Effects of carotid endarterectomy on cognitive functioning and perceived health

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Effecten van een carotis endarteriëctomie op het cognitief functioneren en de waargenomen gezondheid

(met een samenvatting in het Nederlands)

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Voor
Harien

En voor
Jesse en Sem

Contents

Chapter 1

General introduction

Stroke is the third major cause of death and the major cause of disability in the western world. It is the clinical manifestation of tissue starvation within the cerebral hemispheres due to blood vessels obstruction or hemorrhage.

Prevention of stroke includes treatment with antiplatelets (like aspirin) or anticoagulants (like warfarin), and modification of atherosclerosis risk factors, such as hypertension, elevated cholesterol levels, diabetes mellitus, and cigarette smoking. Carotid endarterectomy (CEA) is indicated when a significant obstruction is present in one of the internal carotid arteries. This surgical procedure, in which the carotid stenosis is removed, was first performed by DeBakey and colleagues in 1954.[1] The number of CEAs increased enormously since then.

Large randomized trials have shown that CEA is most effective in the prevention of stroke in patients with a stenosis of the carotid artery of 70 to 99%.[2-6] The North American Symptomatic Carotid Endarterectomy Trial (NASCET), for example, showed a 2-year risk reduction of any ipsilateral stroke from 26 to 9% in patients with a transient ischemic attack (TIA) or nondisabling stroke and severe ipsilateral stenosis before randomization.[2] The surgical benefit also persisted in the next 3 years and after that.[4,7] The Asymptomatic Carotid Surgery Trial (ACST) reported a 5-year decrease in the risk of stroke from about 12 to about 6% in *a*symptomatic patients with severe stenosis (70% or more) preoperatively.[6] Surgery is of less and even no benefit with lower grades of stenosis.[4,7,8]

Despite these long-term gains, symptomatic patients are faced with a small but significant risk of developing a cerebrovascular event (which may lead to death) within 1 month after the procedure (about 7%[4] compared to about 3% in medicamentally treated patients during a similar period[2]). The risk appears to be independent of the preoperative severity of the stenosis[4,9] and duration of previous ischemic symptoms (cerebral TIA versus stroke).[9] This early overall disadvantage of CEA is overcome at about 3 months after surgery.[2] In patients with an *a*symptomatic history, the perioperative risk is close to the 3% reported for unoperated patients.[5,6]

Neuropsychological assessment

Interest in neuropsychological assessment before and after CEA was raised by subjective observations of intellectual and cognitive deficits of patients with cerebrovascular insufficiency due to atherosclerotic disease, and reported instances of improvement in such deviations after the operation.[10] The first attempt to evaluate the preoperative functioning and postoperative change objectively was made in 1959,[11] and the first research review on this topic was published in 1977.[10] In the following decades, numerous studies reported improvement in cognitive functions, but also no change and even decline were noticed.[12-22] Improvement has generally been explained by restoration of blood flow to the brain, whereas decline has been attributed to intraoperative emboli and ischemia. However, attempts to exclude alternative hypotheses for the observed changes in cognitive functioning, or for the failure to find changes, often have not been satisfactorily undertaken. This may have contributed to the large heterogeneity in outcome of the previous studies. Before discussing this, I concentrate on another frequently ignored issue: cognitive improvement due to the restoration of adequate cerebral blood flow presumes the existence of subnormal levels of cognitive functioning before surgery.

Cognitive functioning before CEA

Presence of cerebrovascular disease, such as plaques in the carotid arteries, has been associated with worse cognitive performance in large population studies.[23-26] A review, published in 2000,[27] specifically focused on studies including patients with severe occlusive disease of the carotid artery (undergoing surgery or not). Fourteen of the reviewed studies reported cognitive dysfunction, but four did not. Marked differences in patient characteristics, study design, and neuropsychological assessment procedures prevented a definitive conclusion by the authors, however.[27] With respect to this thesis, one may also question the generalizability of the findings to patients prior to CEA, since the majority of studies in the review included patients not (yet) indicated for surgery or who would receive extracranial-intracranial (EC-IC) bypass surgery. In addition, the earlier studies barely paid attention to differences between subgroups of patients, such as those with unilateral versus bilateral stenosis of the carotid arteries, or those with versus without symptomatic history. This information can be useful in predicting who may finally profit most from CEA in cognitive functioning. Moreover, some of the studies included patients with a history of (major) stroke. Cognitive impairment in these subjects may result from structural brain damage, and may thus complicate the attribution of the impairment to the stenosis of the carotid artery as such.

Cognitive change following CEA

Both improvement and decline in cognitive functioning after CEA have been reported in the literature, but also no change.[12-22] Many of the previous studies, however, can be criticized for not taking potentially confounding factors into account, resulting in misconceived conclusions. Postoperative improvement, for example, can be the result of practice effects caused by repeated testing. The use of alternative test versions, if available, may reduce this influence on retesting, but will probably not totally prevent procedural learning. Nonspecific effects from surgery and anesthesia may also directly influence postoperative cognitive performance, or perhaps indirectly through changes in mood states. To control for these effects, research on this topic at least requires the inclusion of a surgical control group.[10,12]

An additional complicating factor in the investigation of cognitive changes after CEA concerns, again, the inclusion of patients with a history of stroke. Improvement in these subjects may be attributed to recovery from the neurological lesion, whereas an explanation for a failure to find improvement (or perhaps even a decline) can be the existence of *permanent* neurological damage in the brain. We were confronted with the first of these scenarios in the pilot phase of our study,[28] when we observed clear improvement of cognitive functions following CEA in a patient who suffered a major stroke several weeks before surgery (see Box). Because of problems in the interpretation of the results in the subgroup of (major) stroke patients, and the risk of influencing the overall cognitive outcome, exclusion of these subjects in neuropsychological assessment seems to be the best option to reliably assess the unique contribution of a restored blood flow to the brain.

Cognitive laterality
One may hypothesize that restoration of cerebral blood flow is more beneficial to cognitive functions mediated by the hemisphere ipsilateral to the operated side rather than to those of the contralateral hemisphere. Improvement in verbal and language functions are then expected in patients operated on the left carotid artery, and enhanced nonverbal or visuospatial functioning in patients operated on the right side. Motor functions of the body side contralateral to the operation may improve as well. A number of studies searched for these side-specific effects,[15,29-37] but there is no consensus in their findings. This might be explained, among others, by the uncritical use of cognitive tasks and by the ignorance of subject factors that are closely related to cerebral function asymmetry, such as handedness and gender. Future research (such as the study described in this thesis) should take these factors into consideration.

Intraoperative embolism
Cognitive difficulties due to intraoperative emboli have frequently been reported after cardiac surgery.[38-41] Comparable deficits may be expected after CEA: particles from the atherosclerotic plaque may come loose during or shortly after surgery, and block smaller arteries located further down, possibly resulting in a decrease of cognitive functioning. The grade of embolism in the main stem of the middle cerebral artery can be registered with transcranial Doppler (TCD) ultrasonography. In spite of this possibility, intraoperative embolism has been linked only rarely to cognitive changes following CEA.[22,42,43]

HPA axis activity
The hormone cortisol is secreted by the adrenal cortex upon activation of the hypothalamus-pituitary-adrenal (HPA) axis in response to physiological or psychological stress. In healthy persons, an increase in cortisol secretion is subsequently inhibited through coupling to receptors, among others, located in the hippocampus.[44] With increasing age the ability to maintain

this homeostasis decreases, at least in a proportion of elderly subjects, resulting in prolonged or continuously elevated cortisol levels. In addition to regulating the negative feedback of HPA axis activity, the hippocampus is involved in learning and memory.[45] A chronic rise of cortisol levels may lead to neurodegeneration of the hippocampus,[46,47] and may thus contribute to the development of memory disorders observed in a number of aged subjects. Whether elevated cortisol levels are an underlying cause of cognitive impairment in patients with atherosclerotic disease, has not been investigated yet. It will be a topic of research in the present thesis.

Reports of patients

Objective evaluation of cognitive functions in CEA patients started after subjective reports of improvement.[11] Objective test performance, however, often does not run parallel to patient reports of their cognitive functions.[48-51] This subjective aspect has generally been ignored in previous research evaluating the effects of CEA, which is remarkable since it is this aspect that is specifically of concern to the patient.[52] Patients *have* reported on their quality of life before and after CEA, but the few studies that focused on this health-related aspect (again) varied widely in their outcomes.[42,53-56] Furthermore, only one previous study followed a multidimensional approach in which both physical and mental aspects of perceived health were evaluated.[56] A complete picture of the effect of CEA on the perception of cognitive functioning and health will give the opportunity to present to patients and their family realistic outcome expectations regarding the chance of improvement, and the specific dimensions in which improvement may occur.

Aims and outline of the thesis

The main aim of this thesis was to investigate the possible beneficial function of CEA on cognitive functioning and on perceived health in a methodological more strict design than previous studies, by taking possible confounding factors as reviewed in this chapter into account. To maintain motivation of patients and reduce the effect of fatigue, the cognitive tests took at most 1 hour to be completed. We also made sure that tests assessing similar cognitive functions did not succeed each other.

Chapter 2 evaluates cognitive functioning in patients with severe atherosclerotic disease of the carotid artery indicated for CEA. Patients with a history of stroke were explicitly excluded. Performance was compared to a group of healthy control subjects, and the influence of mood differences between the two groups was controlled for. Whether CEA has a beneficial effect on cognitive functioning or not, is presented in Chapter 3. Surgical control subjects included patients with comparable surgery of the peripheral arteries (in their legs). Chapter 4 addresses the laterality hypothesis, which assumes ipsilateral effects on cognitive abilities after CEA. Only right-handed male subjects were selected to test this hypothesis. In Chapter 5 the association between perioperative microembolism and cognitive change following CEA is examined. The impact of CEA on patient evaluations of their cognitive functions and health in daily life is investigated in Chapter 6. Chapter 7 focuses on the relation between memory function and salivary cortisol levels in patients with severe atherosclerotic disease. Chapter 8 summarizes and discusses the overall results of this thesis.

BOX Postoperative improvement of cognitive functions after stroke: a case report

EB is a 62-year old retired electrician who suffered a major stroke in the right cerebral hemisphere, resulting in hemiparesis of the left side of the body and a left visual field deficit. Duplex ultrasonography showed a stenosis of 99% in the right carotid artery and between 50 and 65% in the contralateral carotid artery. Seven weeks after the attack, EB underwent CEA to remove the atherosclerotic plaque in the right carotid artery. Surgery was uncomplicated; the electroencephalogram (EEG) showed no changes and no shunt was used. The patient had no hypertension, diabetes mellitus, claudicatio intermittens, or heart problems, but he had a high cholesterol level. He had also been smoking cigarettes each day until 4 years prior to the ischemic attack.

Before the operation EB agreed to participate in our study on the cognitive effects of CEA, and written consent was obtained. He was assessed with neuropsychological tests in the morning of the day before surgery, and 3 months thereafter. The test battery took about 45 minutes to be completed and included the following tests: Digit Span, Dichotic Listening test, Stroop Color-Word Test, Verbal Fluency, Motor Planning Test, Finger Tapping Test, Complex Figure Test. Before the first assessment, on interview, EB reported no hearing or vision problems. With respect to his reading abilities, he reported that he could not stay on the right line. He also noticed a decrease in short-term memory in daily life and difficulties in orientation of space. At the 3 months follow-up, EB remarked that he was more emotionally unstable than before CEA.

Before surgery, EB performed below the mean preoperative scores of other patients with severe atherosclerotic disease of the carotid arteries[28] on most variables. Deviance was more than 2 standard deviations of the mean on the interference score of the Stroop Color-Word Test, the planning times of the Motor Planning Test, and the copy and recall of the Complex Figures Test. Performance on the latter task in fact was noticeable (Figure 1). For example, the left part of the copied figure was not drawn and details in the middle of the figure were drawn twice, being indicative of visual neglect of the left visual field. At the 3 months follow-up significant improvements on this test were noted (Figure 2), as well as on the interference score of the Stroop Color-Word Test and the planning times of the Motor Planning Test.

The postoperative improvements may not be attributed to motivational factors or reduced fatigue on retest because cognitive performance did not change on the other tasks. The increase in performance cannot be explained by practice effects either, which arise when a patient is tested repeatedly, because the procedure of the Complex Figure Test allows checking the figure frequently, and visual memory was severely impaired on the preoperative test session; the Stroop Color-Word Test and Motor Planning Test included practice trials at both test sessions. However, it remains open whether the improvement is due to CEA or to natural recovery from the stroke EB suffered several weeks before the surgical operation.

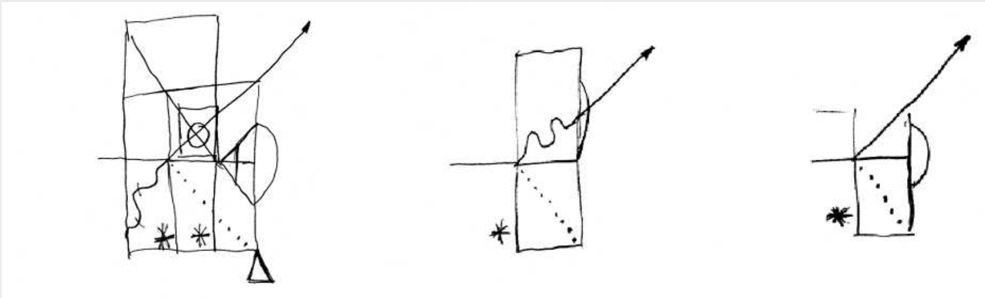

Fig 1. Copy and immediate and delayed recall of the Complex Figure Test before CEA.

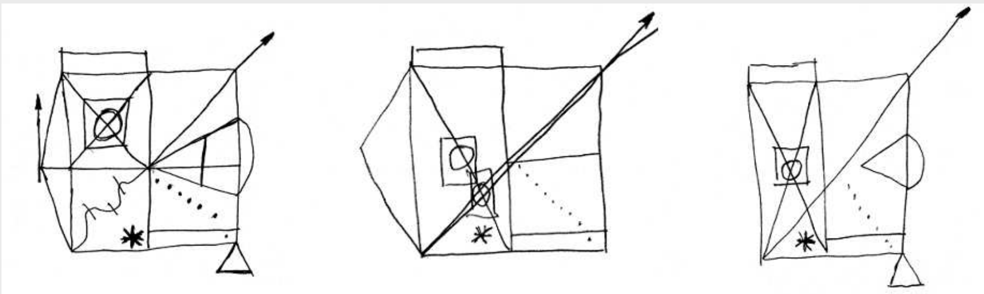

Fig 2. Copy and immediate and delayed recall of the Complex Figure Test 3 months after CEA.

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Chapter 2

Cognitive impairment in carotid artery disease before endarterectomy

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Abstract

Restorative effects of carotid endarterectomy (CEA) on cognitive functioning in patients with severe atherosclerotic disease presuppose the existence of cognitive deficits prior to the intervention. Thorough examination of this premise received only minor attention. The present study assessed symptomatic and asymptomatic patients with severe unilateral or bilateral stenosis of the carotid arteries one day before CEA. Healthy volunteers with similar demographic characteristics served as control subjects. Patients overall showed decreased functioning on tests of attention, verbal and visual memory, verbal fluency, and psychomotor speed and executive functioning, even after correction for the effects of mood. Simple motor skills and visuospatial functioning were not affected. Patients grouped according to the presence and type of previous clinical symptoms and to the severity of the contralateral stenosis only slightly differed from each other. The findings leave open the potential of improving cognitive function after CEA.

Introduction

CEA has become a routine surgical procedure for the prevention of stroke by removing atherosclerotic plaque from the intima of the carotid artery. Its preventive value has been demonstrated especially in symptomatic patients with a severe stenosis (Rothwell et al., 2003). Neuropsychologists have frequently considered the possible beneficial function of CEA on cognitive performance (Lunn, Crawley, Harrison, Brown, & Newman, 1999; Irvine, Gardner, Davies, & Lamont, 1998). An improvement in blood flow to ischemic cerebral regions and a reduction in embolic events have been proposed as mechanisms underlying cognitive improvement (Kishikawa et al., 2003; Baird & Pieroth, 2001).

