)	CASfr (n = 10)	Control (n = 26)	
					p
Age	68.2 (6.7)	64.8 (9.2)	70.5 (7.0)	67.3 (7.1)	.36
Sex (Male)	15 (58%)	7 (70%)	6 (60%)	17 (65%)	.89
Socioeconomic status	29.5 (14.6)	33.1 (13.2)	28 (11.3)	29.6 (12.7)	.85
Symptomatic lesion	12 (46%)	4 (40%)	2 (20%)	-	.35
# Days between symptoms & surgery	40.7 (39.7)	19.3 (15.2)	60.0 (42.4)	-	.42
Left sided surgery	10 (38%)	6 (60%)	5 (50%)	-	.49
Contralateral carotid artery stenosis (>50%)	10 (38%)	5 (50%)	7 (70%)	-	.23
Diabetes Mellitus	8 (31%)	4 (40%)	4 (40%)	6 (23%)	.68
Antihypertensive treatment	19 (73%)	3 (30%)	5 (50%)	17 (65%)	.095
Anticholesterol treatment (statins)	24 (92%)	7 (70%)	9 (90%)	23 (88%)	.33
Familial vascular risk factors	20 (77%)	7 (70%)	8 (80%)	16 (62%)	.33

Values are in Mean (SD) or n (%).

Table II. Linear regression analysis of the five cognitive domains with S-100β and embolic load as predictors.

Cognitive Domain	*F*	*df1, df2*	*p*
Long-term memory	2.31	3 , 19	.12
Attention	.62	3 , 19	.61
Executive functioning	.82	3 , 19	.50
Fine motor abilities	.54	3 , 19	.66
Visuospatial functioning	1.04	3 , 19	.40

However, a significant difference between the treatment groups for perioperative embolization was observed, $F(2,24)=55.91$, $p<.001$. CASdp ($M=584$) was associated with a significant higher embolic load than CEA ($M=62$, $p<.001$) and CASfr ($M=184$, $p<.001$) and CEA was also associated with fewer emboli than CASfr ($p=.02$; Figure I).

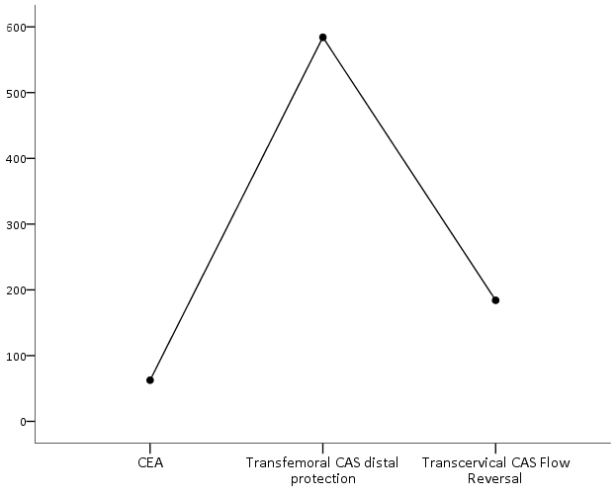

Figure I. *Mean sum of perioperative emboli for each patient group.*

Since the last measurement of S-100β (24h post surgery) was missing in some patients (n= 5) and the acute effect of the surgery on S-100β at 24 hours had already dissolved, we decided to perform the repeated measures test only on the four first measurements to avoid list wise deletion of cases and a subsequently lower statistical power. There was an expected transient increase of the S-100β level in every group, $F(2.45,56.43)=30.97$, $p<.001$, but no significant group differences $F(2,23)=.69$, $p=.51$ or interactions $F=(4.91,56.43)=1.55$, $p=.19$, could be detected (Figure II). There was no correlation between the amount of perioperative emboli and rise of S-100β, $r=-.18$, $p=.44$

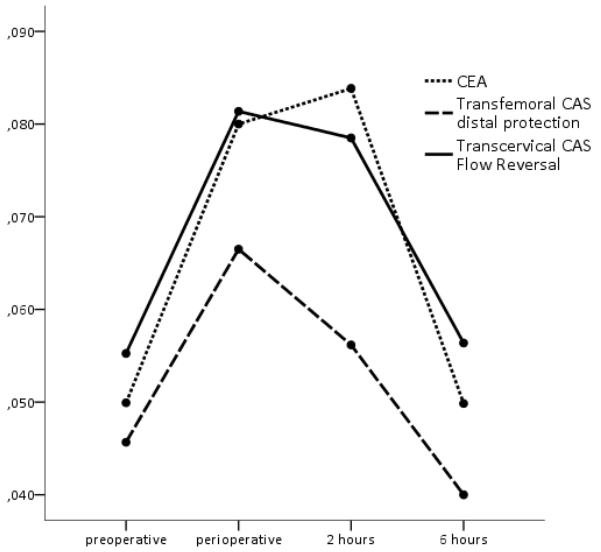

figure II. *Serum S-100B (µg/L) values over time for all patient groups.*

Discussion

CEA, CASdp, and CASfr resulted in a similar cognitive evolution, around 10-20% of patients shows either cognitive improvement or deterioration after revascularization (see Plessers et al.[10]). None of the changes in the five cognitive domains could be predicted using S-100β serum levels and perioperative embolic load. It appears to be difficult to predict which patients will show postoperative cognitive decline. Many studies trying to find a relationship between S-100β and cognition after carotid revascularization failed to find an association[32-35] and it was concluded that the predictive value of S-100β on cognition is inconclusive.[20] The transient increase in S-100β early after CASdp and especially CEA has been noted in several studies, and is most often regarded as a consequence of an impaired blood-brain barrier caused by balloon dilation or clamping rather than the consequence of brain damage.[35-39] Indeed, the fact that a correlation between S-100β and embolic load could not be demonstrated in this study, seems to implicate that S-100β may not be an ideal measure for cerebral infarction after carotid revascularization, but actually represents changes in the blood-brain barrier.[35-39] We did not find a group difference between CEA, CASdp, and CASfr on S-100β, which confirms the findings of Brightwell et al.[22] who compared CEA with CASdp.

In contrast, TCD analysis unveils significant differences in perioperative embolic load between the treatment modalities. Previous studies[14-16] have shown that CASdp is associated with a higher embolic burden than CEA. Furthermore, this study shows that CASfr causes less embolization than CASdp. It appears that direct carotid access and dynamic flow reversal protects the brain better against micro-embolization than transfemoral carotid stenting with distal protection. This study confirms that distal filters do not always result in a reduction of perioperative micro-embolization.[40] Direct carotid access avoids any manipulation in the aortic arch while flow reversal is possibly more effective because protection is in place prior to crossing the lesion.[7] Furthermore, the protected phase (i.e. the flow reversal) allows theoretically zero embolization.[7] The low embolization rate during CEA can however not yet be achieved with CASfr.

The detected embolic load did not predict cognitive decline after surgery, as also found by other studies.[15, 41, 42] Probably other factors such as embolic size and type (gaseous versus particulate) are more important than the mere number of emboli, i.e. larger and particulate emboli are expected to have a worse outcome than small and gaseous emboli.[9] Up until now, current technology allows no valid differentiation between gaseous and particulate emboli.[43, 44] Technological advances may have the potential to further improve the clinical relevance of TCD monitoring.

This exploratory study illustrates that it is difficult to predict postoperative cognitive deterioration, even when combining different data sets such as perioperative embolization and S-100β. It appears that cognitive evolution after revascularization is unpredictable.[41] Indeed, recent studies and systematic reviews point out that the vast majority of studies that have attempted to correlate cognitive changes with the amount and size of new DW-MRI ischemic lesions after revascularization have failed to find this association.[9, 45] Most of these lesions appear silent. In contrast, research has described that restoring a preoperative low blood flow in MCA is associated with improved cognition following intervention,[46-49] while postoperative hyperperfusion is linked with cognitive decline.[50-52] It seems that embolization, DW-MRI and S-100β remain unable to predict cognitive changes so far, while measures focusing on perfusion, may be the key to successfully detect patients at risk for cognitive decline or patients who are likely to benefit from carotid revascularization.[46-53]

Although our study is limited due to a small sample size and the lack of brain MRI data, we can conclude that if there is an effect of perioperative embolization and S-100β on cognition, this effect is not very robust. Other studies have often failed to find associations between these measures and cognition in CEA and CASdp[15, 32, 33, 41, 42] and the combination of these measures does also not appear to predict cognitive deterioration as shown in this study. The strength of this study is that differences in S-100β serum levels and perioperative embolization between CEA, CASdp, and CASfr have been studied including its effect on cognitive alterations using a comprehensive neuropsychological test battery. Our study did not rely on short screenings instruments such as the MMSE, which are considered insufficient.[9, 54] Finally, we had no drop-outs at 1 month, preventing possible subgroup confounders.

Conclusion

In conclusion, this study shows no clear influence of S-100β serum levels and perioperative embolization on cognitive changes after carotid revascularization. CEA, CASdp, and CASfr show a similar inverted u-curve in S-100β values. CASdp is associated with a higher embolization rate in comparison with CEA and CASfr, while CEA is associated with fewer emboli than CASfr. Further research remains warranted.

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Chapter 4

Transcervical carotid stenting with dynamic flow reversal demonstrates embolization rates comparable to carotid endarterectomy

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Abstract

Purpose: To evaluate a series of patients treated electively with carotid endarterectomy (CEA), transfemoral carotid artery stenting with distal filter protection (CASdp), and transcervical carotid stenting with dynamic flow reversal (CASfr) monitored continuously with Transcranial Doppler (TCD) during the procedure to detect intraoperative embolization rates.

Methods: Thirty-four patients (mean age 67.6 years; 24 men) with significant carotid stenosis underwent successful TCD monitoring during the revascularization procedure (10 CEA, 8 CASdp, and 16 CASfr). Ipsilateral microembolic signals were segregated into 3 phases: preprotection (until internal carotid artery cross-shunted or clamped if no shunt was used, filter deployed, or flow reversal established), protection (until clamp/shunt was removed, filter retrieved, or antegrade flow re-established), and postprotection (after clamp/shunt or filter removal or restoration of normal flow)

Results: CASdp showed higher embolization rates than CEA or CASfr in the preprotection phase ($p<0.001$). In the protection phase, CASdp was again associated with more embolization compared with CEA and CASfr ($p<0.001$). In the postprotection phase, no differences between the revascularization therapies were observed. CASfr and CEA did not show significant differences in intraoperative embolization during any of the phases.

Conclusion: Transcranial Doppler recordings demonstrated a significant reduction in embolization to the brain during transcervical carotid artery stent placement with the use of dynamic flow reversal compared to transfemoral CAS using distal filters. No significant differences in microembolization could be detected between CEA and CASfr. The observed lower embolization rates and lack of adverse events suggest that transcervical CAS with dynamic flow reversal is a promising technique and may be the preferred method when performing CAS.

Introduction

To reduce the stroke risk in patients with significant carotid stenosis, carotid endarterectomy (CEA) and carotid artery stenting (CAS) are both used as revascularization strategies.[1,2] However, many studies have shown that CAS with distal protection filters (CASdp) is associated with higher incidences of stroke and postoperative lesions on diffusion-weighted magnetic resonance imaging (DW-MRI).[3] Proximal protection is increasingly being used to reduce these rates.[4,5] Transcervical CAS with dynamic flow reversal (CASfr) has the additional advantage of avoiding manipulations in the arch and has been associated with low stroke and death rates and significantly fewer new DW-MRI lesions compared to CASdp.[6,7] As manipulation within the aortic arch and origin of the common carotid artery (CCA) is avoided and angioplasty is performed during flow reversal, emboli should not be able to flow to the brain.[6,8]

Transcranial Doppler (TCD) monitoring is a noninvasive technique that records the ultrasound echoes generated by blood flow in the cerebral arteries.[9] TCD of the middle cerebral artery (MCA) is an effective tool when studying intraoperative embolization during carotid revascularization.[10] In agreement with its higher prevalence of new DW-MRI lesions, CASdp has consistently demonstrated a greater embolic load than CEA on TCD.[11-13] Although CASfr is capable of reducing the embolic showers that are typically observed in embologenic phases of CASdp, such as stenting and balloon dilation,[14] no direct comparison has yet been performed between CASfr and the other common revascularization procedures as regard their effects on embolization. To this end, this study examines intraoperative embolization detected by TCD during CEA, CASdp, and CASfr. The microembolic signals were analyzed during the different phases of the procedure to assess the embolic risk inherent to each surgical phase.

Methods

Patient Sample

Of the 48 patients with significant internal carotid artery stenosis (≥80% for asymptomatic and ≥60% for symptomatic cases on duplex ultrasound) and no ostial CCA or tandem lesions enrolled in this study, TCD could not be performed in 14 patients due to practical difficulties or an inadequate transtemporal insonation window, mostly in older women.[15,16] Thus, the analysis focuses on 34 patients (mean age 67.6 years; 24 men) who were monitored with TCD throughout the entire carotid revascularization procedure (10 CEA, 8 CASdp, and 16 CASfr). The Ghent

University Hospital Ethical Committee approved this study, and all participants gave written informed consent.

Carotid Revascularization

The operator's choice of CEA or CAS was based on anatomical characteristics and patient comorbidities. CEA was always carried out under general anesthesia using selective shunting and Dacron patchplasty. CAS was carried out under local anesthesia with selective predilation, mandatory stenting, and selective postdilation. CAS patients were on dual antiplatelet therapy before and after treatment. In transfemoral CAS, the same distal filter embolic protection was always used (Emboshield; Abbott Vascular, Redwood City, CA, USA), while in transcervical CAS, dynamic flow reversal was created between the CCA and the contralateral common femoral vein using the ENROUTE Neuroprotection System (Silkroad Medical, Sunnyvale, CA, USA). The technique of transcervical stenting with flow reversal has been previously described in detail.[17] All patients were clinically evaluated by a neurologist the day before surgery and after 1 month.

Transcranial Doppler Ultrasonography

Intraoperative TCD monitoring was performed unilaterally using a commercially available TCD system (DWL Doppler-Box; Compumedics Germany GmbH, Singen, Germany). A 2-MHz transducer was placed over the ipsilateral temporal window before the start of surgery. Following identification of the ipsilateral MCA, recordings during the intervention were made from incision until closure, and several markers were included to indicate critical phases in the surgery (ie, clamping, contrast injection, balloon dilation, stenting, etc).

Embolic signals were defined as unidirectional peaks >7 decibels lasting <300 ms within the recording. Emboli were detected according to consensus criteria[10] and were typically associated with a characteristic "chirp," "snap," or "moan" sound. The occurrence of emboli was segregated in 3 major phases (1) preprotection: before clamping, deployment of the distal filter, or flow reversal; (2) protection: during shunting, flow reversal, or with the filter in situ; and (3) postprotection: from restoration of normal flow by removal of the clamp, cessation of flow reversal, or filter retrieval until application of the bandage.

When there was a high concentration of emboli and it became impossible to differentiate between the separate emboli, the duration of these "embolic showers" was recorded. For each

surgical phase, a discrete emboli count was also calculated. Micelles of contrast fluid can evoke embolic-like signals on TCD.[18] Furthermore, fluid-filled syringes always contain small air bubbles, even after thorough venting.[19] Since these small air bubbles are of low clinical value, embolic signals directly related to the injection of contrast fluid were discarded.

To ensure high reliability of the TCD analysis, a random sample of 6 cases was analyzed independently by 2 authors (N.P., E.M.L.C) in a different laboratory using in-house software developed in MATLAB based on the same detection consensus criteria.[10] Embolic signals from these patients were also divided according to the 3 phases (preprotection, protection, postprotection).

Table 1. Demographic, Clinical, and Procedure Characteristics.[a]

	CEA (n=10)	CASdp (n=8)	CASfr (n=16)	p
Age, y	65.7±4.3	62.4±9.9	71.3±9.5	0.048
Men	6	5	13	0.43
Diabetes	3	4	5	0.61
Antihypertensive agents	6	3	11	0.32
Statin therapy	10	6	15	0.16
Symptomatic lesion	6	4	8	0.87
Time between symptoms and surgery, d	37.5±38.7	20.5±17.5	59.9±57.1	0.37
Procedure time, min[b]	101.9±17.3	40.5±8.8	76.5±20.7	—
Protection time, min[c]	30.0±6.1	9.7±1.8	12.6±7.3	—
General anesthesia	10	1	4	—

Abbreviations: CASdp, carotid artery stenting with distal protection filters; CASfr, transcervical carotid artery stenting with dynamic flow reversal; CEA, carotid endarterectomy.