Postoperative improvement in cognitive functions presupposes the existence of cognitive impairment prior to the intervention. Thorough examination of this premise, however, received only minor attention. Of importance in this context are the selection of an appropriate control group and the distinction of subgroups of patients with respect to the presence and type of previous ischemic symptoms. A control group ideally should include healthy persons or patients without cerebrovascular or other vascular or neurological diseases. Subjects with peripheral arterial disease, for example, are not to be preferred as control subjects because stenoses of the peripheral and carotid arteries are often correlated (Cinà, Safar, Maggisano, Bailey, & Clase, 2002; Pilcher, Danaher, & Khaw, 2000; Cheng, Wu, Ting, Lau, & Wong, 1999; House et al., 1998).

In comparison to patients prior to lumbar spine injury, Heyer and colleagues (2002) observed a worse functioning before CEA in patients who suffered a transient ischemic attack or stroke on tests of conceptual and psychomotor tracking, perceptual and visuospatial organization, and verbal fluency. Patients without previous ischemic symptoms showed a reduced performance on a tracking task only (Heyer et al., 2002). Hamster and Diener (1984) found impairments in visual memory, attention under stress, and perceptuomotor functions compared to healthy persons. Patients with a history of stroke and those without previous ischemic symptoms did not differ in this study from patients had a transient ischemic attack. Relatively normal preoperative cognitive functioning has been described as well in patients with a history of transient ischemic attacks in comparison to healthy subjects (Iddon, Sahakian, & Kirkpatrick, 1997; Van den Burg, Van Zomeren, Boontje, Haaxma, & Wichmann, 1985) or to patients with unrelated disease (Boeke, 1981). One of these studies actually observed a slower motor reaction in their patients, but this disappeared after accounting for previous stroke (Van den Burg et al., 1985).

The previous investigations are thus inconclusive regarding the nature and degree of cognitive impairments in patients prior to CEA. This might be explained by factors such as the choice of cognitive tests, inadequate matching of control subjects on demographic characteristics, the timing of assessment, and the kind of analyses employed. Differences between the studies in the composition of their patient samples according to the presence or absence of previous ischemic symptoms and to the duration of these symptoms may be an explanation for the varying results as well. Even if patients with a history of stroke are excluded, the homogeneity of a symptomatic subgroup can be questioned. Patients who had retinal symptoms, for example, are certainly symptomatic in a clinical sense (European Carotid Surgery Trialists' Collaborative Group, 1998; North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991), but since the ophthalmic artery branches off right before entering the cerebral hemisphere, they might be regarded as *a*symptomatic with regard to the cerebral area. It is this area that is particularly referred to in neuropsychological examinations. None of the previous studies specified the location of the ischemic signs in their patients. Therefore, the risk of cognitive impairment in those atherosclerotic subjects who solely showed retinal symptoms is still unclear.

The present study evaluated a wide range of cognitive functions in patients with a severe stenosis of one or both carotid arteries one day before CEA. Healthy volunteers with similar demographic characteristics served as control subjects. In secondary analyses, patients were categorized according to the presence and type (hemispheric or retinal) of previous clinical symptoms and to the degree of the contralateral stenosis. Those with previous stroke were explicitly not included. Because mood effects of the upcoming operation might affect cognitive performance (Lunn et al., 1999; Irvine et al., 1998), we checked for its influence by including significant mood differences between groups as covariates in the analyses.

Methods

Subjects

Sixty-four patients with a severe stenosis (70-99%) of one or both carotid arteries were recruited from patients on a waiting list for unilateral CEA in the St. Antonius Hospital in Nieuwegein, the Netherlands. Those with a history of minor or major stroke (as became evident from their medical records) were excluded. Stenosis was asymptomatic in 23 patients and symptomatic in 41 patients; symptoms involved one or more episodes of hemispheric transient ischemic attack in 22 subjects and solely retinal transient ischemic symptoms in 19 subjects. The degree of carotid stenosis was assessed with duplex ultrasonography in accordance with the method of the NASCET (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991). Twenty-six patients had severe unilateral stenosis of the right and 18 patients of the left carotid artery; the degree of stenosis of the contralateral artery was less than 70% in these patients. Severe bilateral stenosis was observed in the remaining 20 patients (including 7 with an occlusion of the not to be operated artery). Three and 11 patients, respectively, had previously undergone ipsilateral or contralateral CEA. Most of these patients (2 and 8, respectively) were asymptomatic in the present study (which is not very surprising since these patients are carefully controlled after previous CEA).

The control group was composed of 44 healthy subjects. They were recruited by an advertisement in a local newspaper and received a small reward for their participation. On interviewing, none reported a history of cerebrovascular or psychiatric disease. The ethics committee of the hospital approved the study protocol. Written informed consent was obtained from all subjects. Characteristics of the patient group and the healthy control group are summarized in Table 1.

Table 1. Characteristics of patients (*n* = 64) and healthy control subjects (*n* = 44).

	Patients	Controls
Age, year, mean ± SD	65.3 ± 7.3	66.6 ± 4.6
Males	78%	80%
Middle or higher education	53%	50%
Hypertension	64%	11%
Hypercholesterolemia	55%	14%
Diabetes mellitus	14%	2%
Heart disease	52%	14%

Procedure and measures

Patients were examined in the hospital one day before CEA, the healthy control subjects in the department laboratory. At the start of the assessment, subjects were asked about their level of education, tobacco and alcohol use, and psychiatric and medical history. The medical questions concerned, among others, previous myocardial infarction and coronary artery surgery, and presence of other vascular risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus. Additional medical information was obtained from the medical records.

The neuropsychological test battery was administered by research assistants, trained to conduct and score these tests under supervision of an experienced neuropsychologist (E.R.B), and took about one hour to be completed. The battery evaluated a wide range of cognitive functions, including attention and working memory, verbal memory, visual memory, verbal fluency, psychomotor speed and executive functioning, pure motor functions, and visuospatial function.

Attention and working memory were assessed with Digit Span forward and backward (Lezak, 1995), and the sum score of the Dichotic Listening Test (Brand, Bossema, Van Ommen, Moll, & Ackerstaff, 2004). The Dichotic Listening Test measures the relative superiority of the right or left ear in recognizing three pairs of digits presented simultaneously to each ear through headphones. Twenty test trials were preceded by eight practice trials.

Verbal memory was examined with the visually presented Word Learning Test (Brand, Jolles, & Gispen-de Wied, 1992), which consists of an immediate recall of a list of 15 words (three trials), and a delayed recall and a recognition subtest after 15 minutes.

The Doors Test (Baddeley, Emslie, & Nimmo-Smith, 1994) judges *visual recognition memory*. Subjects have to recognize 12 memorized doors out of 12 pictures, each consisting of four doors. Part B is more difficult than part A because the doors in part B are more alike.

Verbal Fluency is measured by asking the subject to generate in one minute as many words as possible beginning with a certain letter ('N' and 'P') or belonging to a specific semantic category ('animals' and 'occupations') (Lezak, 1995).

Psychomotor speed and executive functioning were investigated with the Trail Making Test parts A and B (Lezak, 1995) and the Motor Planning Test (Brand, Van der Wijk, & Hijman, 1990). The Motor Planning Test distinguishes between planning of motor behavior and motor speed. The subject holds a start button on a button box until one of three other buttons is lit and then presses this target button, and immediately returns to the start button. Computer registered measures are the time lapse between onset of the light and release of the start button (planning time), and the time between releasing the start button and pressing the target button (movement time). The median times across 14 trials for both hands were averaged. These test trials were preceded by six practice trials for each hand.

The Finger Tapping Test (Lezak, 1995) measures *manual dexterity*: subjects press and release a button with both the dominant and nondominant index finger respectively as fast as possible in four series of a 10-second period. The first series of each hand was taken as a practice trial.

Visuospatial function was examined with the Line Orientation Test, which is based on Benton's Line-Orientation Task (Lezak, 1995). A series of 36 pairs of line segments are presented on a computer screen and the subject is asked to judge whether the lines are parallel or not by pressing a 'yes' or 'no' button on a button box. The median reaction time of the correct responses was recorded. Test trials were preceded by 10 practice trials.

The tests of Word Learning, Motor Planning, Finger Tapping, and Line Orientation were administered and (partly) scored using the software package of MINDS (Brand, 1999).

Before the start of the cognitive assessment, patients and healthy subjects completed the Dutch shortened Profile of Mood States (POMS) (Wald & Mellenbergh, 1990). This 32-item scale covers five different mood dimensions: anger, tension, depression, vigor, and fatigue.

Statistical analysis

Patients and healthy control subjects and subgroups of patients were compared on age (univariate analysis of variance, ANOVA), sex ratio, and educational level (χ^2 test); patient subgroups were formed on the basis of the presence and type of ischemic symptoms (hemispheric or retinal) and the degree of contralateral stenosis (less than 70% versus equal to or more than 70%). Differences in cognitive test scores between groups were analyzed with multivariate and univariate analysis of variance (MANOVA and ANOVA). This analysis assumes equality of group variances, which we checked with the Levene statistic. Differences between subgroups of patients (according to previous symptoms), and between these subgroups and healthy control subjects, were further analyzed with multiple post hoc comparisons using the Bonferroni correction. The possible influence of medical risk variables was investigated in the same way. We corrected for significant differences in mood scores by entering these as covariates in the analyses (MANCOVA and ANCOVA). The alpha significance level was set on $p = .05$.

Results

Patients and healthy control subjects were comparable in age ($F(1,106) = 1.07$, $p = .304$), sex ratio ($\chi^2(1) = 0.03$, $p = .859$), and educational level ($\chi^2(1) = 0.10$, $p = .749$). As expected, the patient group included much more subjects with vascular risk factors (such as hypertension, hypercholesterolemia, diabetes mellitus, and heart disease) than the healthy control group. When comparing the two groups on the cognitive tests, a significant overall group effect was demonstrated ($F(17,90) = 7.02$, $p < .001$)[1]. Differences were significant on 9 of the 17 separate test variables

[1] Missing values on the Dichotic Listening Test (11 patients, 4 healthy subjects), as a result of serious hearing problems, were imputed for patients

(Table 2), including tests of attention (Digit Span forward), delayed verbal memory (Word Learning Test), visual memory (Doors Test A and B), verbal fluency (letters and categories), and psychomotor speed and executive functioning (Trail Making Test A and B, Motor Planning Test planning time). Patients performed worse than healthy subjects on all these tasks. Levene statistic revealed unequal group variances on the Doors Test B, and Trail Making Test. However, accounting for this did not change the results.

Table 2. Comparison of neuropsychological performance (mean ± SD) of patients and healthy control subjects.

	Patients	Controls	*F*	*p*
Digit Span forward	5.4 ± 1.0	6.0 ± 1.2	8.39	.005
Digit Span backward	4.1 ± 1.1	4.2 ± 1.5	0.13	.722
Dichotic Listening	77.4 ± 11.9	79.0 ± 11.9	0.43	.514
Word Learning immediate recall	20.7 ± 5.5	22.2 ± 6.2	1.75	.189
Word Learning delayed recall	6.2 ± 2.6	7.5 ± 3.1	6.00	.016
Word Learning recognition	24.9 ± 2.3	25.8 ± 2.4	3.50	.064
Doors A	9.7 ± 1.4	10.6 ± 1.4	10.49	.002
Doors B	5.2 ± 1.9	7.2 ± 2.4	19.16	<.001
Verbal Fluency letter	11.7 ± 4.2	13.9 ± 4.8	6.69	.011
Verbal Fluency categories	16.8 ± 4.4	20.3 ± 4.0	17.51	<.001
Trail Making A (s)	43.7 ± 17.7	34.9 ± 9.5	9.09	.003
Trail Making B (s)	102.5 ± 37.4	81.4 ± 27.7	10.11	.002
Motor Planning planning (ms)	469 ± 78	398 ± 65	24.56	<.001
Motor Planning movement (ms)	170 ± 53	170 ± 47	<0.01	>.999
Finger Tapping dominant hand	54.7 ± 9.6	51.9 ± 8.9	2.40	.125
Finger Tapping nondominant hand	49.9 ± 9.9	47.9 ± 8.9	1.39	.288
Line Orientation (ms)	840 ± 194	850 ± 199	0.06	.803

Asymptomatic patients and those with hemispheric or retinal transient ischemic symptoms did not differ from each other in age ($F(2,61) = 1.23$, $p = .298$), sex ratio ($\chi^2(2) = 0.40$, $p = .821$), and educational level ($\chi^2(2) = 1.84$, $p = .399$). Figure 1 shows the performances of the three subgroups as standardized deviations from the healthy control group (i.e. the difference between the mean score of the particular patient group and of the healthy control group divided by the standard deviation of the healthy control group). Significant deviations are marked with asterisks. As can be seen, patients with hemispheric and retinal symptoms were impaired on more tests than patients without previous ischemic symptoms.

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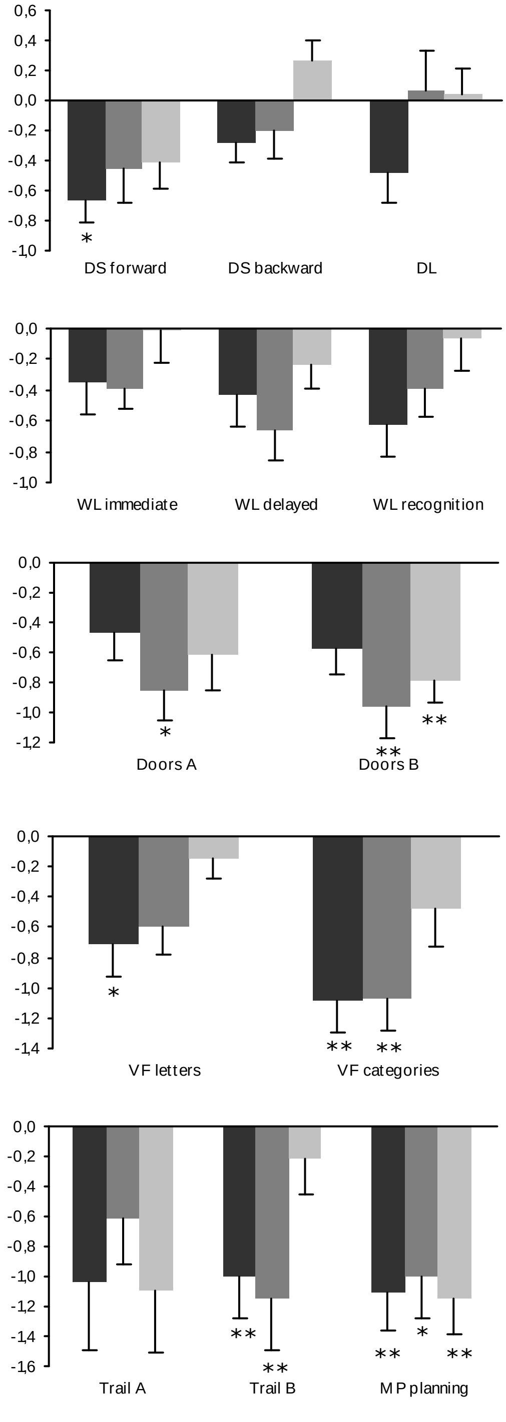
and healthy subjects separately by using linear regression analysis on the basis of related variables and an additive error term (Streiner, 2002). Missing scores on the Trail Making Test B (3 patients), due to difficulty with the test, were replaced by arbitrary high scores. Post-hoc ANOVA on the data without these corrections did not change the pattern of the statistical outcomes.