[a]Continuous data are presented as the means ± standard deviation; categorical data are given as the counts.

[b]Time from incision until end of closure.

[c]Shunt, filter, or flow reversal time.

Statistical Analyses

Between-group differences throughout the procedure were assessed with repeated measures analysis of variance (ANOVA). Chi-square tests were performed to compare categorical variables (eg, clinical symptoms) in cross tables, and one-way ANOVA was used to compare normally distributed continuous variables (eg, the number of emboli and duration of embolic showers). Post-

hoc tests were performed with a Bonferroni correction. Inter-rater agreement was assessed by calculating the Pearson product moment correlation coefficient. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS; version 22; SPSS, Inc., Chicago, IL, USA).

Results

Apart from an unexpected difference in age, the 3 groups displayed no significant differences in demographic or disease characteristics (Table 1). Intervention characteristics are also shown in Table 1. All revascularization procedures were technically successful (<30% residual stenosis). One CASdp patient had a minor in-hospital stroke and a CEA patient suffered cranial nerve injury, but no death occurred post intervention. Two patients in the flow reversal group developed an iatrogenic CCA dissection. The first occurred upon introduction of the arterial sheath, probably owing to the learning curve. In the second case, the Rummel loop was used as a tourniquet to stop inflow, but despite careful manipulation, the heavily calcified CCA was dissected. An additional stent was placed via the transfemoral route in each CCA.

The most embolization occurred in the protected phase for CASdp and CASfr, while the highest embolization rates during CEA were observed in the postprotection phase (Figure 1). Throughout the procedure, large between-group differences were detected for the number of emboli as well as seconds of embolic showers ($F_{2,31}=57.91$, $p<0.001$, $\eta p^2=0.79$ and $F_{2,31}=14.37$, $p<0.001$, $\eta p^2=0.48$, respectively). For both variables, CASdp showed a higher frequency of emboli compared with CEA or CASfr ($p<0.001$), while no significant differences could be detected between CEA and CASfr ($p=0.486$ and $p=0.493$ for emboli and showers, respectively; Figure 1).

During the preprotection phase, no differences were detected between the interventions for the total duration of showers ($F_{2,33}=2.34$, $p=0.113$, $\eta p^2=0.13$), but there was a significant difference in the number of discrete particulate emboli ($F_{2,33}=35.00$, $p<0.001$, $\eta p^2=0.69$). CASdp generated more discrete emboli than CASfr ($p<0.001$) and CEA ($p<0.001$). No differences could be detected between CEA and CASfr ($p=0.177$).

During the protection phase, significant differences for embolic showers and discrete emboli were observed ($F_{2,33}=30.02$, $p<0.001$, $\eta p^2=0.66$ and $F_{2,33}=59.12$, $p<0.001$, $\eta p^2=0.79$, respectively). For both variables, CASdp differed significantly from CEA and CASfr ($p<0.001$),

but no differences were detected between CEA and CASfr for discrete emboli or embolic showers (p=0.424 and p=0.296, respectively).

In the postprotection phase, all techniques showed a similar incidence of embolic showers and discrete emboli ($F_{2,33}=0.33$, $p=0.719$, $\eta p^2=0.02$ and $F_{2,33}=0.27$, $p=0.769$, $\eta p^2=0.02$, respectively).

Inter-rater analysis showed excellent correlations for the discrete emboli [$r=0.994$, $p<0.001$ ($n=18$)], as well as for the embolic showers [$r=0.917$, $p<0.001$ ($n=18$)].

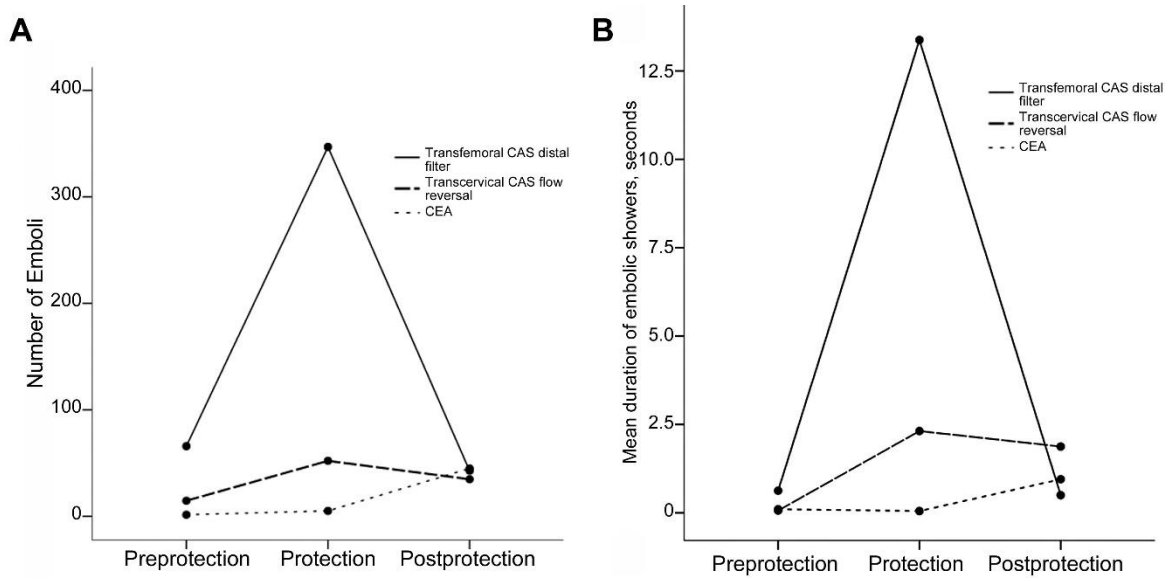

Figure 1. *(A) Mean number of discrete emboli for each group in each phase. (B) Mean duration of embolic showers for each group in each phase.*

Discussion

As in other studies,[11,12] our investigation found that filter-protected transfemoral CAS was associated with a significantly higher embolic load compared with CEA throughout the procedure. This study, however, also showed that transcervical CAS with dynamic flow reversal was associated with fewer emboli than filter-protected CAS and yielded embolization rates comparable to those of CEA.

When looking in detail at which phases of the intervention are responsible for these differences, it appears that CASfr and CEA already show less embolization in the preprotection phase before the EPD, shunt, or flow reversal are in place. This can be explained by the fact that CEA and CASfr with a direct cervical approach are able to treat the lesion site directly, while in

CASdp, manipulation in the aortic arch and the origin of the CCA may dislodge emboli that migrate to the brain. This is in line with other studies suggesting that contralateral DW-MRI lesions after CASdp[3,7,20] are most likely caused during the preprotection phase before entering the CCA. The study of Leal et al.[7] showed no contralateral hemispheric infarcts in CASfr patients, while 2 of 11 new DW-MRI lesions detected in CASdp patients were contralateral. Gupta et al.[11] failed to find a significant difference between CASdp and transfemoral CAS with flow reversal in the preprotection phase, indicating the importance of transcervical access to avoid early embolization. The duration of embolic showers did not reveal any differences in the preprotection phase because these showers are very infrequent before manipulating the lesion site.

During stenting and angioplasty, CASdp shows a higher frequency of discrete emboli as well as embolic showers. In many cases, the dynamic flow reversal eliminates embolization during stenting and angioplasty completely, as also reported by Ribo et al.[14] and Flores et al.[8] Although distal protection filters are designed to reduce intraoperative embolization, some studies have found them to be associated with an even higher incidence of microembolization than unprotected stenting.[8,21,22] Furthermore, the beneficial effects of the EPD on reducing new DW-MRI lesions are not observed universally.[3,23,24]

There are several explanations why distal embolic protection filters may not be able to protect the brain. Macroemboli are propelled into the filter and consequently may disintegrate into smaller particles, resulting in a higher apparent microembolic load on TCD.[21] Other explanations could be that the deployment of the EPD itself causes more emboli, or the EPD does not appose the artery optimally, or particles smaller than the pore size of the EPD pass unhindered to the brain.[25,26]

In the postprotection phase, after shunt removal and release of the clamps in CEA, retrieval of the EPD, or restoration of normal antegrade flow in CAS, no differences could be observed between the different treatment strategies. All showed a short burst of emboli, followed by none or infrequent particles.

Although it is a common finding that CASdp is associated with more intraoperative embolization than CEA, direct comparisons may be partially distorted because contrast injection occurs only in CAS and generates emboli-like signals that are often picked up by automatic detection programs. Because micelles of the contrast agent can generate TCD signals,[18] embolic loads may be overestimated for CAS. To avoid this problem, we discarded the signals directly

related to contrast injection. Nonetheless, CASdp was still associated with a higher embolization rate. The reliable detection of embolic events in this study was further confirmed by the high inter-rater correlations for detecting discrete emboli and embolic showers.

As it is unclear whether distal protection filters have a beneficial effect, other cerebral protection methods have been proposed, using an antegrade flow stop or even reversal of flow in the internal carotid artery.[8,27,28] Unfortunately, the clinical benefits of these methods based solely on reducing embolic risk are also unclear.[29] While comparisons between proximal embolic protection and distal protection filters sometimes show contradictory results,[29-34] studies using direct transcervical access with dynamic flow reversal consistently suggest better outcomes than CASdp.[6,7] Gupta et al.,[11] for example, showed that transfemoral CAS with flow reversal may lower embolization rates, although this difference failed to reach significance. Our results show that direct cervical access combined with dynamic flow reversal during angioplasty and stenting is able to significantly decrease the number of emboli compared to distal filters. In the present study, a dynamic flow reversal method is used, where the flow reversal is 10 times as strong in the high-flow mode and 5 times as strong in the low-flow mode as the Gore flow reversal system (W.L. Gore and Associates, Flagstaff, AZ, USA). This, in combination with avoiding aortic arch manipulations, explains the current low embolization rate.

Some advantages of CASfr compared with CEA are the common use of local anesthesia, lower incidences of cranial nerve injury and myocardial infarction, and the short duration of flow reversal. A disadvantage is that the proximal ipsilateral CCA should be healthy and ideally 5 cm long to obtain safe access. Case selection is done using duplex ultrasound, evaluating both the CCA entry point and length. If the neck is obese but there is sufficient CCA length, the procedure can be carried out, preferably under general anesthesia, by creating a subcutaneous tunnel to avoid kinking of the sheath. Furthermore, a puncture in the femoral vein is also made in addition to a small incision in the neck. Around 5% to 10% of patients may experience intolerance to the reverse flow.[6] This can be overcome by increasing blood pressure, minimizing the duration of the reverse flow, switching from the high- to low-flow mode, or if necessary, unclamping the CCA and restoring normal antegrade flow.[6] Although CEA is still considered the gold standard, when for any reason CAS is preferred as a better treatment option, CASfr appears to be a safer method than CASdp in appropriately selected cases.

Although studies on CASfr are still scarce, it has been shown that transcervical stenting with dynamic flow reversal is able to overcome many limitations of transfemoral carotid stenting with distal protection filters, revealing stroke and new DW-MRI lesions rates that are comparable with CEA.[6,7] This study is consistent with these findings, since the embolic load during CASfr was comparable with that during CEA.

Limitations

First, there was no DW-MRI data to confirm the effect of higher embolization rates on new structural brain lesions post intervention as shown in previous research.[35] Second, the number of dropouts due to insonation problems was high, especially in older women, although this is a problem inherent to the TCD technique[15, 16] and is not specific to this study. A third limitation was the limited number of patients.

Conclusion

CASfr is an effective method to reduce the number of emboli released during carotid stenting. In the preprotection phase, CASfr and CEA showed lower embolization rates than CASdp, probably because they avoided the aortic arch and provided direct access to the lesion site. During the protection phase, CEA and CASfr again had less embolization than CASdp. No significant differences between CEA and CASfr could be detected regarding intraoperative embolization. Future research examining differences between revascularization techniques as regards intraoperative embolization is warranted to confirm our results.

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Chapter 5

General discussion and future perspectives

General Discussion

The major aim of this thesis was to elucidate the effect of carotid revascularization on cognitive functioning. Moreover, the effect of a newer CAS technique - transcervical carotid artery stenting with dynamic flow reversal (CASfr) - was evaluated in its ability to reduce perioperative embolization compared with conventional CAS using distal protection filters.

In the systematic review of **Chapter 1**, we showed that none of the selected studies comparing CEA and CASdp could find significant differences in cognitive functioning between the two treatment modalities. The majority of patients remain cognitively stable after revascularization, but a minority (10 to 20%) does experience cognitive alterations. Symptomatic status and side of intervention do not appear to influence postoperative cognition while in several studies increasing age was a significant predictor of cognitive decline or less improvement than expected.[1] However, at the same time we unveiled that several methodological issues may obfuscate a straightforward interpretation of the data. Especially the failure to implement a control group, the lack of information about the symptomatic status and type of symptomatic events, the wide variety of cognitive tests and statistical methods used, and sometimes high drop-out rates hamper the ability to directly compare different studies or perform a meta-analysis.

In **Chapter 2** we confirmed the findings of our review by showing that CEA and CASdp have similar effects on cognition, plus we showed that CASfr produces comparable results. We used a control group of patients with peripheral arterial disease matched for sex, age, and SES. This control group showed comparable baseline cognitive impairments as the treatment group, probably because they share similar co-morbidities and risk factors as patients with significant carotid artery disease, such as arterial hypertension, hypercholesterolemia, diabetes, and active smoking.[2] A comparable cognitive baseline status of the control group is important, since subjects with a higher IQ are known to benefit more from previous testing – that is, higher baseline IQ scores evoke higher practice effects.[3] With a healthy control group, the expected practice effects may consequently be overestimated which can result in a higher chance of concluding that the treated group shows cognitive decline.

Recent articles published since our review that respected similar inclusion criteria have been studied, but only three included a control group; one CAS study[4], one CEA study[1], and one CEA versus CAS study.[5] Interestingly, all three studies recruited carotid patients on best medical treatment (BMT) as a control group.

Yoon et al.[4] compared 23 CAS patients (12 asymptomatic and 11 symptomatic) with 10 control patients with a significant carotid stenosis on BMT. Only symptomatic patients seemed to benefit from revascularization, while asymptomatic and control cases did not show any cognitive changes at three months. The sample size was small and only two out of the 20 tested variables showed a difference between symptomatic and asymptomatic patients, which is in contrast with previous larger CAS studies.[6, 7] Therefore, the results of this study should be interpreted with caution.

Carta et al.[1] compared 35 patients who underwent CEA (11 symptomatic, 24 asymptomatic) with 11 patients (4 symptomatic, 7 asymptomatic) on BMT. After 6 months, 30% of CEA patients showed cognitive improvement compared to 0% of patients on BMT. Although a general increase in cognitive scores is to be expected due to practice effects, the significant difference between the two groups suggests that CEA may improve cognitive functions, at least in a subgroup of carotid artery stenosis patients.[1] Keep in mind that this study was non-randomized and that patients refusing invasive therapy may form a specific subgroup, which could also explain the observed cognitive differences between the two groups.

In contrast with Carta et al.[1], Wapp et al.[5] did not find any differences in cognitive performance between 20 CEA, 10 CAS, and 28 patients on BMT at one-year follow-up assessment, despite using a comprehensive neuropsychological test battery. Improved cognitive scores were noted in all groups, probably due to practice effects. In the control group, improvement was noted in fewer tasks than after CEA or CAS, but no significant differences between the groups could be detected, suggesting that the effect of invasive treatment on cognition is small.[5] This was also a non-randomized study.