0,6
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DS forward
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Doors A
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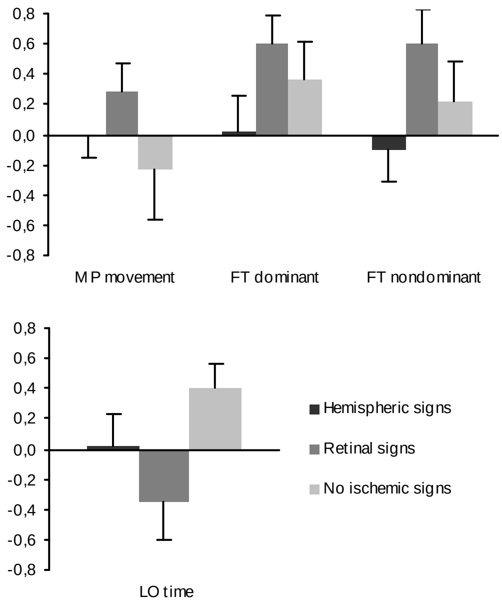
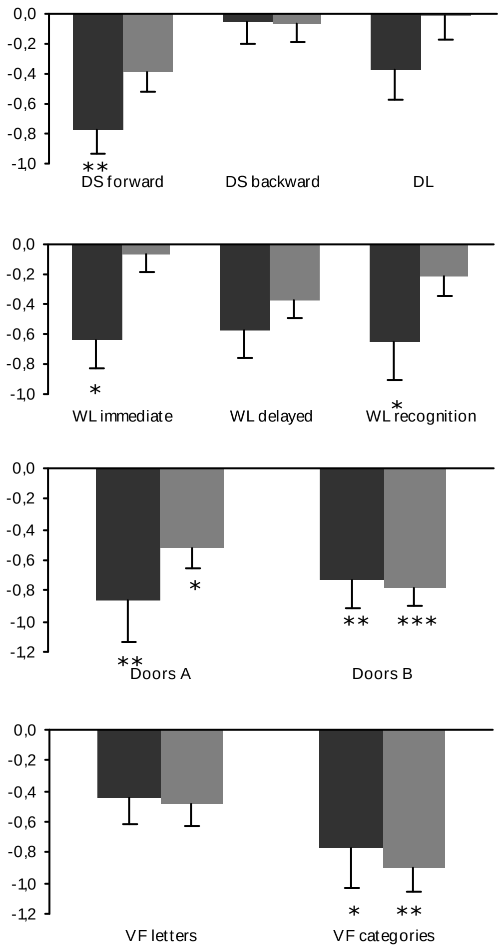


Fig 1. Cognitive performances (expressed as standardized deviations) of asymptomatic patients and patients who suffered a hemispheric or retinal transient ischemic attack compared to healthy subjects. DS = Digit Span; DL = Dichotic Listening; WL = Word Learning; VF = Verbal Fluency; Trail = Trail Making; MP = Motor Planning; FT = Finger Tapping; LO = Line Orientation. Patient subgroup versus healthy control group: * $p < .05$, ** $p < .01$.

In the mutual comparison of the three subgroups, a significant overall group effect was observed ($F(34,92) = 1.59$, $p = .042$). Only three of the individual tasks discriminated between the subgroups, namely the tests assessing working memory (Digit Span backward, $F(2,61) = 3.69$, $p = .031$), executive functioning (Trail Making Test B, $F(2,61) = 3.27$, $p = .045$), and visuospatial function (Line Orientation Test, $F(2,61) = 3.39$, $p = .040$). Post-hoc analyses showed that patients with hemispheric symptoms performed significantly worse than asymptomatic patients on Digit Span backward ($p = .042$), whereas patients who showed retinal symptoms had a significantly longer reaction time on the Line Orientation Test than patients without ischemic symptoms ($p = .035$). Mean scores on exactly these two tests were somewhat (but not significantly) better for asymptomatic patients than for healthy subjects.

No differences existed between patients with severe unilateral or bilateral stenosis in age ($F(1,62) = 0.20$, $p = .889$), sex ratio ($\chi^2(1) = 0.06$, $p = .807$), and educational level ($\chi^2(1) = 0.11$, $p = .736$). The two subgroups did not differ in presence or type of previous ischemic symptoms either ($\chi^2(2) = 2.68$, $p = .262$). Their performances are shown in Figure 2 as standardized deviations from the healthy control group. Impairments on a number of tests were shown in both subgroups. In mutual comparison, patients with severe bilateral disease of the carotid arteries performed overall significantly worse than patients with severe unilateral disease ($F(17,46) = 1.94$, $p = .038$). There was just one discriminating test variable, namely the immediate recall of the Word Learning Test ($F(1,62) = 6.31$, $p = .015$); patients with severe stenosis of both carotid arteries performed worse than those with a lesser degree of contralateral stenosis.



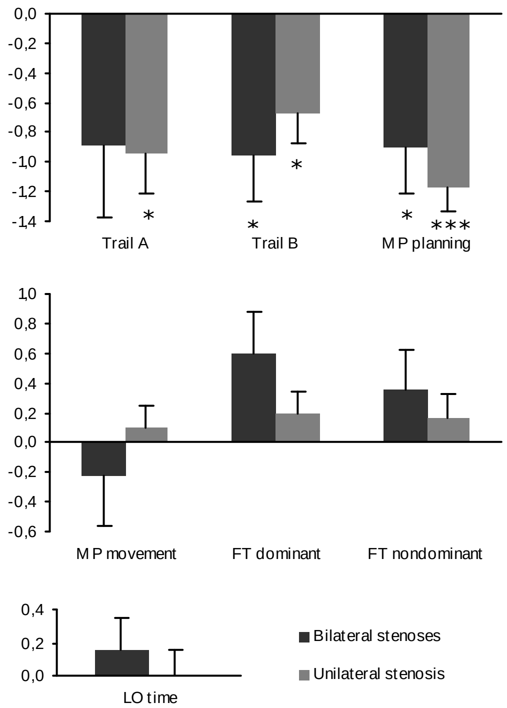


Fig 2. Cognitive performances (expressed as standardized deviations) of patients with severe bilateral or unilateral stenosis of the carotid artery compared to healthy subjects. DS = Digit Span; DL = Dichotic Listening; WL = Word Learning; VF = Verbal Fluency; Trail = Trail Making; MP = Motor Planning; FT= Finger Tapping; LO = Line Orientation. Patient subgroup versus healthy control group: * $p < .05$, ** $p < .01$, *** $p < .001$.

Seven of the patients with severe unilateral stenosis at present had previously undergone contralateral CEA. Classifying these subjects as bilateral patients barely changed the overall difference between the unilateral and bilateral subgroup ($F(17,46) = 1.91$, $p = .041$), but increased the differences on the individual tests somewhat, so that these became significant also on the DS forward ($F(1,62) = 5.58$, $p = .021$) and the recognition trial of the Word Learning Test ($F(1,62) = 6.48$, $p = .013$).

Further analyses revealed that none of the medical risk factors (presence of hypertension, hypercholesterolemia, diabetes mellitus, or heart disease) was consistently associated with the cognitive performances of patients.

Patients had significantly higher scores than healthy control subjects on scales of depression, fatigue, and tension, and a significantly lower score on the vigor scale (Table 3). Correction for these differences only slightly reduced the overall group effect in cognitive functioning ($F(17,85) = 6.76$, $p < .001$) and the difference on one of the individual tests (Trail Making Test

A, $F(1,101) = 5.29$, $p = .024$). There were no significant mood differences between any of the subgroups of patients.

Table 3. Comparison of mood states (mean ± SD) in patients and healthy control subjects.

	Patients	Controls	*F*	*p*
Anger	3.6 ± 5.2	3.5 ± 3.4	0.01	.931
Depression	3.7 ± 5.5	1.5 ± 2.5	6.27	.014
Tension	6.9 ± 5.8	4.1 ± 3.4	7.94	.006
Fatigue	4.5 ± 5.2	2.0 ± 2.7	8.23	.005
Vigor	11.4 ± 4.0	14.8 ± 3.1	22.51	<.001

Discussion

It was found that patients with a severe stenosis of one or both carotid arteries but without apparent evidence of brain damage have impaired cognitive functioning, even if preoperative mood is taken into account. The impairments were present in the domains of attention, verbal and visual memory, verbal fluency, psychomotor speed, and executive functioning. Simple motor skills and visuospatial performance were intact and imply that the impairments on the other cognitive tasks cannot be explained by a reduced motor speed of patients. The findings of our study are largely in agreement with earlier reports, in which particularly reductions in verbal and visual memory, executive functioning, and psychomotor skills before CEA were detected (Hamster & Diener, 1984; Hemmingsen et al., 1986; Parker, Smarr, Granberg, Nichols, & Hewett, 1986). A more recent study found a reduced performance on approximately the same tests of verbal fluency and psychomotor function, but also on a visuospatial task (Heyer et al., 2002). The latter task, however, involved the copy of a complex figure and relied more on typical visuoconstructive skills than our relatively simple task of comparing the slopes of two lines.

We hypothesized that the risk of cognitive impairment would differ for various clinical subgroups. Patients with bilateral stenosis indeed seemed to have a somewhat worse cognitive performance than patients with unilateral stenosis, but the differences were marginal. Inadequate cerebral blood circulation thus seems to play only a minor role. Future research is necessary to establish whether the cognitive problems that we observed can be reversed by CEA, thus demonstrating the role of reinstatement of adequate brain perfusion on cognitive performance.

In agreement with the findings of Heyer et al. (2002), patients with previous hemispheric or retinal transient ischemic attacks were impaired (if compared to the healthy controls) on a higher number of tests than those without previous ischemic symptoms. However, mutual comparison of the three subgroups of patients showed significant differences on just 3 out of the 17 test variables. Moreover, these were largely due the fact that the asymptomatic patients even performed slightly (but certainly not significantly) *better* than healthy control subjects. Hamster and Diener (1984) noticed no differences between patients with and without ischemic symptoms either, but they did not discriminate between those with retinal or hemispheric signs. Nevertheless, despite some differences, our findings do not clearly support the necessity of a distinction of clinical subgroups.

We deliberately did not include patients with a history of stroke, to reduce the possibility that substantial brain damage would account for the cognitive impairment. Although several studies reported no differences between patients with either a transient ischemic attack or stroke (Hamster & Diener, 1984; Hemmingsen, Mejsholm, Boysen, & Engell, 1982; Mononen, Lepojärvi, & Kallanranta, 1990; Vanninen et al., 1996), worse cognitive function in stroke patients compared to patients with transient ischemic symptoms has been noted as well (Rao, Jackson, & Howard, 1999; Van den Burg et al., 1985). Because we did not assess signs of brain damage with imaging techniques, it remains unclear to what extent the cognitive decline in our study can be attributed to small infarcts or other brain abnormalities, such as atrophy or paraventricular white matter lesions (De Groot et al., 2002; Mungas et al., 2002; O'Brien et al., 2003).

Within our patient group, we observed no effect of various vascular risk factors, such as hypertension and diabetes mellitus, on cognition. However, our observation does not refute a possible influence of these variables on cognitive functioning (Knopman et al., 2001). In addition, antithrombic, antihypertensive, and other medications may have affected neuropsychological performance (Waldstein & Elias, 2001).

Overall, patients compared to healthy control subjects showed less vigor and more tension, fatigue and depression. Correction for these differences did not affect differences in task performance. Nevertheless, because mood may affect the motivation and energy of subjects to perform tasks to the best, examination of the influence of stress factors on cognitive performance is always recommended to avoid overestimation of cognitive defects.

In conclusion, atherosclerotic patients with severe occlusive disease of one or both carotid arteries, but without history of stroke, are impaired in several cognitive functions. Patients who suffered hemispheric or retinal transient ischemic symptoms differed only marginally from those with an asymptomatic history. The findings leave open the potential of improving function after CEA.

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Chapter 3

Does carotid endarterectomy improve cognitive functioning?

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Abstract

Background: Carotid endarterectomy (CEA) might improve cognitive functioning, but studies thus far have produced mixed results. The aim of the present study was to examine the effect of CEA on cognitive functions in a methodological more strict design: first by testing the presumption of preoperative cognitive impairment and second by a better control for the possible influence of nonspecific effects of practice and surgery. *Methods:* Preoperative performance on a neuropsychological test battery of 56 patients with severe occlusive disease of the carotid artery, but without history of major stroke, was compared to the performance of 46 healthy control subjects, and 23 patients before endarterectomy of the superficial femoral artery (remote endarterectomy). The degree of cognitive change in the two patient groups was compared at 3 and 12 months postoperatively. We assessed mood to control for possible momentary affective influences on cognition. *Results:* Before CEA, patients showed reduced functioning compared with that seen in healthy control subjects in terms of attention, verbal and visual memory, planning of motor behavior, psychomotor skills, and executive function. Performance of patients before remote endarterectomy was reduced as well. Improvements in several cognitive functions were observed after *both* types of surgical interventions, and were attributed to psychologic relief from uncomplicated surgery and to practice. *Conclusions:* No specific restorative effect of CEA on cognitive functioning was observed. The preoperative impairment in several cognitive domains might be caused by factors that patients with various types of vascular disease may have in common, such as small-vessel disease or other undetected abnormalities within the brain.

Introduction

Carotid endarterectomy (CEA) has become a routine surgical procedure for the prevention of stroke in patients with atherosclerotic disease in the carotid arteries.[1-3] Neuropsychologists have frequently considered the possible beneficial function of CEA on cognition.[4,5] They propose recovery from repeated embolic episodes and restoration of adequate blood flow to the brain as underlying mechanisms for cognitive improvement.[6,7] However, two essential methodological issues have often been ignored in research on this topic. One is that the existence of cognitive deficits before the intervention should be ascertained first to assess the room for improvement after the procedure. This can be established by comparing the preoperative cognitive functions of patients to the performance of healthy subjects. A second demand is the correction of cognitive changes for positive effects from practice caused by repeated testing and perhaps from psychologic relief after (uncomplicated) surgery, *as well as* controlling for the possible negative influences of surgery and anesthesia on cognitive outcome.

Therefore, the current study also included vascular patients undergoing peripheral vascular surgery (of their legs) as a control group to overcome these nonspecific effects.

An additional complicating factor in previous research concerns the inclusion of patients with a history of (major) stroke. Improvement after CEA in these patients may be attributed to recovery from the neurological lesion,[8-10] whereas an explanation for a failure to find improvement can be the existence of permanent neurological damage[8,11,12] Because of problems in the interpretation of the results in this subgroup, and the risk of influencing the overall cognitive outcome, exclusion of these patients in neuropsychologic assessment seems to be the best option to reliably assess the unique contribution of restored blood flow to the brain.

The present prospective study was aimed at examining the possible improvement in cognitive functioning caused by CEA, taking into account the potentially confounding factors as summarized. We also considered the possible effect of (changes in) mood on test performance. We expected that patients with carotid artery disease (before CEA) would have worse cognitive functioning than healthy subjects and that patients after CEA improve more than patients after remote endarterectomy (REA).

Subjects and methods

Sixty patients with severe stenosis (≥70% as assessed with duplex ultrasonography) of one or both carotid arteries were recruited between September 2000 and December 2002 from patients on a waiting list for CEA in the St. Antonius Hospital in Nieuwegein, the Netherlands. Patients were only included if they had no history of major stroke. A surgical control group (without a history of stroke) was composed of 23 patients with symptomatic femoropopliteal occlusive disease who were going to have endarterectomy of the superficial femoral artery through a single groin incision with the so-called ring-strip cutter device.[13] This REA is highly comparable to CEA with respect to duration, anesthesia, and expected recovery time. Similarities also exist in the medical background of the patients. A healthy control group consisted of 46 subjects without any evidence of cerebrovascular or neurological disease or a psychiatric history. They were recruited by an advertisement in a local newspaper and received a small financial reward for their participation. The ethics committee of the hospital approved the study protocol and written informed consent was obtained from all subjects.

Patients were examined in the hospital 1 day before surgery, and 3 months and 1 year postoperatively, and healthy controls only once in the department laboratory. At the start of the first assessment, subjects were asked about their level of education, tobacco and alcohol use, and psychiatric and medical history. The medical questions concerned, among others, previous myocardial infarction or coronary artery surgery and the presence of other vascular risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus. Additional medical information of patients was obtained from the medical records. Educational level was categorized according to the 7-point ranking system of Verhage.[14] This system reflects the educational system in the Netherlands and has the advantage that it also takes uncompleted education into account. A subject was classified as a smoker if he was a current cigarette smoker or quit cigarette smoking in the year before the first assessment. Subjects subsequently filled out the Edinburgh Handedness Inventory[15] and the Dutch shortened Profile of Mood States.[16] The Profile of Mood States consists of 32 items covering five different mood dimensions: anger, tension, depression, vigor, and fatigue.

A neuropsychologic battery of about 1 hour was administered. The tests, the cognitive domains that were covered, and the variables that were derived from the tests are described in Table 1. In the Digit Span[17] increasing sequences of numbers have to be repeated in the same or reversed order as they were presented auditorily. The Word Learning Test[18] is based on the more familiar Rey Auditory Verbal Learning Test[19] and requires the subject to learn a list of 15 monosyllabic words and subsequently retrieve them from memory. The words refer to concrete objects and are displayed on a computer screen to standardize presentation. Alternative but parallel versions are used at random between subjects and across sessions (with the restriction, of course, that no one received a version twice). In the Doors Test[20] the subject is asked to memorize a series of 12 colored photographs of doors. The subject then has to recognize the memorized door among three other distracting doors fitting the same general label (e.g., 'church door'). There are two series; series B is more difficult than series A because the doors in series B are still more alike. In the Verbal Fluency Test[18] the subject has to generate as many words as possible within 1 minute, beginning with a specified letter ('N' and 'P') or

Table 1. Cognitive test battery.