It is obvious that overall, the cognitive impact of revascularization is rather limited. Suggesting that every significant asymptomatic carotid artery stenosis should be regarded as symptomatic because of cognitive deterioration, and should therefore be revascularized is not justified. Nonetheless, a subgroup of 10 to 15% of patients each with significant asymptomatic carotid artery stenosis may on one hand be at risk for cognitive decline following intervention or may on the other hand benefit from carotid revascularization. Identifying these patients is paramount as it may influence the decision to intervene or continue best medical therapy. In case of expected cognition deterioration, surgery for asymptomatic patient should be discouraged, while in case of expected positive effects, it may be advocated to revascularize these patients.

In **Chapter 3** we tried to find predictors of cognitive change, regardless of the type of carotid revascularization. S-100β and perioperative embolization as detected by TCD appear not able to predict cognitive decline in patients without neurological complications after revascularization. It looks like cognitive evolution after revascularization is unpredictable.[8] Although our limited sample size may have caused a type II error, several other studies also failed to find associations between S-100β[9-12] or embolization[8, 13, 14] and cognition after carotid revascularization. It appears that changes in serum S-100β are influenced by impairments in the blood-brain barrier, which interferes with its ability to predict cognitive deterioration after carotid revascularization.[12, 15-18]

In the current situation, CASdp results in an almost tenfold higher global embolic load than CEA. When looking for a correlation between these extremes and subtle cognitive differences it is difficult to find significant associations. Consequently, discarding irrelevant signals is important to improve the clinical relevance of TCD monitoring. To this end, differentiation between the size and type (gaseous versus particulate) of emboli may play a crucial role.

Similarly, recent studies show that the majority of studies attempting to correlate the size and amount of new DW-MRI lesions to postoperative cognition rendered fruitless.[19, 20] Although silent brain infarctions occur more frequently after CAS than after CEA, this does not seem to have an impact on cognitive function one month post intervention.[21] An alternative for gray matter damage detected by DW-MRI, may be white matter damage detected by diffusion tensor imaging which has been shown to correspond with cognitive impairment.[22] On the other hand, in a recent ICSS

substudy,[23] cognitive evolution after 6 months was not related to the severity of white matter lesions at baseline.

Changes in cerebral perfusion induced by carotid revascularization have also been linked to postoperative cognition. Using computed tomography perfusion, Cheng et al.[24] found a close relation between perfusion changes and changes in cognitive tests. Patients with a baseline impairment of the MCA blood flow were more likely to experience improvement in MCA flow after CAS.[24] This improvement in MCA blood flow was associated with greater cognitive improvement in attention and executive functioning after CEA.[25] The repair of a preoperative low relative cerebral blood flow in the ipsilateral cerebral hemisphere has been shown to significantly improve postoperative cognitive function in patients after CEA.[26, 27] Yoshida et al.[28] showed that increases in cerebral glucose metabolism as measured by positron emission tomography (PET) are associated with cognitive improvement after CEA and vice versa. Finally, postoperative hyperperfusion is associated with postoperative cognitive decline regardless of the presence any new lesions on DW-MRI.[22, 29, 30] These studies all seem to suggest that an important link between revascularization, cerebral perfusion, and postoperative cognition does exist.

In a recent study[31], the hypothesis of changes in brain perfusion as a mediator for cognitive improvement after revascularization was studied in patients with a fetal-type (FTP) configuration of the posterior part of the circle of Willis. In this variant, the PCA is largely or sometimes exclusively supplied by the internal carotid via the posterior communicating artery and less or not by the vertebrobasilar system.[32] A unilateral or bilateral FTP is found in 12 to 38% of cases.[32] Since a larger part of the brain is dependent on the blood flow through the internal carotid, patients with FTP are more prone to develop vascular insufficiency.[31, 32] Carotid revascularization is therefore expected to have a higher positive effect since an increased blood flow in the carotid has an effect on a larger part of the brain. Nevertheless, the fetal variant was associated with cognitive decline instead of improvement after carotid revascularization.[31] This is in conflict with the hypothesis that improving brain perfusion may enhance cognitive function. However, this correlation between the FTP and postoperative cognition does point out that there is a link between carotid revascularization, cerebral perfusion, and cognition. A possible explanation may be the selective use of shunting. If shunts were seldom used, cerebral ischemia may have occurred due to decreased

blood flow during CEA explaining the worse results in the FTP group. Based on this hypothesis, the low cerebral blood flow during surgery may have a higher impact than the beneficial effects of revascularization. Another explanation for the decline is that revascularization might have caused hyperperfusion. Since for FTP patients, the restoration of flow in the internal carotid has a larger impact, the brain may not be able to cope with this sudden increase in blood flow resulting in hyperperfusion. In any case, the predictors of cognitive alterations after surgery are still not clear. It appears difficult to predict cognition after carotid revascularization. Perfusion related measures seem promising, but more research is necessary to further elucidate the precise mechanisms for cognitive changes.

Chapter 4 focused on the differences in perioperative embolization during various revascularization modalities: transcervical access with dynamic flow reversal, filter protected CAS, and CEA. It appears that the transcervical stenting causes less embolization before treating the lesion site. Avoiding aortic arch and common carotid manipulations proves to be valuable in reducing early embolization. Moreover, dynamic flow reversal is able to reduce or avoid embolization during stenting and angioplasty as suggested by Ribo et al.[33] In the postprotection phase, no differences were noted between the three procedures. CASfr has cerebral protection in place prior to crossing the carotid lesion and the dynamic flow reversal is more effective in reducing embolization and protecting the brain than distal filter protection.

While comparisons between proximal embolic protection devices and distal protection filters sometimes show conflicting results,[34-40] studies using direct transcervical access with dynamic flow reversal consistently suggest better outcomes than CASdp.[41-43] Especially the larger sheath and increased reversal flow rate of CASfr may explain its ability to significantly reduce embolization.

It is interesting to note that in the same institution CASfr was in Chapter 3 associated with a higher embolic load than CEA, while in Chapter 4 CASfr the number of emboli was similar. There are several explanations for this ambivalence. Firstly, in Chapter 4, symptomatic stroke patients were also included resulting in a larger sample size and higher statistical power. Secondly, in Chapter 3, the global embolic load during the entire procedure was measured, while in Chapter 4, the embolic load was divided in three surgical phases. Thirdly, CASfr patients included in

Chapter 3 were the first patients treated at our unit with this new technology and may resemble the learning curve associated with this new technology. The increased experience of the vascular surgeons and the improved ENROUTE system (Silkroad medical, Sunnyvale, CA), with changes to the arterial 8F sheath, may explain the lower embolization rates in those patients treated later during these research projects.

Limitations

The main limitation of this research is the small sample size. One could argue that larger groups and subsequent statistical power might have allowed us to identify significant group differences between the various revascularizations regarding cognitive outcomes. Nonetheless, post-hoc power analysis based on the observed performance differences, predicts that 400 to 500 patients in each group would have had to be included in order to detect significant group differences. Although this observation does not exclude the possibility of genuine group differences when these sample sizes are reached, it does suggest that possible differences are probably modest. This is consistent with other research as described in Chapter 1; none of the reviewed studies on the cognitive effects of CEA and CAS showed significant differences between the two treatment modalities. This thesis has also studied the effect of CASfr on cognition and compared it with CASdp and CEA, but again, no significant differences were noted.

Similarly, in Chapter 2, the inability to predict cognition post-carotid revascularization using TCD and S-100β could be the consequence of low statistical power. But again, several recent studies have also been unable to find a similar association.[8-10, 13, 14]

A second limitation is the nonrandomized design of the studies included in this thesis. This design was chosen since randomization is not easy to achieve in carotid revascularization because treatment allocation should be patient-specific and depends on comorbidities, anatomical and lesion characteristics, and the patient's preference. Differences in patient characteristics may have influenced stroke risk, perioperative embolization, and cognitive abilities. Nonetheless, analysis of demographic variables did not show any relevant differences between the treatment groups in any of our studies.

A third limitation is that our studies lacked DW-MRI data or perfusion measures as assessed by PET or SPECT. Especially perfusion measures seem promising in predicting cognitive outcome. However, the TCD recordings allowed us to differentiate between the different stages of carotid revascularization which provided valuable information to determine which specific surgical acts are prone to evoke embolization.

A fourth limitation is the lack of a power calculation before starting the studies. Although it would be difficult to estimate the cognitive performance and variances in advance, it might have added to the persuasiveness of our data.