Test	Cognitive domain	Test variable
Digit Span	Attention and verbal working memory	Number in same order Number in reversed order
Word Learning Test	Verbal memory: learning and retrieval	Total score trial 1-3 Delayed recall score
Doors Test	Visual memory: recognition	Total score series A Total score series B
Verbal Fluency	Executive functioning	Number of letter words Number of category words
Trail Making Test	Psychomotor speed and executive functioning	Time part A, s Time part B, s
Motor Planning Test	Planning and movement speed	Planning time, ms Movement time, ms
Finger Tapping Test	Motor capacity	Number dominant hand Number nondominant hand

belonging to a specific semantic category ('Animals' and 'Occupations'). The scores of the two letter and category trials, respectively, were averaged. The Trail Making Test[18] requires the subject to connect consecutive numbers as fast as possible (part A), and then alternate between numbers and letters (part B). In the Motor Planning Test,[21] which is a motor choice reaction-time test, the subject holds a start button on a button box until one of three other buttons is lit, then presses this target button, and immediately returns to the start button. The time between light onset and release of the start button is the planning time, and the time between releasing the start button and pressing the target button is the movement time (average of both hands). In the Finger Tapping Test[18] the subject has to press and release a button on a button box with the index finger as fast as possible during a 10-second period. Test trials of the latter three tests are preceded by practice trials. The Word Learning Test and Motor Planning Test were administered and (partly) scored using the software package of MINDS.[22]

Characteristics of the groups were compared with univariate analyses of variance (ANOVA; age, handedness), the Kruskal-Wallis Test (educational level), and the χ^2 test (sex ratio and the presence of vascular risk factors). Incidental missing values on the Motor Planning Test and Finger Tapping Test caused by technical problems in the second or third test assessment were imputed by means of the Expectation-Maximization estimation method. This method predicts a missing value by using all the information in the available data.[23] Post hoc ANOVA on the data without these corrections did not change the statistical outcomes. To examine the pattern and degree of cognitive impairment before surgery, patients were compared with healthy control subjects by using ANOVA and multiple post hoc comparisons (among the three groups) with the Bonferroni correction. The effect of the type of surgery on each cognitive test variable was assessed with 2 (Type of surgery: CEA or REA) by 3 (Time of assessment: I, II, or III) ANOVA with Time of assessment as a repeated measures factor. This design produces main effects for Type of surgery and Time of assessment, and an interaction effect for the interaction between these two variables. The interaction effect indicates whether one group improves (or declines) more than the other across time. Because the design includes more than two assessment times, in case of a significant overall time effect (i.e., across all three assessments), the contrasts between specific times were analyzed post hoc. Furthermore, we corrected for significant group differences in mood (change) scores by entering these as covariates in the analyses. Two-sided P values of less than .05 were considered significant.

Results

Three patients who underwent CEA were lost after the first assessment because they considered the measurement to be too difficult or fatiguing, and one patient did not complete the final assessment because of severe disease unrelated to atherosclerosis. Another patient was excluded because of temporary hemiparesis immediately after the operation. Of the 56 remaining patients who underwent CEA, 34 had one or more retinal or hemispheric transient ischemic attacks, and two had a minor stroke. Twenty-nine patients underwent operations on the right carotid artery, and 27 underwent operations on the left carotid artery. Contralateral stenosis was less than 50% in 30 patients, between 50% and 69% in 12 patients, and between 70% and 99% in 9 patients; a contralateral occlusion was found in 5 patients. For logistic reasons the degree of carotid artery stenosis in the patients undergoing REA was not assessed.

Characteristics of both patient groups and of the healthy control group are summarized in Table 2. There were no differences in age, educational level, sex ratio, and left versus right handedness. As expected, the patient groups included much more subjects with heart disease and vascular risk factors (e.g., cigarette smoking, hypertension, hypercholesterolemia, and diabetes mellitus) than the healthy control group.

Table 2. Characteristics of patients undergoing CEA or REA and of healthy subjects.

	CEA patients	REA patients	Healthy subjects	*P* value
Age, y, mean ± SD	66.2 ± 7.2	65.6 ± 8.0	66.7 ± 4.5	.80
Males, %	84	87	80	.78
Middle or higher education, %	50	52	50	.50
Right handedness, %	86	91	89	.81
Heart disease, %	52	70	13	<.001
Hypertension, %	65	57	13	<.001
Hypercholesterolemia, %	52	65	13	<.001
Cigarette smoking, %	32	30	11	.08
Diabetes mellitus, %	14	17	2	.07

CEA, carotid endarterectomy; *REA*, remote endarterectomy.

Mean cognitive performance on the first assessment of both types of patients and of healthy control subjects are shown in Table 3. Significant overall group differences were noticed in attention (Digit Span forward), verbal memory (Word Learning Test delayed recall), visual memory (Doors A and B), planning of motor behavior (Motor Planning Test planning time), psychomotor skills (Trail Making Test A), and executive functioning (Trail Making Test B, Verbal Fluency Test letters and categories; Table 3). Post hoc comparisons with Bonferroni correction showed that patients before CEA performed significantly worse than healthy control subjects on all of these variables, whereas patients before REA had an impaired performance compared with that of healthy control subjects only on the Doors Test B, Motor Planning Test planning time, and Verbal Fluency categories. Differences between the two patient groups before surgery, however, never reached significance. The significant post hoc comparisons are shown in the final column of Table 3.

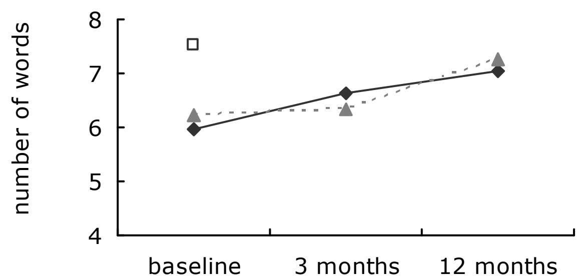
Table 3. Cognitive performance (mean ± SD) of patients before CEA or REA and of healthy control subjects.

	Healthy subjects	CEA patients	REA patients	*P* value	Post hoc test
DS forward	6.0 ± 1.2	5.4 ± 0.9	5.5 ± 1.1	.03	C<H
DS backward	4.2 ± 1.5	4.1 ± 1.1	4.4 ± 1.0	.79	
WL total score	22.2 ± 6.1	20.3 ± 5.5	20.9 ± 4.9	.23	
WL delayed score	7.5 ± 3.1	6.0 ± 2.6	6.2 ± 2.5	.02	C<H
DT A	10.6 ± 1.4	9.6 ± 1.4	9.7 ± 2.0	.004	C<H
DT B	7.1 ± 2.3	5.1 ± 2.0	5.3 ± 1.8	<.001	C,R<H
VF letters	14.0 ± 4.9	11.7 ± 4.1	12.2 ± 3.9	.02	C,R<H
VF categories	20.2 ± 4.0	16.8 ± 4.2	16.9 ± 4.1	<.001	C<H
TM A	35.1 ± 9.4	43.9 ± 15.4	42.2 ± 13.9	.004	C<H
TM B	81.3 ± 24.5	98.9 ± 33.2	96.4 ± 37.5	.02	C<H
MP planning	402 ± 60	468 ± 67	487 ± 70	<.001	C,R<H
MP movement	168 ± 41	167 ±45	172 ± 38	.90	
FT dominant	51.7 ± 8.9	54.5 ± 9.2	52.8 ± 11.6	.32	
FT nondominant	47.7 ± 8.9	49.9 ± 9.8	48.6 ± 10.2	.49	

P values indicate the significance of group differences. The post hoc test reflects *which* of the three groups differ significantly from each other ($P < .05$). *CEA*, carotid endarterectomy; *REA*, remote endarterectomy; *DS*, Digit Span; *WL*, Word Learning Test; *DT*, Doors Test; *VF*, Verbal Fluency; *TM*, Trail Making Test; *MP*, Motor Planning Test; *FT*, Finger Tapping Test; *C*, patients before CEA; *R*, patients before REA; *H*, healthy control subjects.

Cognitive performance of patients before and at 3 months and 1 year after CEA or REA are displayed in Table 4. Significant improvements up to 1 year were demonstrated for the retrieval of verbal material (Word Learning Test delayed recall), one test of executive functioning (Trail Making Test B), planning speed of movement (Motor Planning Test), and Finger Tapping with the dominant hand. These improvements are visualized in Figure 1; the time contrasts are given in the final column of Table 4. However, no significant effects of the Type of surgery or the interaction between Type of surgery and Time of assessment were observed for any of the cognitive tests (*P* values ranged from .13 to .93 and from .30 to .93, respectively). This means that the cognitive performances of the two patient groups did not differ from each other across time and that the CEA group did not improve

(a)



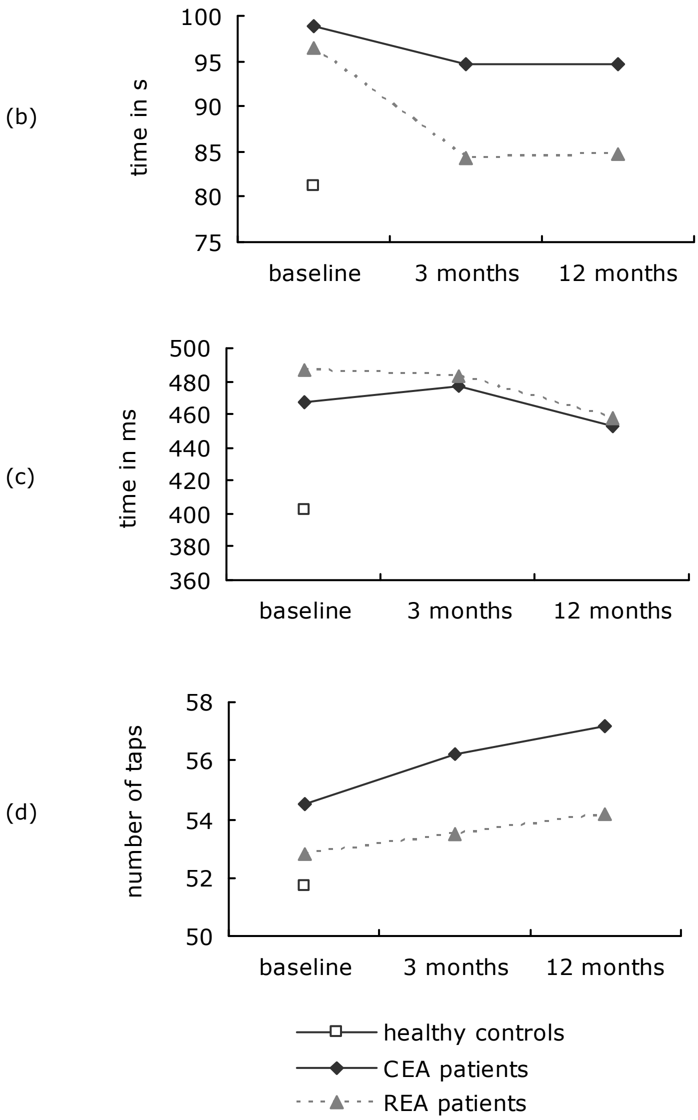


Fig 1. Performances of healthy control subjects, and of patients before (baseline) and at 3 and 12 months after CEA or REA on the (a) Word Learning Test delayed recall, (b) Trail Making Test part B, (c) Motor Planning Test planning, and (d) Finger Tapping Test dominant hand. Only the time effect (across the two groups) on each of these tests was significant.

Table 4. Cognitive performances (mean ± SD) of patients before and at 3 and 12 months after CEA or REA.

	CEA patients			REA patients			*P* value	Post hoc
	Before	3 months	12 months	Before	3 months	12 months	(Time)	contrast
DS forward	5.4 ± 0.9	5.6 ± 1.1	5.6 ± 0.9	5.5 ± 1.1	5.8 ± 1.0	5.7 ± 1.2	.12	
DS backward	4.1 ± 1.1	4.0 ± 1.1	3.9 ± 1.0	4.4 ± 1.0	4.2 ± 0.9	4.5 ± 1.2	.44	
WL total	20.3 ± 5.5	21.0 ± 5.6	22.0 ± 5.9	20.9 ± 4.9	21.8 ± 6.0	22.3 ± 5.5	.06	
WL delayed	6.0 ± 2.6	6.6 ± 2.6	7.1 ± 2.6	6.2 ± 2.5	6.3 ± 2.7	7.3 ± 3.0	.001	I,II<III
DT A	9.6 ± 1.4	9.7 ± 1.5	9.9 ± 1.4	9.7 ± 2.0	10.0 ± 1.5	10.2 ± 1.2	.15	
DT B	5.1 ± 2.0	5.5 ± 2.2	5.8 ± 2.2	5.3 ± 1.8	5.6 ± 2.0	6.2 ± 1.8	.06	
VF letters	11.7 ± 4.1	11.8 ± 4.5	11.9 ± 4.3	12.2 ± 3.9	13.0 ± 4.0	13.5 ± 5.2	.09	
VF categories	16.8 ± 4.2	17.4 ± 4.4	17.4 ± 4.3	16.9 ± 4.1	16.7 ± 4.2	17.7 ± 4.4	.12	
TM A	43.9 ± 15.4	42.5 ± 13.7	42.8 ± 14.1	42.2 ± 13.9	39.2 ± 11.3	36.6 ± 10.9	.11	
TM B	98.9 ± 33.2	94.7 ± 36.7	94.6 ± 34.8	96.4 ± 37.5	84.4 ± 27.7	83.8 ± 30.6	.008	I<II,III
MP planning	468 ± 67	477 ± 69	454 ± 71	487 ± 70	483 ± 77	458 ± 66	.02	I,II<III
MP movement	167 ± 45	172 ± 44	177 ± 51	172 ±38	181 ± 51	180 ± 43	.07	
FT dominant	54.5 ± 9.2	56.2 ± 7.2	57.2 ± 8.7	52.8 ± 11.6	53.5 ± 12.7	54.2 ± 10.7	.04	I<III
FT nondominant	49.9 ± 9.8	51.8 ± 8.4	52.1 ± 10.1	48.6 ± 10.2	49.3 ± 10.8	49.4 ± 9.7	.07	

P values indicate the significance of time differences (across both patient groups). The post hoc contrasts reflect *when* exactly the time differences became significant ($P < .05$). *CEA*, carotid endarterectomy; *REA*, remote endarterectomy; *DS*, Digit Span; *WL*, Word Learning Test; *DT*, Doors Test; *VF*, Verbal Fluency; *TM*, Trail Making Test; *MP*, Motor Planning Test; *FT*, Finger Tapping Test; *I*, preoperative assessment; *II*, assessment at 3 months postoperatively; *III*, assessment at 12 months postoperatively.

more than the REA group on the tests. The expected *specific* effect (i.e., after correcting the practice effects for *nonspecific* surgical effects) of CEA on cognitive functioning thus could not be demonstrated.

With respect to the five mood factors, patients before CEA reported less vigor than healthy control subjects ($P < .001$), and patients before REA noticed less vigor ($P < .001$) and more fatigue ($P = .01$) compared with healthy control subjects. Correction for these differences in the statistical analyses only slightly weakened the preoperative differences in cognitive functioning. Patients after both CEA and REA reported a significant decrease in tension ($P \leq .001$). Correction for this change (preoperative minus postoperative score at 1 year) only reduced the time effect that was observed on the Motor Planning Test, so that the effect on this variable was no longer significant ($P = .46$).

Discussion

The prophylactic effect of CEA against stroke has been established indisputably in large randomized trials.[1-3] Disagreement still exists, however, with respect to the possible restorative role of the operation on cognitive functioning.[4,5] The aim of the present study was to investigate this role by taking into account several potentially confounding factors.