Future directions and guidelines

In this thesis, we showed the importance of using a proper control group when studying the cognitive sequelae after different carotid revascularization techniques. Practice effects are a major limitation in studies without a control group. Although several researchers[25, 44] correctly claimed that different forms of material (i.e. different sets of the same test) reduce practice effects, even tests designed to minimize practice effects such as the RBANS, are prone to practice effects.[45] Practice effects occur for nearly all tests, especially between the first and second assessment, though the frequency and timing of the assessments have an important influence on the size of these effects.[45] Besides the practice effects, patients can become 'test wise' which can also result in significantly increased test scores over time.[46] To avoid alternative explanations, control groups are therefore deemed necessary.[45]

It is important to not solely compare postoperative test results, as is sometimes performed,[47, 48] but to take baseline measurements into account. Otherwise, postoperative differences between groups might be the mere reflection of small differences at baseline. When using difference scores, such as subtracting the preoperative test score from the postoperative test score, the real effect of the intervention on cognition can be estimated. An ideal control group would comprise patients with asymptomatic carotid stenosis since the natural cognitive evolution in patients with significant carotid artery stenosis on BMT would be incorporated. Carotid patients not offered revascularization may experience cognitive decline over time, while those after carotid

revascularization may remain stable. Hypothetically, a stable cognitive status post revascularization may be a good result, as further cognitive deterioration is avoided. Therefore, a multicenter randomized controlled trial should directly compare cognitive functioning in carotid patients randomized between BMT and carotid revascularization.

When evaluating BMT, it is also important to control for medication adherence, especially in patients with an undiagnosed cognitive impairment.[49] Identifying patients with limited cognitive ability is important to increase supervision for medication intake.[49]

Based on our findings, several recommendations can be generated that are vital for future research about cognition and carotid artery disease.

Firstly, information about the (a)symptomatic status, the type of cerebral protection used in CAS, and type of anesthesia used are often lacking, making it difficult to interpret the results. Transparency regarding exclusion criteria is also essential to interpret the findings.

Secondly, when examining postoperative cognition, it may be useful to differentiate between the cognitive domains instead of using a global cognitive sum score. The latter may not be able to pick up subtle cognitive differences. Reporting the number of patients improving or deteriorating post-carotid treatment is paramount since carotid revascularization does not always have the same effect in every carotid stenosis patient.

Thirdly, the statistics used have an important influence on the results reported. Zhou et al.[50], for example, reported correlations between cognitive outcome on the RAVLT and DW-MRI findings. In their study, a sum score of the RAVLT at the follow-up assessment of at least one point lower than at baseline was regarded as a deteriorated cognitive function. However, a difference of only one point on the total sum score is neither clinically relevant nor statistically significant. These arbitral decisions heavily influence the results. Therefore, to define and detect cognitive alteration, we advocate using at least one standard deviation difference from the baseline score.

Fourthly, several studies investigate the effects of revascularization one day post-treatment. Although it may be interesting to study the factors that contribute to these early changes, cognitive functioning immediately postoperatively is likely to be influenced by other factors not directly related to revascularization such as the type or duration of anesthesia. Moreover, the clinical

relevance of these early cognitive changes for patients is probably limited. Thus, we would recommend to assess cognitive functioning at least five days post intervention.

Fifthly, when examining cognitive function it is important to perform a comprehensive testing. Short screening instruments, such as the MMSE and MOCA, are insufficient and may for example result in the fact that only memory function is tested, while visuomotor or executive functions are neglected. Moreover, these short testing instruments are prone to ceiling effects, as many patients achieve the maximum score on the MMSE. Screening instruments like the MMSE have been devised to detect major cognitive disorders (dementia), not to assess milder cognitive impairment. It has been shown that floor and ceiling effects may influence the observed cognitive outcomes after carotid revascularization.[51]

As stated above, surgical techniques and best medical treatment are constantly evolving. Consequently, when reviewing the literature of carotid revascularization, it is important to focus on recent publications. Stroke and death risks in CAS have decreased from 1993 to 2006 which is due to better case selection, improved medical treatment, development of newer stenting and cerebral protection devices, technical advances, and better training curricula.[52] Furthermore, older publications[53, 54] are more likely to report positive results in contrast with recent studies. As suggested previously[54], this may be the result of fewer methodological biases in more recent studies. Thus it is advisable to directly compare surgical techniques rather than with historical data to avoid a flawed comparison.

The issue whether to treat asymptomatic carotid patients is still a matter of debate. Expected cognitive outcomes may play an important role in the decision-making. Large prospective multicenter longitudinal studies on the cognitive effects of carotid revascularization are needed and the link between improved perfusion in the brain and cognition should be further explored. Focusing on cognitive effects of revascularization in subgroups of patients, such as carotid patients with the fetal-type variant of the circle of Willis, may prove useful in testing hypotheses that arise from correlation studies.

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Summary

Carotid artery stenosis has been identified as an important risk factor for stroke. To reduce the stroke risk, carotid endarterectomy (CEA) is often performed and proven safe and effective in symptomatic as well as asymptomatic carotid stenosis patients. CAS with distal filter protection (CASdp) is proposed as an alternative for CEA, especially in high-risk patients, and is associated with a lower incidence of cranial nerve injury and myocardial infarction. However, stroke and new diffusion-weighted magnetic resonance imaging (DW-MRI) lesions are more prevalent when compared with CEA. Transcervical CAS with dynamic flow reversal (CASfr) is a newer technique designed to provide a more direct access to the lesion site and reduce embolization. Results show a low stroke rate and reduced number of DW-MRI lesions when compared with CASdp. Besides these primary outcome measures, the effect of carotid revascularization on cognition is not clear. Moreover the effect of CASfr on postoperative cognition has not been studied thoroughly.

In **Chapter 1** we performed a systematic review of the literature since 2007 trying to clarify the effect of carotid revascularization on cognition. This emphasis on recent literature was made to ensure that the included studies used the more advanced revascularization techniques, devices, and BMT in order to provide a high ecological validity. Only studies that implemented a comprehensive neuropsychological testing and performed assessments at least five days post-treatment were included. Furthermore, we focused on studies using a control group to ensure the emphasis of the review was on methodologically solid studies. The systematic review showed that CEA and CASdp have a similar effect on cognition post intervention; no significant differences could be observed between the two treatment modalities in any of the reviewed studies. However, a subgroup of patients may experience either improvement or deterioration.

In **Chapter 2**, the results of a comparative study are described in which we studied the effects of CEA and two forms of CAS (CASdp and CASfr) on cognition. With all three methods, similar results were obtained. Patients with peripheral arterial disease (PAD) were recruited as controls. Both the control and study groups showed cognitive dysfunction at baseline, probably due to similar risk factors such as current smoking, hypercholesterolemia, hypertension, diabetes, and so on. The similarity between our controls and carotid patients, especially in baseline cognitive

status, prevents confounding factors that arise in studies using healthy controls as a comparison. Finally, as also found in the review, our study unveiled that a subgroup of around 10 to 15% presented cognitive improvement, while another subgroup of the same size showed cognitive deterioration.

Identifying patients at risk for cognitive decline or susceptible for improvement is a challenge. In **Chapter 3** we have attempted to identify those patients with cognitive deterioration post intervention by using S-100β and perioperative embolization levels. These two variables were unable to reliably predict cognitive decline. Although the numbers in our study were limited, other recent studies were also unsuccessful in predicting cognition using these same variables. The transient increase in S-100β, observed in all revascularization therapies, was most likely the consequence of impairment in the blood-brain barrier.

CASdp was associated with a higher embolic load than CASfr and CEA. Nonetheless, the impact of this embolic load on cognitive outcomes remains unclear. Differentiation between emboli regarding their size and type (particulate versus gaseous) may improve the clinical relevance of TCD monitoring. Perfusion related measures are promising, but the mechanisms by which revascularization results in either mitigation of previous hypoperfusion or in postoperative hyperperfusion are poorly understood.

Chapter 4 zoomed in on perioperative embolization during various phases of the carotid revascularization. In the preprotection phase, CASfr and CEA caused lower embolization rates than CASdp, most likely because they provide a direct access to the lesion site. Likewise, in the protection phase, CASfr and CEA caused a significantly lower embolic load than CASdp. The dynamic flow reversal appears to better protect the brain against emboli during CAS than the distal embolic protection filters. In the postprotection phase, no differences could be observed between the three procedures. We showed that CASfr is effective to reduce the embolic load during angioplasty and stenting with similar embolic levels as CEA. Combined with previous stroke and DW-MRI studies, our data suggest that when a surgeon decides to perform CAS and the anatomy is suitable, CASfr may be a safer treatment option.

Research on the cognitive effects of carotid revascularization will remain important. Since the mere presence of a significant carotid stenosis is a predictor of cognitive dysfunction, assessing the effect of revascularization on cognition is essential. If patients are at risk for further cognitive decline, the surgeon may decide not to intervene in asymptomatic patients, while if cognitive improvement is expected, decision-making may be straightforward.

Samenvatting

Beroertes zijn een belangrijke oorzaak van sterfte en functionele beperking in onze maatschappij. Carotisstenose, de vernauwing van de interne halsslagader, is een belangrijke risicofactor voor beroerte waarbij het risico toeneemt met de graad van de stenose. Een stenose komt voor wanneer plaque zich opbouwt in de carotis interna. Deze plaque bestaat uit vet, cholesterol, calcium, en andere bestanddelen uit het bloed. Deze plaque wordt mettertijd harder en kan de carotis vernauwen of zelfs blokkeren wat kan zorgen voor een verminderde bloedtoevoer naar de hersenen. Daarnaast kunnen ook kleine stukjes van de plaque afbreken en in de hersenen vast komen te zitten in een kleiner bloedvat waardoor eveneens een beroerte veroorzaakt kan worden. Het risico op een carotisstenose stijgt voor zowel mannen als vrouwen met de leeftijd en zal dus met de toegenomen levensverwachting een steeds belangrijker probleem worden.

Om het risico op beroerte te verminderen, wordt carotis endarterectomie (CEA) uitgevoerd bij patiënten die symptomen hebben als gevolg van de stenose zoals al dan niet tijdelijke verlammingsverschijnselen, maar ook bij asymptomatische patiënten. Tijdens CEA wordt de binnenste laag van de carotis, intima en delen van media, weggenomen. Carotis stenting is een alternatief voor CEA, meer specifiek voor hoog-risico patiënten, en vermindert de kans op schade aan de hersenzenuwen en myocard infarct. Tijdens CAS wordt een punctie gemaakt in de femorale arterie een katheder endovasculair geleid via de aortaboog naar de carotis waar de stent geplaatst wordt en indien nodig ballondilatatie uitgevoerd kan worden. Vaak wordt er, om de hersenen te beschermen tegen embolisatie tijdens de procedure, aan de distale kant van de stenose een zogenaamd embolic protection device gebruikt. Dit is een openklapbare filter ontworpen om debris afkomstig van de plaque op te vangen. Alhoewel zowel CEA en CAS veilig bevonden zijn, blijkt CAS met distale filters (CASdp) geassocieerd met een hogere prevalentie van letsels op hersenbeeldvorming en een verhoogd risico op beroerte in vergelijking met CEA.

Met als doel het risico op beroertes en laesies te verminderen zijn andere beschermingsmethodes ontwikkeld zoals stenting met een transcervicale toegang en omkering van de bloedstroom in de behandelde carotis (CASfr). In plaats van de katheder omhoog te leiden vanuit

de femorale arterie wordt er een kleine incisie in de hals gemaakt en de stent zo rechtstreeks geplaatst. Daarnaast wordt er een arterioveneuze shunt gemaakt tussen de carotis communis en de vena femoralis en zal de bloedstroom in de behandelde carotis tijdens de interventie omgekeerd worden om het debris afkomstig van de plaque weg te leiden van de hersenen.

De effecten van CEA en CAS op cognitie zijn het onderwerp van een steeds groeiend onderzoeksveld. Carotis revascularisatie kan leiden tot cognitieve achteruitgang door perioperatieve embolisatie of onderbreking van de bloedstroom. Daarentegen kan het verwijderen van een stenose en de daaruit volgende verbetering van de bloedsdoorstroming naar de hersenen resulteren in een cognitieve verbetering. Het is tot op heden niet duidelijk welk netto effect revascularisatie heeft op cognitie.

Om het effect van carotis revascularisatie op cognitie na te gaan hebben we in **Hoofdstuk 1** een systematische review uitgevoerd van alle publicaties sinds 2007. De focus werd gelegd op recente artikels omdat de medische technieken en standaard medische therapie (bv statines) steeds evolueren en het daarom belangrijk is vooral te kijken naar de meest recente studies aangezien deze een betere reflectie zijn van de huidige medische realiteit. Daarnaast werden studies enkel geïncludeerd wanneer ze een uitgebreide neuropsychologische testing omvatten en zich niet beperkten tot korte screeningsinstrumenten. Om de effecten van anesthesie te vermijden werden verder studies enkel geselecteerd indien de cognitieve testings na 5 dagen of meer plaatsvonden. Tot slot was er een duidelijke focus op studies die controlegroepen gebruiken. Dat is belangrijk omdat door gebruik te maken van een controlegroep, de studie rekening kan houden met oefeneffecten. Hoe vaker iemand een bepaalde test aflegt, hoe beter diens prestatie zal zijn, los van de onderliggende cognitieve functies. Uit de review bleek dat er geen duidelijke significante verschillen zijn tussen CEA en CASdp wat betreft hun effect op cognitie. Er blijken wel subgroepen van 10 a 15% van de patiënten te zijn die cognitieve verbetering dan wel achteruitgang tonen, los van de specifieke soort revascularisatie die gebruikt werd.

In **Hoofdstuk 2** werden deze resultaten geëxtrapoleerd naar CASfr. CEA, CASdp en CASfr resulteerden in gelijkaardige veranderingen in cognitie. Als controlegroep werden patiënten met perifeer arterieel lijden (PAD) gerekruteerd. Zowel de patiënten met PAD als de patiënten met

carotis stenose blijken al tijdens de baseline meting cognitieve problemen te vertonen. Dat is hoogstwaarschijnlijk het gevolg van gemeenschappelijke factoren zoals hypercholesterolemie, hypertensie, diabetes, roken, enz. Deze gelijkaardige baseline is belangrijk omdat aangetoond werd dat personen met een hoger IQ een hoger oefeneffect kunnen vertonen bij herhaalde testingen. In deze studie vonden we, in overeenstemming met de review, dat 10 a 15% van de carotispatiënten cognitieve verbetering of achteruitgang ondervindt wanneer we ze vergelijken met de controlepatiënten.

In **Hoofdstuk 3** probeerden we te achterhalen of het eiwit S-100β en de perioperatieve embolisatie zoals gedetecteerd door transcranieel Doppler (TCD) monitoring ons in staat stellen om te voorspellen welke patiënten cognitieve achteruitgang zullen vertonen. Cognitieve achteruitgang kon in deze studie echter niet voorspeld worden. Alhoewel deze resultaten mogelijks verklaard zouden kunnen worden door de kleine steekproef en dito statische kracht van het onderzoek, blijken ook andere studies niet in staat een relatie te vinden tussen S-100β, perioperatieve embolisatie en cognitie. Een lichte tijdelijke toename in S-100β werd gedetecteerd voor alle interventies en is waarschijnlijk het gevolg van een wijziging in de bloed-hersen-barrière. Verder was CASdp geassocieerd met een hogere embolisatie tijdens de operatie vergeleken met CASfr en CEA, maar de klinische relevantie hiervan m.b.t. postoperatieve cognitie is evenmin duidelijk. Indien toekomstige technologische verbeteringen ons toelaten om te differentiëren tussen embolen volgens hun grootte en aard (gasvormig versus vast), zal de klinische relevantie van TCD monitoring waarschijnlijk verder verbeterd kunnen worden. Het identificeren van patiënten die vatbaar zijn voor cognitieve veranderingen zal een belangrijk topic blijven. Mogelijk hebben perfusiegerelateerde criteria meer kans om succesvol deze patiënten te identificeren.