Cognitive restoration presumes the existence of preoperative cognitive impairment, but previous studies often failed to verify this. In comparison with a healthy control group, we indeed observed reduced performance before CEA in terms of attention, verbal and visual memory, planning of motor behavior, psychomotor skills, and executive functions. Patients with peripheral vascular disease performed very similarly. Although the CEA group differed significantly from the healthy control group on a larger number of tests than the REA group, inspection of the means showed that this is due to the difference in power of these comparisons (smaller sample size in the REA group). The contrast between both patient groups and healthy controls persisted after correction for differences in vigor and fatigue. Simple motor skills were intact in all patients, however, indicating that the impairments on the other cognitive tasks cannot be explained by a reduced motor speed of the patients. The findings are largely in agreement with some earlier reports, in which reductions in visual memory, executive functioning, and psychomotor skills before CEA were detected.[24,25]

The establishment of preoperative impairment left open the potential of improving cognitive functions after CEA. We examined this possibility by including the patients with severe atherosclerotic disease undergoing peripheral vascular surgery (REA) as a control group. These subjects were highly similar with respect to demographic and medical characteristics, and therefore, it may be assumed that possible practice effects are the same for both types of patients. This may not be the case for healthy persons or patients with unrelated disease, such as hospitalized patients with spinal or orthopedic problems, who served as control subjects in other studies. Moreover, because CEA and REA with the ring-strip cutter device are highly comparable in vascular procedure, except for its locus, we were also able to control for the possible negative influence of surgery and anesthesia on cognitive outcome and positive effect from psychologic relief after uncomplicated surgery, in contrast to studies that included patients with carotid artery disease not undergoing endarterectomy as control subjects. In this accurate methodological design, in which important positive as well as negative confounding influences were controlled for, a *specific* effect of CEA on cognitive functions was not observed.

As mentioned, the preoperative performance of patients with carotid artery disease was impaired, but to the same extent as that of patients with peripheral vascular disease, which was found by other studies as well.[11,26,27] One reason for this can be the relatively high prevalence of carotid artery stenosis in patients with peripheral vascular disease.[28-31] Nevertheless, because removal of the stenosis during CEA did not result in a specific improvement of functioning, the reduced performance in both patient groups probably reflect the common underlying (chronic) disease of generalized atherosclerosis.[27] This may be associated, more precisely, with structural brain abnormalities arising from chronic hypoperfusion caused by accumulating atherosclerotic plaque in other intracerebral arteries, or from occlusion of blood vessels by series of microemboli. Because we did not assess signs of brain damage with imaging techniques, it remains unclear to what extent the cognitive decline in our study can be attributed to small infarcts or, for example, atrophy or white matter lesions, such as leukoaraiosis.[32-35]

No specific cognitive effect of CEA was found, but improvement on a number of tests was indeed observed in *both* patient groups (Figure 1). Controlling for the postoperative decrease in tension reduced one of these time effects, indicating the relative importance of taking mood factors into account.[4,5] Because we cannot think of any physiological argument why patients after *REA* would improve in cognitive functions, we attribute the overall improvements to relief from surgery and to practice.

Cognitive decline after CEA has been observed in the literature, particularly if testing was done within several days after the operation.[4] The original design of our study included an assessment at the day of discharge from the hospital, most often the third day after surgery. Our patients found this early postoperative measurement to be very uncomfortable and fatiguing. Because we believed that the cognitive achievements were likely to be influenced by this discomfort and we were afraid of losing patients by this in the follow-up assessments, we abandoned this measurement and focused on the more stable and clinically more relevant measurements at 3 and 12 months after the operation.[36]

Although a restorative effect from CEA on cognitive functioning was not found, its protective value against cognitive decline can only be reliably examined in large trials in which patients with severe atherosclerotic disease of the carotid artery are randomly assigned to optimal medical care alone or to optimal medical care plus CEA.[6] However, because the efficacy of the operation in reducing the risk of stroke in patients with high-grade stenosis had been clearly established already in 1991,[1,37] such a design would ethically be controversial nowadays, even for asymptomatic patients.[3]

In conclusion, the present study showed no specific restorative effect of CEA on cognitive functioning. The preoperative impairment in several cognitive domains might be caused by factors that patients with different types of vascular disease may have in common, such as small-vessel disease or other undetected abnormalities within the brain.

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Chapter 4

Testing the laterality hypothesis after left or right carotid endarterectomy: no ipsilateral effects on neuropsychological functioning

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Abstract

Carotid endarterectomy (CEA) is performed to prevent stroke, but the possible restorative function of CEA on neuropsychological functioning has frequently been considered. Restorative effects might be more clear in functions mediated by the hemisphere ipsilateral to the operated side rather than to those of the contralateral hemisphere. The present study examined this hypothesis in 45 right-handed male patients with CEA of either the left or right carotid artery. Patients with a history of stroke were explicitly excluded. Only tasks sensitive to hemispheric specialization were included. Preoperatively, patients performed significantly worse than healthy controls in the planning of motor behavior, verbal fluency, and visual recognition. Three months after surgery, performance only increased in left hand finger tapping, irrespective of the side of surgery. This could be attributed to practice. In conclusion, ipsilateral effects on neuropsychological functioning after CEA were not demonstrated, although instruments and sample characteristics were optimal in light of hemispheric functional asymmetry.

Introduction

CEA has become a routine surgical procedure to prevent stroke by removing atherosclerotic plaque from the intima of the carotid artery. Its preventive value has been demonstrated in both symptomatic and asymptomatic patients with a severe stenosis (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study, 1995; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group, 2004; Rothwell et al., 2003). The possible beneficial effect of this operation on neuropsychological functioning has frequently been considered (Irvine, Gardner, Davies, & Lamont, 1998; Lunn, Crawley, Harrison, Brown, & Newman, 1999). An improvement in blood flow to ischemic cerebral regions and spontaneous recovery from frequent embolic events before surgery were proposed as mechanisms underlying neuropsychological improvement (Baird & Pieroth, 2001; Kishikawa et al., 2003).

A number of studies searched for side-specific effects on cognitive functioning, based on the hypothesis that restoration of blood supply to the brain is more beneficial to functions mediated by the hemisphere ipsilateral to the operated side than to those of the contralateral hemisphere. Improvement of verbal and language functions are thus expected in patients operated on the left carotid artery, and enhanced nonverbal or visuospatial functioning in patients operated on the right side. Motor functions of the body side contralateral to the side of surgery may improve as well.

Ipsilateral cognitive effects after CEA indeed have been found. Hemmingsen and colleagues (1986) reported improvement in a word pairs test and story recall in patients operated on the left carotid artery, and improvement in a visual gestalts test in patients operated on the right carotid artery. Mononen, Lepojärvi, and Kallanranta (1990) found improved functioning in patients with left-sided surgery on a number of verbal but not on visual tests, whereas patients with right-sided surgery had enhanced performance in tests of visual memory, but to a lesser degree also in verbal tests.

Some studies found at least mixed results. Lind et al. (1993) observed an improvement in verbal attention, but also in visual memory (a right hemisphere function) in patients operated on the left side. Right-side operated patients did not improve in this study. Greiffenstein, Brinkman, Jacobs, and Braun (1988) noticed gains in mental speed and verbal recall in patients operated on the right but not the left side. Left and right hand finger tapping improved in this study irrespective of the side of surgery. Contralateral effects have also been reported. These occurred more notably in patients operated on the right side (improved verbal functions) than in those with left-sided surgery (Bornstein, Benoit, & Trites, 1981; De Leo et al., 1987). Other studies did not observe side-specific effects (Boeke, 1981; Casey, Ferguson, Kimura, & Hachinski, 1989; Incalzi et al., 1989; Van den Burg et al., 1985), although in one of these reports a stronger improvement in a sentence construction test was seen in the left-side operated patients (Van den Burg et al., 1985).

The diversity in outcomes of the studies might be due to factors that are often claimed as confounding, such as differences between studies in patient selection variables, the choice of cognitive tests, and the postoperative test interval. Patients with a history of stroke, for example, were included in the majority of studies, but their distribution was not necessarily equal across the left and right operated groups, or information on this was lacking. This can be problematic since neuropsychological improvement after CEA in stroke patients might be explained by recovery from the neurological lesion rather than by the removal of the stenosis as such (Bornstein et al., 1981; Casey et al., 1989). Because of problems in the interpretation of the results, and the risk of influencing the overall outcome of the study with respect to possible laterality effects, exclusion of these patients seems to be the best option.

The often uncritical use of cognitive tasks can be an important explanation as well, for the varying results with respect to differential hemispheric effects. Tasks with some verbal aspect, for instance, may too easily and superficially be claimed to measure left-hemisphere functions, perhaps ignoring visuospatial or visualizing aspects that may be implicitly involved in the task. We suggest that hemispheric effects can be obtained more unequivocally from tasks measuring hemispheric involvement in a more direct and pure manner (Owens et al., 1980). To accomplish this, we included only relatively direct laterality tasks, such as a dichotic listening task, a finger tapping task, and a multiple choice reaction time task.

In addition, in searching for side-specific effects researchers have often ignored (or failed to specify) subject factors that are closely related to cerebral functional asymmetry, such as handedness and gender. Because hemispheric specialization manifests itself most pronounced and reliable in right-handed male subjects (Bryden, 1982), we included only patients with these characteristics.

The aim of the present study thus was to evaluate whether hemispheric-specific effects can be observed in patients operated on the left or right carotid artery, using tasks specifically sensitive to hemispheric laterality, in a sample with most pronounced hemispheric functional asymmetry. Patients with a history of stroke were explicitly excluded. This study is partly a replication of our earlier study, in which we found no ipsilateral improvement related to the side of surgery (Brand, Bossema, van Ommen, Moll, & Ackerstaff, 2004). Apart from the refinements as mentioned above, the present study included more patients and, moreover, a healthy control group.

Methods

Subjects

We examined 45 right-handed male patients who underwent CEA for severe atherosclerotic disease (a stenosis of 70% or more) in the left or right carotid artery in the St. Antonius Hospital in Nieuwegein, the Netherlands. Those with a history of stroke were explicitly excluded. Separating the patient group into subgroups for left or right CEA permitted each to serve as a control group for the other on the tests assumed to measure functions primarily mediated by one of the two hemispheres (Casey et al., 1989; De Leo et al., 1987; Hemmingsen, Mejsholm, Boysen, & Engell, 1982; Hemmingsen et al., 1986). Another control group was composed of 25 healthy male subjects with right hand preference. They were recruited by an advertisement in a local newspaper and received a small financial reward for their participation. None of these subjects had clinical evidence of cerebrovascular disease or a psychiatric history. The ethics committee of the hospital approved the study protocol and written informed consent was obtained from all participants.

Instruments

Patients were examined in the hospital 1 day before and approximately 3 months after CEA, and healthy controls in the department laboratory with an interval of 3 months. At the start of the first assessment, subjects were asked about their level of education, tobacco and alcohol use, and psychiatric and medical history. The medical questions concerned, among others, previous myocardial infarction and coronary surgery, and presence of other vascular risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus. Additional medical information was obtained from the medical records. Patients also completed the Edinburgh Handedness Inventory (Oldfield, 1971).

The neuropsychological tests were the following. The Dichotic Listening Test (Van Strien & Bouma, 1988) measures the relative superiority of the right or left ear in recognizing three pairs of digits presented simultaneously to each ear through headphones. Twenty test trials were preceded by eight practice trials. Usually a right ear advantage is found, indicating a better left than right hemisphere processing for verbal material (Lezak, 1995).

In the Finger Tapping Test (Lezak, 1995) subjects press and release a button with the right or left index finger separately as fast as possible during a 10-second period. For each hand, the mean number of taps across three test trials is recorded. The test trials were preceded by one practice trial for each hand.

The Motor Planning Test (Brand, van der Wijk, & Hijman, 1990) distinguishes between planning of motor behavior and motor speed. The subject holds a start button on a button box until one of three other buttons is lit, then presses this target button, and immediately returns to the start button. Computer registered measures are the time lapse between onset of the light and release of the start button (planning time), and the time between releasing the start button and pressing the target button (movement time). The median times (in ms) across 14 trials was calculated for each condition and each hand separately (right hand first in each condition). Test trials were preceded by six practice trials for each hand.

The Verbal Fluency Test has been classified as being mainly mediated by the left hemisphere (Lezak, 1995). Subjects are asked to generate in one minute as many words as possible beginning with a certain letter (‘N’ and ‘P’) or belonging to a specific semantic category (‘animals’ and ‘occupations’).

Right rather than left hemispheric involvement was supposed to be dominant in performing the Doors Test (Baddeley, Emslie, & Nimmo-Smith, 1994). Subjects are asked to memorize a series of 12 colored photographs of doors. The subject then has to recognize the memorized door among three other distracting doors, fitting the same general label (e.g. ‘church door’). There are two series; series B is more difficult than series A because the doors in series B are still more alike.

The Motor Planning Test and the Finger Tapping Test were administered and (partly) scored using the software package of MINDS (Brand, 1999).

Statistical analysis

Characteristics of the groups were compared with an analysis of variance (ANOVA) (age), the Mann-Whitney *U* test (angiographic findings, previous ischemic symptoms), and the χ^2 test or Fisher’s exact test (lower versus middle or higher education, presence versus absence of vascular risk factors). To examine the pattern and degree of neuropsychological impairment before surgery, patients scheduled for CEA of the right or left carotid artery were compared preoperatively to the healthy control subjects using one-way ANOVA. The effect of the side of surgery and of the procedure itself on each neuropsychological test variable was subsequently assessed with 2 (Side of surgery) x 2 (Assessment time) ANOVA with Assessment time as a repeated measures factor. Differences between patients and healthy control subjects were examined in the same way. A two-tailed *p* value less than or equal to .05 was considered to reflect a statistical significant result. A *p* value between .05 and .10 was presumed as a tendency toward significance.

Results

Twenty patients underwent surgery of the left and 25 patients of the right carotid artery. Demographic characteristics of the total patient group, the healthy control group, and the patient subgroups are summarized in Table 1. No differences between groups on any of these variables were found.

Table 1. Demographic and hand characteristics of the total patient group and healthy control group, and of patients scheduled for CEA of the right or left carotid artery.

	All patients (*n*=45)	Healthy subjects (*n*=25)	*p*	Patients - Right (*n*=25)	Patients - Left (*n*=20)	*p*
Age, y, mean ± SD	66.6 ± 7.2	66.7 ± 4.7	.95	65.4 ± 7.4	68.1 ± 6.8	.22
Educational level			.83			.84
Lower	47%	44%		48%	45%	
Middle or higher	53%	56%		52%	55%	
Hand preference	9.4 ± 1.9	9.7 ± 1.3	.47	9.6 ± 1.1	9.2 ± 2.6	.48

Medical characteristics of the two subgroups of patients are given in Table 2. Significantly more patients with diabetes mellitus and also more patients who suffered a hemispheric transient ischemic attack were included in the group being scheduled for surgery of the right carotid artery. The group indicated for left-sided surgery included slightly more patients with moderate or severe contralateral stenosis. These three variables were included as covariates in the mutual comparison of the two subgroups with respect to cognitive functioning.

Table 3 shows the neuropsychological performances of the healthy control group and of the two patient groups on both test sessions. Scores on the Dichotic Listening Test were missing as a result of serious hearing problems for 9 patients and 4 control subjects. Other scores were incidentally missing, mainly due to technical problems.

Baseline performance

Compared to healthy control subjects, but irrespective of the side scheduled for surgery, patients preoperatively had significantly longer planning times

Table 2. Medical characteristics of patients scheduled for CEA of the right or left carotid artery.

	Patients - Right	Patients - Left	P
Hypertension	64%	60%	.78
Heart disease	52%	55%	.84
Hypercholesterolemia	40%	60%	.18
Diabetes mellitus	24%	0%	.03
Degree of contralateral stenosis			.07
Stenosis <50%	60%	30%	
Stenosis 50-69%	16%	25%	
Stenosis 70-99%	12%	35%	
Occlusion	12%	10%	
Previous ischemic symptoms			.04
None	24%	55%	
Amaurosis fugax	28%	20%	
Transient ischemic attacks	48%	25%	

on the Motor Planning Test with both the right hand (right-sided CEA patients: $F(1,44) = 20.32$, $p < .001$; left-sided CEA patients: $F(1,38) = 7.07$, $p = .01$) and the left hand (right-sided CEA patients: $F(1,44) = 19.58$, $p < .001$; left-sided CEA patients: $F(1,38) = 5.10$, $p = .03$), as well as a significantly lower score in generating words belonging to a specific category in the Verbal Fluency Test (right: $F(1,48) = 4.60$, $p = .04$; left: $F(1,43) = 7.98$, $p = .01$), and both versions of the visual recognition task (Doors A - right: $F(1,48) = 10.39$, $p < .01$; left: $F(1,43) = 12.42$, $p = .001$; Doors B - right: $F(1,48) = 12.71$, $p = .001$; left: $F(1,43) = 12.08$, $p = .001$). Furthermore, patients who would be operated on the left carotid artery had, surprisingly, a significantly better right hand Finger Tapping performance than healthy controls ($F(1,42) = 4.17$, $p = .05$). The two patient groups did not significantly differ from each other preoperatively.