In **Hoofdstuk 4** gingen we verder in op de embolisatie tijdens de verschillende chirurgische fasen van de interventie. In de fase voordat de cerebrale bescherming - zoals de distale filters of omkering van de bloedstroom - geïnstalleerd is, blijken CASfr en CEA reeds minder embolisatie te veroorzaken dan CASdp. Dit is waarschijnlijk het gevolg van het feit dat de eerste twee direct toegang tot de plaats van de laesie bieden, terwijl bij CASdp er een hele weg via de arteria femoralis, aortaboog naar de carotis afgelegd moet worden. Het manipuleren van de wires en botsen tegen de wand van aangetaste bloedvaten kan ervoor zorgen dat er tijdens die fase reeds

embolisatie voorkomt. Ook tijdens de fase waarin de cerebrale bescherming aanwezig is, blijken CEA en CASfr beter te presteren dan CASdp. De omkering van de bloeddoorstroming in de carotis blijkt dus effectiever te zijn in het reduceren van embolisatie tijdens het stenten en de ballondilatatie dan de distale filters. In de laatste fase, na het verwijderen van de cerebrale bescherming, resulteren alle revascularisatietherapieën in gelijkaardige embolisatieniveaus. CASfr blijkt dus globaal beter te presteren dan CASdp in het reduceren van perioperatieve embolisatie en lijkt dus de aangewezen optie indien een chirurg beslist om carotis stenting uit te voeren.

Onderzoek naar de cognitieve gevolgen van carotis revascularisatie zal een belangrijk onderwerp voor toekomstig onderzoek blijven. De aanwezigheid van een significante carotisstenose heeft een impact op cognitie en het nagaan van de effecten van revascularisatie is daarom relevant. In een ideaal scenario zou de beslissing om chirurgisch in te grijpen, zeker in het geval van asymptomatische patiënten, mee kunnen bepaald worden door het verwachte effect op de cognitieve functies. Bij patiënten bij wie een positief effect op cognitief vlak verwacht wordt, kan dan beslist worden in te grijpen terwijl er bij patiënten bij wie een negatief effect verwacht wordt een meer terughoudende houding kan worden aangenomen.

Appendix

Cognitive domains and neuropsychological tests.

Cognitive Domain and Neuropsychological Test	*Description*
Long-term memory	
AVLT, Sum	Participants are given a list of 15 unrelated words repeated by the examiner over five different trials and are each time asked to repeat.
AVLT, delayed recall	First a list of 15 unrelated words are given. Subsequently the participant is asked to repeat the original list of 15 words and then again after 45 minutes.
CFT, delayed recall	Participants are given a complex figure which they have to copy. Afterwards they must draw the figure from memory and then again after 45 minutes.
Attention	
SS (forwards)	In this task the participant has to mimic the examiner as he/she taps a sequence of up to nine identical spatially separated blocks. The sequence starts out simple, using two blocks, but becomes more complex until the subject's performance suffers.
DS (forwards)	In this task the participant has to repeat a sequence of up to nine numbers. Also in this case, the sequence starts out simple, using two numbers, and becomes increasingly difficult.
SS-C	This test consists of nine digit-symbol pairs followed by a list of digits. Under each digit the participant has to write down the corresponding symbol as fast as possible.
D-2	In this task participants have to cross out any letter ‘d’ with two marks around. The surrounding distractors are similar to the target stimulus, such as a ‘p’ with two marks or a ‘d’ with one or three marks.
TMT-A	For this test the participant is instructed to connect a set of 25 dots in sequential order as quickly as possible.

Executive functioning	
SS (backwards)	This is identical as the Spatial Span task, but in this case, the participant has to repeat the sequence in backward order.
DS (backwards)	This is identical as the Digit Span task, but in this case, the participant has to repeat the sequence in backward order.
SCWT	For this test, the participant gets presented several color names each printed in a different color ink. The participant has to name ink colors as quickly as possible.
Phonological verbal fluency, COWAT	In this case participants have to name as many words as possible from a phonemic category, such as words beginning within the letter 'N', within 60 seconds.
Semantic verbal Fluency from the GIT	In this case participants have to name as many words as possible from a semantic category, such as animals or fruits, within 60 seconds.
TMT-B	This is identical as the Trail Making Test Part A, but in this case, the participant has to alternate between numbers and letters (1, A, 2, B, etc.).
Fine Motor Abilities	
Grooved Pegboard Left/Right	Participants are asked to put pegs in holes as fast as possible with either their left or right hand
Spatial Functioning	
Judgement of Line Orientation	For this test, participants are asked to match two angled lines to a set of 11 lines that are arranged in a semicircle.
Line Bisection Task	In this test, several horizontal lines are presented. The participant is asked to dissect the line at the midpoint

AVLT = Auditory Verbal Learning test; CFT = Complex Figure Task; SS = Spatial Span from the Wechsler Memory Scale-III (WAIS-III); DS = Digit Span from the WAIS-III; SS-C = Symbol Substitution coding task from the WAIS-III; D-2 = d2 Test of Attention; TMT = Trail Making Test (Parts A and B); SCWT = inference factor of the Stroop Color and Word Test; COWAT = Controlled Oral Word Association Test (letters NAK); GIT = Groninger Intelligence Test.

Curriculum Vitae

Publications
Peer-reviewed journal articles

Willaert, W.I.M., Aggarwal, R., Van Herzeele, I., Plessers, M., Stroobant, N., Nestel, D., Cheshire, N., & Vermassen, F. (2012). Role of patient-specific virtual reality rehearsal in carotid artery stenting. *British Journal of Surgery*, *99*(9), 1304-1313.

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Posters & oral presentations

Plessers, M., Vandekerckhove, M., Beeckmans, K., Weiss, R., Van Overwalle, F., Markowitsch, H.J., & Cluydts, R. (2011). Impaired Facial Emotion Recognition in Patients with Ventromedial Prefrontal Hypoperfusion. Poster presented at the 3rd Scientific Meeting of the Federation of European Societies of Neuropsychology (ESN), September 7-9, Basel (Switzerland).

Plessers, M., Van Herzeele, I., Vingerhoets, G., & Vermassen, F. (2014). TCT-559: The Link Between S100β And Audio-Verbal Memory Performance In Patients After Carotid Revascularization. Poster presented at Transcatheter Cardiovascular Therapeutics (TCT) congress, September 13-17 2014, Washington D.C. (USA). *Journal of the American College of Cardiology, 64(11 Suppl B).*

Plessers, M., Van Herzeele, I., Vingerhoets, G., & Vermassen, F. (2015). The Link Between S100β And Audio-Verbal Memory Performance In Patients After Carotid Revascularization. Poster presented at the 43rd Annual Meeting of the International Neuropsychological Society (INS), February 4-7 2015. Denver, Colorado (USA).

Plessers, M., Van Herzeele, I., Vingerhoets, G., & Vermassen, F. (2015). Neurocognitive Functioning After Carotid Endarterectomy and Carotid Stenting With Filter Protection or Flow Reversal. Poster presented at the Leipzig Interventional Course (LINC), January 27-30 2015, Leipzig (Germany).

Plessers, M., Van Herzeele, I., Vermassen, F., & Vingerhoets, G. (2015). Neurocognitive Functioning After Carotid Endarterectomy and Carotid Stenting With Filter Protection or Flow Reversal. Oral presentation at the Multidisciplinary European Endovascular Therapy (MEET) congress, June 8-9 2015, Nice (France).

Teaching

General Psychology (2010-2014) – 1st Bachelor speech therapy & audiology UGent
Neuropsychology (2011-2015) – 2nd Bachelor speech therapy & audiology UGent
Neuropsychological Assessment (2011-2015) – 1st Master experimental psychology UGent

Additional training

April 2012	Workshop assistant training (teaching, didactics, giving feedback, evaluation, …) *Ghent University*
March - May 2011	Didactics training (presentations, efficient communicating, student guidance, …) *University College Ghent*
April 2011 & June 2014	Workshops ‘Transcranial Doppler Ultrasonography and analysis’ led by Mr. Tim Hartshorne and Dr. Emma Chung *Royal Infirmary Leicester*
November 2009	Post Graduate Cognitive Behavior Therapy for Insomnia *Free University Brussels*
15-16 December 2008	Workshop ‘Brain Voyager’ by Armin Heinecke *Maastricht University*