Effects of surgery

Within the patient group, a significant improvement between the preoperative and postoperative assessment time was demonstrated for left hand Finger Tapping ($F(1,38) = 4.64$, $p = .04$). No significant effect of Side of surgery (or interaction effect between Side of surgery and Assessment time) was observed on any of the neuropsychological test variables.

To investigate time differences while taking practice effects into account, we compared the performances of the total patient group to those of the healthy control group. A significant main effect of Assessment time was shown on the difficult version (part B) of the Doors Test ($F(1,68) = 4.03$, $p = .05$) and trends on the left ear score of the Dichotic Listening Test ($F(1,53) = 3.75$, $p = .06$) and finger tapping with both the left and right hand ($F(1,66) = 3.07$, $p = .09$ and $F(1,66) = 3.63$, $p = .06$, respectively);

Table 3. Neuropsychological performances (mean ± SD) of healthy control subjects and of patients who underwent CEA of the right or left carotid artery.

	Baseline			3 months		
	Healthy subjects	Patients - Right	Patients - Left	Healthy subjects	Patients - Right	Patients - Left
Left hemisphere measures						
DL right ear	44.1 ± 9.9	48.1 ± 9.9	46.0 ± 9.4	44.9 ± 9.2	49.0 ± 9.8	50.3 ± 6.9
FT right hand	53.0 ± 9.3	53.1 ± 10.6	58.5 ± 8.0*	54.8 ± 9.3	56.2 ± 8.4	58.7 ± 5.5
MP planning right hand	410 ± 67	492 ± 56***	474 ± 85*	410 ± 57	487 ± 55	479 ± 96
MP movement right hand	157 ± 41	165 ± 46	161 ± 43	153 ± 45	168 ± 48	155 ± 28
VF letters	12.6 ± 4.7	11.5 ± 4.6	11.4 ± 3.1	13.0 ± 3.8	12.4 ± 5.2	12.1 ± 3.6
VF categories	19.7 ± 4.1	17.2 ± 4.1*	16.2 ± 4.3**	19.5 ± 4.9	17.6 ± 4.5	17.2 ± 4.1
Right hemisphere measures						
DL left ear	31.2 ± 9.5	27.6 ± 11.7	34.4 ± 11.2	34.5 ± 9.8	30.5 ± 12.6	33.0 ± 11.3
FT left hand	49.5 ± 9.5	49.7 ± 10.1	52.1 ± 9.2	50.7 ± 10.1	52.5 ± 8.3	52.8 ± 7.5
MP planning left hand	396 ± 63	470 ± 51***	450 ± 89*	385 ± 62	473 ± 63	469 ± 95
MP movement left hand	165 ± 40	164 ± 44	162 ± 44	167 ± 45	167 ± 37	161 ± 32
Doors Test A	10.8 ± 1.4	9.4 ± 1.8**	9.5 ± 1.1**	10.8 ± 1.3	9.4 ± 1.3	9.7 ± 1.7
Doors Test B	7.5 ± 2.6	5.0 ± 2.3**	5.1 ± 1.8**	8.2 ± 2.5	5.2 ± 2.5	5.7 ± 1.9

DL, Dichotic Listening Test; FT, Finger Tapping Test; MP, Motor Planning Test; VF, Verbal Fluency Test.
Baseline differences between patient subgroup and healthy control group: * $p < .05$, ** $p < .01$, *** $p < .001$.

performance on all tests in the second assessment was better than in the first. There were no significant interaction effects between Group (Patients versus Healthy control subjects) and Assessment time.

The scores of patients on the Dichotic Listening, Finger Tapping, and Motor Planning Test were analyzed post-hoc in 2 x 2 x 2 ANOVA, with the left versus right Ear or Hand as an additional factor. In addition to a 'new' main effect of Assessment time on the Dichotic Listening Test, pointing towards improvement ($F(1,32) = 6.91$, $p = .01$), a significant Ear effect was shown, indicating a right ear advantage ($F(1,32) = 35.71$, $p < .001$). We also observed a higher right than left hand Finger Tapping score ($F(1,41) = 42.05$, $p < .001$), and a longer right than left hand planning time on the Motor Planning Test ($F(1,40) = 12.78$, $p = .001$). A right versus left hand contrast was not noticed in the movement times of the Motor Planning Test.

Discussion

The present study did not produce evidence for ipsilateral effects on neuropsychological functioning after CEA, although hemispheric involvement was measured in a relatively direct and pure manner, and subject factors closely related to cerebral functional asymmetry (gender and handedness) were constant.

Patients were impaired both preoperatively and postoperatively on test variables reflecting the planning of motor behavior, verbal fluency, and visual recognition. Dichotic listening and pure motor skills were not affected. This at least implies that the impairments on the other cognitive tasks cannot be explained by a reduced motor speed of the patients. The findings are largely in agreement with other studies, in which particularly reductions in psychomotor skills, executive functioning, and visual memory before CEA were detected (Bossema et al., 2005a; Hamster & Diener, 1984; Hemmingsen et al., 1986; Parker, Smarr, Granberg, Nichols, & Hewett, 1986; Heyer et al., 2002), and demonstrates that detrimental effects of carotid occlusive disease on neuropsychological functioning indeed exist (for a review see Bakker, Klijn, Jennekens-Schinkel, & Kappelle, 2000).

No significant effect of the side of operation was observed on any of the neuropsychological test variables. In addition to the use of more direct laterality tests, the inclusion of right-handed male patients and the exclusion of stroke patients should have resulted in an association between the surgery side and ipsilateral functions. These three considerations were missing in other studies searching for ipsilateral improvement after carotid endarterectomy. Only one study (Greiffenstein et al., 1988) included exclusively males, whereas information on handedness was provided by just three of the studies (Boeke, 1981; Greiffenstein et al., 1988; Kishikawa et al., 2003) reviewed. Inclusion (and perhaps uneven distribution) of patients with a history of minor or major stroke was also common (De Leo et al., 1987; Hemmingsen et al., 1986; Kishikawa et al., 2003; Lind et al., 1993; Mononen et al., 1990; Van den Burg et al., 1985).

Improvement in patients after CEA was demonstrated only for the left hand Finger Tapping score, but irrespective of the side of surgery. This time effect, however, was statistically comparable in size to that in the healthy control group. Improvements across all groups were shown in the left ear score of the Dichotic Listening Test, the Finger Tapping Test with both the dominant and nondominant hand, and the difficult part of the visual recognition test (Doors Test B). An improved left ear score in CEA patients was also found in our earlier study (Brand et al., 2004). In that study it was explained by a better functioning of the contralateral hemisphere and by a left-hemisphere dominance for verbal material. The present data indicates, however, that the improvements on this test, the finger tapping test, and the visual recognition test are due to practice, since the improvements did not differ significantly between patients or healthy control subjects.

We included three tests that measured unilateral specialization in *both* hemispheres, namely the Dichotic Listening Test, the Finger Tapping Test, and the Motor Planning Test. Within the patient group indeed an overall right ear advantage (Dichotic Listening Test) was shown, indicating the usual larger left- than right-hemispheric involvement in verbal processing (Lezak, 1995). The right hand preference of our patients was confirmed on the Finger Tapping Test, but not in the movement times of the Motor Planning Test. Perhaps the extra visuospatial element in the latter task, activating the right hemisphere, undid the left hemisphere dominance in this assignment. This actually may be more so in the preceding planning of the movement, because even a faster left than right hand planning speed was observed. However, since the task might be somewhat more difficult than simple finger tapping, the few practice trials that preceded the test trials perhaps might not have been enough to become fully competent in the task. Because trials with the left hand were always performed after those with the right (preference) hand, patients may have learned from the right hand trials, and this may alternatively explain the shorter initiation times of the left hand.

The number of patients in the present study was relatively small, but the sample size was still larger than in other studies and our own earlier study on ipsilateral effects due to CEA. Moreover, our patient sample was quite homogeneous with respect to previous clinical symptoms due to the exclusion of patients with a history of stroke, and also rigorously selected on male gender and right hand preference. Nevertheless, we found no evidence for ipsilateral effects on cognitive functioning after CEA. In fact, not any improvement beyond practice effect was observed following the operation, although preoperative impairments were demonstrated. This is in line with our earlier report that CEA has negligible effects on cognitive functioning (Bossema et al., 2005b) and that, apparently, other factors restrained our patients to improve. These may include silent infarction or other brain abnormalities, such as atrophy or white matter lesions (De Groot et al., 2002; Gunning-Dixon & Raz, 2000; Mungas et al., 2002; Sabri et al., 1999), presence of vascular risk variables, such as hypertension or diabetes mellitus (Knopman et al., 2001), and arteriosclerotic narrowing or blockage in the vertebrobasilar arterial network (Dull et al., 1982). However, we did not assess signs of brain damage with imaging techniques, neither did we have angiographic information of the vertebrobasilar system and, therefore, it remains unclear to what extent the cognitive disturbances in our study can be attributed to one or a combination of these factors. Disentangling this seems to be a very difficult, but challenging task.

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Chapter 5

Perioperative microembolism is not associated with cognitive outcome three months following carotid endarterectomy

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Abstract

Objective: To investigate the association between perioperative microembolism and cognitive outcome 3 months after carotid endarterectomy (CEA). *Design:* Prospective study. *Materials and methods:* Patients were tested 1 day before and 3 months after surgery with neuropsychological tests measuring a wide range of cognitive functions. Number of microemboli was monitored with transcranial Doppler ultrasonography in 58 patients during the operation and in a random subgroup of 27 patients directly following the procedure. *Results:* Forty patients (69%) had intraoperative embolism, varying from 1 to 33 isolated microemboli and/or 1 to 11 embolic showers. Postoperative emboli were present in 22 of the 27 patients (81%), ranging from 1 to 142 isolated microemboli. More than 10 microemboli (including showers) were detected in 13 patients (22%) intraoperatively and in 6 patients (22%) postoperatively. Twenty-two patients (38%) showed deterioration in three or more cognitive function variables at 3 months. There were no significant associations between any cognitive change or deterioration score and presence or number of intraoperative and/or postoperative emboli. *Conclusions:* The degree of microembolism during and immediately following CEA is generally small and seems to be of no significance with respect to postoperative cognitive functioning. Future research should include a larger group of patients to allow reliable subgroup analysis.

Introduction

Cognitive difficulties due to intraoperative microemboli have been reported following cardiac surgery.[1-4] Comparable deficits may be expected after CEA. Although this latter operation is aimed at the prevention of future ischemic attacks, the risk of minor and major neurological symptoms is increased during and immediately after the procedure.[5-7] Embolism appears to be the principal underlying cause.[8,9] Microembolisation occurs in a majority of CEAs and it is associated with intraoperative and postoperative ischemic symptoms, such as transient ischemic attacks (TIAs) and stroke,[9-11] as well as with clinically silent lesions.[11,12]

In addition to neurological consequences, cognitive decline has been demonstrated in a proportion of patients after CEA.[13-18] Cerebral emboli were suspected to be responsible for this too.[16,18,19] Only one study truly examined the relation between intraoperative microembolisation and cognitive functioning after CEA.[20] No overall correlation between the total number of intraoperative emboli and the number of tests with a cognitive deterioration several days after the operation was observed, but the occurrence of more than 10 microemboli during the initial carotid dissection period was associated with a decrease on at least one cognitive test.[20] The cause of cognitive decline in the majority of patients remains unclear.

Perhaps microemboli immediately following surgery played a part in this, since they also predict postoperative stroke.[21,22] However, Gaunt and colleagues did not consider this possibility. Furthermore, because cognitive performance seems to be rather unstable shortly after surgery it might be better and clinically more interesting to measure cognitive functioning several weeks after the operation.[23]

The present prospective study investigated the association between microembolism and cognitive outcome 3 months after CEA. Degree of embolism was assessed with transcranial Doppler (TCD) ultrasonography during the operation in all patients and immediately after the operation in a random subgroup of patients. Cognitive functioning was measured extensively before and after surgery with neuropsychological tests.

Materials and methods

Fifty-eight patients underwent CEA in the St. Antonius Hospital in Nieuwegein, the Netherlands. Mean age was 65.8 ± 7.2 years and 48 of them were male. About half (48%) had at least middle education (secondary school or middle professional training). Thirty-nine patients had recently suffered one or more ischemic episodes: 18 had amaurosis fugax, 18 had hemispheric TIAs, and three had minor stroke. Those with a history of major stroke were excluded to reduce the heterogeneity of the sample. The degree of carotid artery stenosis was assessed with duplex ultrasonography. All patients had severe stenosis (70% or more) on the side scheduled for CEA. Contralateral occlusion was found in five patients, whereas the stenosis of the contralateral artery in the remaining patients varied from less than 70% to subtotal (99%). Twelve patients previously had undergone ipsilateral or contralateral CEA.

Patients were examined in the hospital 1 day before and about 3 months after CEA. At the start of the preoperative session, they were asked about their level of education, tobacco and alcohol use, and psychiatric and medical history. The medical questions concerned previous myocardial infarction or coronary artery surgery and presence of other vascular risk factors, such as current cigarette smoking, hypertension, hypercholesterolaemia, diabetes mellitus, and heart disease. Additional medical information was obtained from the medical records. It appeared that 22 patients were current smokers or quit smoking in the year before the operation, 39 patients had hypertension, 30 had hypercholesterolaemia, 10 had diabetes mellitus, and 28 had a history of heart disease.

The ethics committee of the hospital approved the study protocol and written informed consent was obtained from all subjects.

Carotid endarterectomy

All patients underwent CEA under general anaesthesia using nitrous oxide and halothane or isoflurane. CEA was performed in a standardised way by an experienced vascular surgeon or by a specialist vascular trainee under supervision. Before cross-clamping, an intravenous injection of heparin (5000 IU) was administered. A Javid shunt was selectively used in nine patients on the basis of electroencephalogram and TCD criteria.[24] All patients were given a standardised preoperative antiplatelet treatment of 100 mg Aspirin daily, which was continued postoperatively.

TCD monitoring

Continuous TCD monitoring was performed using a 2 MHz TCD ultrasound probe (EME/Nicolet, Pioneer 4040, Madison, USA). The sample volume of the pulsed Doppler system was located at a depth of 45 to 55 mm with the probe positioned on the temporal bone to insonate the main stem of the middle cerebral artery. The probe was fixed in place with a head strap. An experienced sonographer on-line observed the Doppler spectra, and the audio Doppler signal was made audible during the entire operation.

Isolated microemboli were identified according to the criteria of the Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium.[25] Because embolic signals that occur in so-called 'showers' could not be counted individually, the number of heartbeats with showers of microemboli was counted in these cases (one such a shower was considered to be 10 microemboli for statistical purposes). A macroembolus was defined as an embolus that partially or completely obstructed the main stem of the middle cerebral artery for a period of several seconds or minutes. The TCD emboli variables were analysed during (1) dissection (skin preparation to carotid clamping), (2) clamping or shunting, (3) clamp release (the first 10 seconds at restoration of flow through the carotid arteries), and (4) wound closure (termination of manipulation to the end of the operation). Postoperative monitoring outside the operating room restarted about half an hour after wound closure and was continued for one hour, divided in 15 minutes sections for analysis.

Cognitive testing

Cognitive functions were measured with neuropsychological tests. Tests were administered by neuropsychological research assistants, who had been trained to conduct and score the tests under supervision of an experienced neuropsychologist. Tests took about 1 h to be completed. A wide range of cognitive functions was evaluated, including attention, working memory, verbal and visual memory, language, executive function and psychomotor speed, and manual dexterity. In total 18 variables from the following tests were included: Digit Span forward and backward,[26] Dichotic Listening Test - total score,[27] visually presented Word Learning Test - immediate recall, delayed recall, and recognition,[28] Doors Test A and B,[29] Verbal Fluency letters and categories,[26] Trail Making Test A and B,[26] Motor Planning Test compatible and incompatible condition - initiation and movement times,[30] and Finger Tapping Test dominant and nondominant hand.[26]

Data analysis
Relations between cognitive change or deterioration scores and the number of emboli during and/or immediately after CEA were examined by means of nonparametric Spearman rank correlations. The cognitive change score is the difference between the preoperative and postoperative score on a test variable (with positive change scores indicating improvement and negative scores indicating decline). The deterioration score reflects the number of tests with a decline on the postoperative score of more than 1 SD from the preoperative score. An overall cognitive change score was calculated by summing the standardised change scores on each variable and dividing this score by the number of variables. Mann-Whitney *U* tests were applied to examine cognitive differences (on the individual test change scores, overall change score, or deterioration score) between patients with and without intraoperative and/or immediately postoperative emboli. The association between cognitive deterioration on at least three tests (dichotomous variable) and intraoperative and/or postoperative embolism was tested in a 2 x 2 frequency table with Pearson Chi-square or Fisher's exact test. The statistical significance level was set at $p<0.01$ to correct for multiple testing, but at $p<0.05$ if the overall cognitive change or the deterioration score were analysed.

Results

Intraoperative microembolism
All patients ($n=58$) were successfully monitored during CEA. Forty of them (69%) had intraoperative embolism (Table 1): 1-33 isolated microemboli were detected in 37 patients (64%) and 1-11 embolic showers in 8 patients (14%). If a shower is considered to be 10 microemboli, the median number of emboli (in the patients with intraoperative embolism) across all operative phases was 7.0. No macroemboli were monitored. The 11 embolic showers that were observed in one person all occurred during the dissection period. The seven remaining patients with showers of emboli had 3-4 showers or less. More than 10 emboli (including showers) were observed in 13 patients (22%). Embolism most often occurred after clamp release, when the cerebral blood flow was restored (Table 1).

Postoperative microembolism
Immediate postoperative monitoring was successfully performed in a random subgroup of 27 patients. Twenty-two of them (81%) showed embolism, varying from 1 to 142 isolated microemboli (median: 4.5) (Table 1). There were no macroemboli or embolic showers. More than 10 emboli were observed in six persons (22%), including one patient with a striking total amount of 142 emboli.

Table 1. Prevalence and frequency (median and range) of perioperative microemboli.

	Prevalence	Median	Range
Intraoperatively (n=58)			
Dissection	10 pts (17%)	2.5 emboli	1 isolated – 11 showers
Clamping or shunting	8 pts (14%)	5.5 emboli	2 isolated – 3 showers
Clamp release	31 pts (53%)	5.0 emboli	1 isolated – 3 à 4 showers
Wound closure	12 pts (21%)	3.5 emboli	1 isolated – 1 shower
Total	40 pts (69%)	7.0 emboli	1 isolated – 11 showers
Postoperatively (n=27)			
First 15 minutes	17 pts (63%)	2.0 emboli	1 – 46 isolated
Second 15 minutes	16 pts (59%)	2.0 emboli	1 – 37 isolated
Third 15 minutes	14 pts (52%)	2.0 emboli	1 – 39 isolated
Fourth 15 minutes	12 pts (44%)	2.5 emboli	1 – 21 isolated
Total	22 pts (81%)	4.5 emboli	1 – 142 isolated

Neurological complications

One patient had an episode of amaurosis fugax in the evening before surgery, which was after the preoperative cognitive assessment. In this person, 7 intraoperative (all after clamp release) and 7 postoperative microemboli were detected. One patient showed contralateral hemiparesis immediately after surgery; symptoms were similar to the minor stroke he suffered several months preoperatively. He had one intraoperative embolus (after clamp release) and no postoperative monitoring was performed.

Cognitive changes

Twenty-two patients (38%) showed cognitive deterioration (more than 1 SD) on at least three test variables (Table 2). The person with amaurosis fugax on the evening before surgery deteriorated on four tests, and the person with hemiparesis after surgery on two tests. The patients with 11 intraoperative showers in the dissection period and the one with severe postoperative embolisation declined on one and six variables, respectively.

Table 2. Number (and %) of patients with cognitive deterioration.

	Deterioration
On 0 test variables	8 (13.8%)
On 1 test variable	10 (17.2%)
On 2 test variables	18 (31.0%)
On 3 test variables	8 (13.8%)
On 4 test variables	8 (13.8%)
On 5 or more test variables	6 (10.3%)

Spearman's correlations coefficients between the number of intraoperative and/or postoperative emboli and the cognitive change variables are tabulated in Table 3. We only reported the range of values on the individual cognitive test parameters. Negative values point toward a relation between the number of emboli and cognitive change in the direction of a decline. None of the coefficients were significant according to the predefined level of significance ($p<0.01$ for the individual test parameters, and $p<0.05$ for the overall change and deterioration score).

Table 3. Spearman correlation coefficients between cognitive change scores and the number of intraoperative and/or postoperative emboli.

	Test change scores	Overall change score	Deterioration Score
Intraoperative emboli (*n*=58)	-0.16 to 0.31	0.05	-0.02
Postoperative emboli (*n*=27)	-0.30 to 0.26	0.01	0.13
Intra- and postoperative emboli (*n*=27)	-0.36 to 0.33	-0.20	-0.08

The overall cognitive change score (mean and SD) and the deterioration score in patients with and without intraoperative and/or postoperative microemboli is given in Table 4. Mann-Whitney *U* tests showed no significant differences between the subgroups on these scores (all $p>0.05$) or on the individual test change scores (not listed, all $p>0.01$). Pearson Chi-square and Fisher's exact tests demonstrated no significant differences either, when the patient group was subdivided on the basis of their deterioration score (i.e. less than 3 versus equal or more than 3): all six *p* values were larger than 0.05.

Table 4. Mean (± SD) overall cognitive change scores and deterioration scores in patients grouped by absence or presence of microembolism, or grouped by the number of emboli (at most 10 emboli versus more than 10 emboli).

	Overall change score	Deterioration score
*Intraoperative embolism (*n*=58)*		
Absent (*n*=40)	-0.13 ± 0.31	2.43 ± 1.99
Present (*n*=18)	0.05 ± 0.26	2.41 ± 1.68
At most 10 emboli (*n*=45)	-0.03 ± 0.29	2.53 ± 1.67
More than 10 emboli (*n*=13)	0.09 ± 0.24	2.04 ± 1.96
*Postoperative embolism (*n*=27)*		
Absent (*n*=5)	-0.20 ± 0.35	2.48 ± 2.79
Present (*n*=22)	0.02 ± 0.33	2.66 ± 1.63
At most 10 emboli (*n*=21)	-0.08 ± 0.30	2.64 ± 1.81
More than 10 emboli (*n*=6)	0.16 ± 0.41	2.58 ± 2.10
*Intra- and postoperative embolism (*n*=27)*		
Absent (*n*=3)	-0.43 ± 0.18	3.47 ± 3.45
Present (*n*=24)	0.03 ± 0.32	2.52 ± 1.63
At most 10 emboli (*n*=12)	-0.10 ± 0.30	2.86 ± 1.91
More than 10 emboli (*n*=15)	0.04 ± 0.36	2.44 ± 1.81

Discussion

Although postoperative emboli were taken into account in the present study as well, no evidence was found for an association between embolic load and cognitive outcome 3 months after CEA.

It appears that the degree of embolism during CEA is too small to cause cognitive problems. Though emboli were detected in the large majority of patients, the total number in each patient was generally low. Other studies also reported a relatively low embolic burden during this operation.[9,20,31-33] Perhaps only a high rate of embolism incurs cognitive deficits. Crawley and colleagues compared patients who underwent CEA with those who had carotid percutaneous transluminal angioplasty (PTA).[32] The latter procedure (with or without stent placement) is characterised by an increased risk of intraoperative embolism.[32-34] A decline in neuropsychological performance was shown in both patient groups 6 weeks after surgery, but no differences in cognitive functioning between the two groups were found, despite a significantly higher incidence of microembolic signals during PTA (on average 178 during PTA compared to 10 during CEA).[32] These numbers still contrast with those observed in coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB), for example, where up to thousands of emboli can be detected. Under these circumstances, a clear association between cognitive impairment and embolic load has been observed.[1-4] Recent developments in cardiac surgery, such as the use of specific arterial line filters in the bypass circuit and CABG without CPB (off-pump) have led to a decrease in the amount of emboli during the operation and smaller negative effects on cognitive functioning.[1,2,35,36]

It has been suggested that not only the number but also the nature of emboli might be relevant in the prediction of cognitive change after surgery. Microemboli consisting of air, for example, may have less harmful effects on surgical outcome than solid emboli. Although the distinction between these types of emboli is still a subject of investigation,[37] the constitution of emboli may be deduced from the phase in which they occur: solid emboli may be more frequent during dissection, wound closure, and the first hour after surgery, whereas air emboli may arise particularly during shunting and at clamp release.[10,20,38] Not surprisingly in this context is that the occurrence of a certain amount (i.e. 10) of embolic signals during the *dissection* phase of CEA has been related to intraoperative and postoperative ischemic cerebral symptoms and clinically silent lesions[39] as well as to cognitive deterioration.[20]

The fact that the nature of emboli perhaps determines surgical outcome may explain why an overall correlation between the total embolic count (including both air and solid emboli) and the degree of cognitive change was low in the present study and in two earlier studies.[20,32] Although we observed more than 10 emboli in about a quarter of the patients, only one had a substantial number of embolic showers during dissection of the carotid artery. This patient differed significantly from the other patients on only one cognitive change variable (data not shown). No other patients had severe intraoperative embolism and therefore it was not possible in our study to relate cognitive functioning to emboli occurring in specific operative stages. One patient had a relatively high embolic burden immediately after surgery. This patient showed cognitive deterioration on a relatively high number of test variables. However, based on this single finding no general conclusion can be drawn regarding the possible harmful effect of postoperative embolism on cognition.

Besides the number and nature of emboli, also the size of the embolus as well as the location where it ends up seems to be of importance for neurological[11] and perhaps neuropsychological outcome. Unfortunately, we had no information on these matters.

We measured cognitive functioning after a follow-up period of 3 months, whereas studies focusing on the neuropsychological effects of embolism during coronary artery surgery often performed the postoperative assessment after a couple of days. Long-term harmful influences on cognition in these procedures were found less frequently, although an effect of intraoperative embolism on cognitive functioning 5 years after cardiac surgery has been reported recently.[40] The postoperative time interval in most studies that noted a cognitive decline following CEA was also several days to weeks at most.[13,14,16,18,41,42] No decline (but rather improvement) was reported in research evaluating cognitive performance after a period from several weeks up to years after CEA.[43,44] The Consensus Statement on assessment of neurobehavioral outcomes after cardiac surgery even stated that an assessment should be performed at least several weeks after surgery when performance is more stable.[23] The original design of our study included an assessment at the day of discharge from the hospital, most often the third day after surgery. However, our patients found this to be very uncomfortable and fatiguing. Since we felt that the cognitive achievements were likely to be influenced by this discomfort, we abandoned this measurement.

The small number of patients in our study did not allow reliable subgroup analyses, for example comparison of the effects in patients with and without a symptomatic history, or classified on the basis of other specific disease characteristics, such as the degree of ipsilateral or contralateral stenosis or occlusion. Future research in this field thus will have added value specifically if a large group of patients is tested at various postoperative times and if patients are monitored both during and immediately following CEA.

To summarise, this study was aimed at revealing a relation between microembolism and cognitive change after CEA. The findings showed that the extent of embolism as occurring during or after CEA seems to be of no significance with respect to cognitive outcome 3 months after surgery. However, more research with a larger sample is necessary to confirm this conclusion.

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Chapter 6

Effect of carotid endarterectomy on patient evaluations of cognitive functioning and mental and physical health

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Abstract

The prophylactic effect of carotid endarterectomy (CEA) against stroke has been well established. As a consequence of the restoration of cerebral blood supply and reduced risk of stroke, cognitive functioning and perceived health may improve. Fifty-one patients with severe atherosclerotic disease of the carotid artery, but without history of major stroke, completed the Cognitive Failures Questionnaire and the Short Form 36 Health Survey (SF-36) before CEA, and 3 and 12 months thereafter. Before CEA, patients reported significant but small deviations from the norm in physical function, general health, and vitality. Small improvements after CEA were observed in the perception of physical role function, general health, vitality, and mental health. Patients also retrospectively noted a slight worsening of health in the year before surgery, and some improvement after surgery. The evaluation of cognitive failures did not change. Demographic or medical characteristics, such as a history of temporary ischemic symptoms, occlusion of the contralateral artery, and shunt use during surgery, did not affect outcome. In conclusion, no negative outcomes and even some limited positive effects in the perception of mental and physical health can be expected after CEA.

Introduction

Patients with severe atherosclerotic disease of the carotid arteries are at risk of stroke and cognitive impairment.[1] CEA is aimed at the prevention of cerebral ischemic attacks in both symptomatic[2,3] and asymptomatic patients.[4,5] As a consequence of the restoration of cerebral blood flow and reduced risk of stroke, cognitive functioning and perceived health may improve.

Neuropsychological tests have shown improvement, but also unaltered cognitive functioning, after CEA.[6-8] Objective test performance, however, does not run parallel to patient reports of their cognitive functions.[9-12] This subjective aspect has been ignored in research evaluating the effects of CEA, which is remarkable since it is this aspect that is specifically of concern to the patient.[13] Patients *have* reported on their quality of life before and after CEA, but the few studies that focused on this aspect varied widely in their outcomes.[14-19] This diversity may be caused by various factors, including variation in patient selection characteristics, the choice of the questionnaire, and the timing of the postoperative assessment. Moreover, only two studies followed a multidimensional approach in which both physical and mental aspects of perceived health were evaluated.[18,19] Outcome of CEA in both the short and long run received minor attention too.[14]

The aim of this prospective study was to examine the effect of CEA on patient evaluations of cognitive functioning and of mental and physical health at 3 and 12 months after the operation. The predictive role of certain patient and operation characteristics was also investigated. Patients with a history of major stroke were excluded.

Patients and methods

The study originally included 64 patients with severe stenosis (70% or more) of the carotid artery who were indicated for CEA between September 2000 and December 2002. None of them had a history of major stroke. CEA was performed in 58 patients. Reasons for not having the operation were an occlusion of the to be operated carotid artery and a serious risk of cardiac complications during surgery. Four patients were lost after the first assessment because they appraised an accompanying neuropsychological measurement to be too difficult or fatiguing, and two patients were excluded because they suffered from severe unrelated disease influencing their health perception. Another patient was excluded because of temporary hemiparesis immediately after surgery. Table 1 shows the demographic and medical characteristics of the patients who participated in all three assessments (n=51). The ethics committee of the hospital approved the study protocol. Written informed consent was obtained from all subjects.

Table 1. Patient characteristics (n=51).

Age, year, mean ± SD	65.8 ± 6.9
Males	42 (82%)
Middle or higher education	23 (45%)
Heart disease	26 (51%)
Vascular risk factors	
Hypertension	31 (61%)
Hypercholesterolemia	27 (53%)
Cigarette smoking*	15 (29%)
Diabetes mellitus	7 (14%)
Previous ischemic symptoms	
None	19 (37%)
Amaurosis fugax	12 (24%)
Hemispheric ischemic attack(s)	18 (35%)
Minor stroke	2 (4%)
Previous CEA	11 (22%)
Contralateral occlusion	5 (10%)
Shunt use	8 (16%)

* Current smoking or having quit smoking in the year before surgery.

Perceived health was measured with the Short Form 36 Health Survey (SF-36).[20,21] This reliable and valid self-report questionnaire has shown in numerous studies to be useful in the evaluation of intervention effects. Scales are physical function, physical role function, pain, general health, vitality, social function, emotional role function, and mental health. Raw scores were linearly converted to a 0 to 100 scale, with higher scores indicating a better health status. One item measures health change across one year. A score above 50 on this item reflects a positive retrospective health change, whereas a score below 50 reflects a negative retrospective health change. Normative data for the Dutch population sample between 61 and 70 years of age were available, except for the 'health change' item.[22] Subjective cognitive functioning was assessed with the Cognitive Failures

Questionnaire.[23] This self-report 25-item instrument measures failures in perception, memory, and action in everyday life. The total score ranges from 0 to 100, with higher scores indicating more cognitive failures.

Five patients had in total 6 missing values on scales of the SF-36, which is 0.5% of all values (51 patients, 8 scales, 3 assessment times). These incidental missing values were imputed using the SPSS method Expectation-Maximization. This iterative procedure is considered an effective method to estimate and impute missing data points, because it uses all the information in the available data, such as means, correlations, and the covariance matrix.[24] Scale scores were normally or nearly normally distributed. Pre-to-post surgery changes were investigated with repeated measures analysis of variance. SF-36 scale scores were also compared to Dutch norms of similar age[22] with one-sample *t* tests. Deviations from these norms were expressed as effect sizes, defined as the difference between the mean score of the patient group and the norm group divided by the standard deviation (SD) of the norm group. Values between 0.2 and 0.5 reflect a small deviation from the norm, values between 0.5 and 0.8 a moderate deviation, and values larger than 0.8 a large deviation.[25] Differences in pre-to-post surgery changes between subgroups of patients were analyzed with analysis of variance. A *p* value of .05 or less was considered to be significant. For the health change item it was tested whether the score differed significantly from 50 (the score indicating no change) with one-sample *t* tests.

Results

Fifty-one patients had successful and uneventful CEA and completed the three assessments. The four patients lost after the first assessment had a significantly lower preoperative general health score than the remaining patients (p=.02), but they did not differ significantly on the other perceived health variables. The one patient with temporary hemiparesis after surgery did not differ preoperatively from the other patients on any of the variables.

Table 2. Reported cognitive failures and perceived health (mean ± SD) before CEA, and 3 months and 12 months after surgery, and the outcomes of the repeated measures analysis of variance.

	Before	3 months	12 months	*P*
Cognitive Failures	31.7 ± 12.8	30.2 ± 10.4	30.0 ± 9.4	0.43
Physical function	63.9 ± 25.5	68.1 ± 21.0	65.7 ± 23.1	0.18
Physical role function	56.4 ± 40.9	59.3 ± 37.4	70.6 ± 36.3*	0.02
Pain	75.8 ± 25.7	80.0 ± 23.3	81.2 ± 21.2	0.33
General health	55.1 ± 18.0	60.7 ± 17.7*	60.5 ± 18.0*	0.03
Vitality	58.7 ± 19.2	62.3 ± 18.1	65.3 ± 17.2**	0.03
Social function	76.7 ± 27.1	79.1 ± 21.2	81.7 ± 20.9	0.25
Emotional role function	75.7 ± 36.0	77.8 ± 36.9	85.0 ± 27.8	0.18
Mental health	73.2 ± 17.3	77.7 ± 15.4*	78.2 ± 14.8*	0.05

Comparison to preoperative score: * $p<.05$, ** $p<.01$.

Table 2 shows the mean number of reported cognitive failures and the mean scores on the perceived health scales before and after CEA. Significant improvements up to one year after surgery were shown in physical role function, general health, vitality, and mental health. Analyses of contrasts showed significant increases compared to preoperative levels on two of the eight health scales (general health and mental health) 3 months after surgery, and on four health scales (physical role function, general health, vitality, and mental health) 12 months postoperatively (Table 2). The score on the Cognitive Failures Questionnaire did not change significantly.

On average, patients retrospectively reported a slight worsening of their overall health before surgery (39.2 ± 20.2, $p<.01$) and a slight improvement at both assessments after surgery (62.3 ± 24.2, $p<.01$ and 58.3 ± 22.7, $p=.01$). Table 3 illustrates these findings. It is shown that 84% of the patients preoperatively rated their health as about the same or somewhat worse than to one year earlier, whereas about 70% of the patients postoperatively evaluated their health as about the same or somewhat better than one year earlier, and that even some patients reported a much better overall health after surgery.

Table 3. Percentages of patients with a certain response on the health change item ('Compared to one year ago, how would you rate your health in general now?') before CEA, and 3 months and 12 months after surgery.

Response on the health change item (score)	Before	3 months	12 months
'Much better now than one year ago' (100)	2	18	14
'Somewhat better now than one year ago' (75)	8	28	22
'About the same as one year ago' (50)	41	43	49
'Somewhat worse now than one year ago' (25)	43	10	16
'Much worse now than one year ago' (0)	6	2	0

Figure 1 displays the perceived health scores of patients before CEA and 3 and 12 months after surgery as deviations from the population norm. Improvements until one year after surgery are noticeable in the figure. Deviations from the norm before CEA were significant but small in physical function ($p=.03$), general health ($p=.01$), and vitality ($p<.01$) (Figure 1); a tendency ($p<.10$) towards deviation from the norm was observed for physical role function ($p=.06$). Three months after surgery, patients still perceived a small but significant deviation from the norm in vitality ($p=.04$), whereas 3 and 12 months after the operation they perceived *less* pain than the norm group (both $p<.01$).

It was explored whether certain patient and surgery characteristics were related to changes on the subjective cognitive functioning scale and health variables. There were no significant differences between subgroups of patients based on any demographic or medical characteristic, such as presence of a symptomatic history, occlusion of the contralateral artery, or use of a shunt during surgery (data not shown).

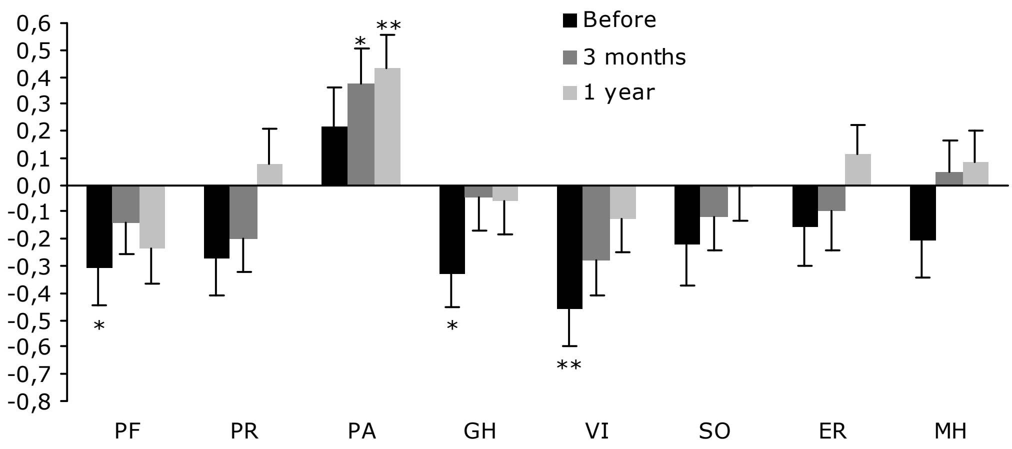

Fig 1. Perceived health before CEA, and 3 and 12 months after surgery compared to population norms of similar age (effect sizes). PF=physical function, PR=physical role function, PA=pain, GH=general health, VI=vitality, SO=social function, ER=emotional role function, MH=mental health. * *p*<.05, ** *p*<.01.

Discussion

The present study examined the short-term and long-term effects of CEA on patient evaluations of cognitive functioning and health in those with severe atherosclerotic disease of one or both carotid arteries but without history of major stroke. In addition to a small retrospectively judged improvement in overall health, patients reported significant but small improvements of physical role function, general health, vitality, and mental health. The number of cognitive failures did not change significantly across the postoperative year.

Previous studies investigating the effects of CEA on perceived health reported improvement,[15-19] but also no change.[14] The varying results may be due to certain patient selection criteria and to methodological differences between the studies, such as the type of questionnaire that was used and the timing of the postoperative assessment. We explicitly excluded patients with a history of major stroke, focused on both physical and mental aspects of health, and included a short-term and a long-term follow-up assessment.

The earlier studies included relatively large numbers of patients with a history of stroke (i.e. between 28 and 36% of the total patient group),[14,17-19] with some patients even having clear residual deficits at the time of assessment.[19] Improvement of health status in these patients may be attributed to recovery from the neurological lesion rather than to the surgical intervention, whereas an explanation for a failure to find improvement can be the existence of *permanent* brain damage influencing health perception. Patients with a history of major stroke were excluded and none of the other patients showed ischemic symptoms at the time of the preoperative assessment. Because of these exclusion criteria, we were better able to examine the effect of CEA on perceived health.

In contrast to an aggregated measure based on observable behaviour,[14-17] the present study assessed health in a multidimensional way. Such an approach may reveal changes on specific dimensions of perceived health and indicate those aspects that deserve special attention in the counseling of patients undergoing surgery. Only small improvements on specific aspects were observed in the present study, in addition to a small positive overall health change as judged by patients retrospectively after surgery. Our results resemble the outcomes of the two other studies that applied a multidimensional approach. These found a small positive overall health change as well,[18] but no effects on separate subscales.[18,19] The authors nonetheless worded their conclusion in a positive vein with respect to the change in perceived health.[18]

The small positive overall health change that patients retrospectively report after CEA is in accordance with two *momentary* evaluations of health: small improvements up to one year after CEA were demonstrated for general health and mental health. These improvements may be explained by an increase in distress before the major surgical procedure, and a postoperative decrease in anxiety due to the knowledge of the reduced risk of stroke and relief after uncomplicated surgery.[15,19] The observation that cognitive failures did not improve after surgery is in agreement with this possibility, and makes the explanation of improved health status due to a restored cerebral blood flow less plausible.

Small improvements in physical role function and vitality became significant only at the latter assessment. It seems that these aspects of health require some time to improve. That two other studies[18,19] did not find a change on separate dimensions of perceived health may be due to the shorter postoperative time interval in their studies. These studies also included a more heterogeneous patient group with respect to the duration and nature of previous ischemic symptoms,[18,19] and did not exclude patients with postoperative complications.[18]

Our explorative analysis on the predictive role of patient and surgery characteristics on changes in perceived health did not reveal any significant differences between subgroups of patients classified, for example, according to demographics, symptomatic background, occlusion of the contralateral artery, or use of a shunt during the operation. A previous finding that only patients with a contralateral occlusion or shunt during surgery improved after surgery,[17] might be explained by the fact that much more subjects with these characteristics were included in that study. Recurrence of significant stenosis after the operation occurred only incidentally in our patient group.

Patients preoperatively showed only small deviations in perceived health from the population norm, meaning that they evaluated their preoperative health status as relatively well and leaving little room for improvement. Although we included only patients with no or just transient ischemic symptoms, the smaller than expected deviations from the norm might be surprising in view of the life-threatening nature of their disease.

Conclusion

CEA patients without history of major stroke report relatively adequate cognitive functioning and health before surgery. Uneventful surgery results in small improvements of perceived health. The study shows that no negative outcomes and even some limited positive effects on perceived mental and physical health are to be expected from CEA.

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Chapter 7

Salivary cortisol and memory function in patients with severe atherosclerotic disease

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Abstract

Patients with different clinical manifestations of atherosclerotic disease show similar impairments in cognitive functions. Since especially decreased memory function is associated with increased cortisol levels, it is suggested that an elevation of cortisol might be the common mechanism underlying cognitive impairment in patients with severe atherosclerotic disease. Forty-six patients with severe occlusive disease of the carotid arteries and 22 patients with femoropopliteal occlusive disease were compared to 45 healthy control subjects. Patients indeed showed significant reductions on a majority of memory tests and also had significantly higher cortisol values at noon and in the afternoon than healthy control subjects. Within the total patient group, however, memory and cortisol were not convincingly and systematically associated with each other.

Introduction

Patients with severe atherosclerotic disease of the carotid arteries are at risk of cognitive impairment, including memory disorders.[1,2] It has been suggested that this is due to the reduction in blood flow to the cerebral hemispheres.[1] Comparable deficits in cognitive functioning, however, can be observed in patients with other clinical manifestations of atherosclerotic disease, such as coronary heart disease[3,4] and peripheral arterial disease.[5-7] These findings suggest a common mechanism underlying the cognitive impairment in all of these categories of vascular patients. In the present study we explored the possibility that this mechanism is an elevation of cortisol level.

Cortisol is secreted by the adrenal cortex upon activation of the hypothalamus-pituitary-adrenal (HPA) axis in response to physiological or psychological stress. In healthy persons, an increase in cortisol secretion is subsequently inhibited through coupling to receptors, among others, located in the hippocampus.[8] With increasing age the ability to maintain this homeostasis decreases, at least in a proportion of elderly subjects, resulting in prolonged or continuously elevated cortisol levels.[9-17]

In addition to regulating the negative feedback of HPA axis activity, the hippocampus is involved in learning and memory.[18] A chronic rise of cortisol levels may lead to neurodegeneration of the hippocampus,[19] and may thus contribute to the development of memory disorders observed in a number of aged subjects,[13,14,19-21] and specifically in those with Alzheimer's disease.[20-29]

Patients with atherosclerosis show memory deficits as well.[1-6] They also have an increased risk of developing dementia of both the vascular and the Alzheimer type.[30-32] However, the role of cortisol with respect to its effect on memory function in this group of subjects has not been investigated yet. This line of research might be relevant to the understanding of a possible physiological mechanism underlying cognitive impairment in patients with atherosclerotic disease, and in the association of atherosclerosis and the risk of dementia.

The aim of the present study was to investigate whether cortisol levels are elevated in patients with severe atherosclerosis, and whether there is a dose-response relationship between cortisol levels and memory function. The examinations took place one day before patients underwent vascular surgery.

Materials and methods

Subjects

Forty-seven patients with severe occlusive disease of the carotid arteries and 24 patients with femoropopliteal occlusive disease were enlisted from a waiting list for carotid endarterectomy and endarterectomy of the superficial femoral artery, respectively, in the St. Antonius Hospital in Nieuwegein, the Netherlands. Patients were excluded only if they had a history of minor or major stroke. A healthy control group consisted of 45 subjects without any evidence of cerebrovascular or neurological disease or a psychiatric history. They were recruited by an advertisement in a local newspaper and received a small reward for their participation. Written informed consent was obtained from all subjects.

In a clinical interview, before the start of the cognitive assessment, subjects were asked about their level of education, tobacco and alcohol use, and psychiatric and medical history. The medical questions concerned, among others, previous myocardial infarction or coronary artery surgery and presence of other vascular risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus. Additional medical information of patients was obtained from the medical records. Educational level was categorized according to the 7-point ranking system of Verhage.[33] This system reflects the educational system in the Netherlands. A subject was classified as a smoker if he was a current cigarette smoker or quit cigarette smoking in the year before the assessment. To be able to examine whether the results should be corrected for the possible influence of mood, subjects also filled out the Dutch shortened Profile of Mood States (POMS).[34] This scale consists of 32 items covering five different mood dimensions: anger, tension, depression, vigor, and fatigue.

Assessment of cortisol levels

Cortisol was assessed from saliva collected with the use of small cotton wool swab (Salivette; Sarstedt, Rommelsdorf, Germany). This noninvasive technique was used at the admission day into the hospital in patients, and at a regular weekday in healthy controls. Subjects received the salivettes at home by mail, and were instructed to collect the samples right after awakening, before lunch, and before dinner. They were asked to rinse their mouth with water at each sampling point, and to refrain from eating, drinking, or smoking in the 30 minutes before sampling. Accidental noncompliance with these instructions and any other peculiarities with regarding to the sampling had to be written down on a form. Patients brought the samples with them to the hospital and handed them to the nursing staff, after which they were stored in the refrigerator. Healthy control subjects kept them in their own refrigerator, until we came to collect them. At the department, the samples subsequently were kept frozen at -20°C until the time of analysis. Analysis was performed with a time-resolved immunoassay with fluorescence detection (DELFIA), which is described elsewhere.[35]

Assessment of cognitive functions and mood
The cognitive assessment took place on the admission day of patients into the hospital, and close to the day of saliva sampling for the healthy control subjects. The battery included the following tests related to memory: Digit Span forward and backward,[36] Word Learning Test immediate and delayed recall,[37] Doors Test part A and B,[38] and Verbal Fluency letters and categories.[36] In the Digit Span, increasing sequences of numbers have to be repeated in the same or reversed order as they were presented acoustically. The Word Learning Test is based on the more familiar Rey Auditory Verbal Learning Test[39] and requires the subject to learn a list of 15 monosyllabic words and subsequently retrieve them from memory. The words refer to concrete objects and are displayed on a computer screen to standardize presentation. The test included three immediate recall trials and a delayed recall trial at approximately 15 minutes. In the Doors Test, the subject is asked to memorize a series of twelve colored photographs of doors. The subject then has to recognize the memorized door among three other distracting doors, fitting the same general label (e.g. ‘church door’). There are two series; series B is more difficult than series A because the doors in series B are still more alike. In the Verbal Fluency Test the subject has to generate as many words as possible within one minute, beginning with a specified letter or belonging to a specific semantic category.

Data analysis
Nine saliva samples (of seven patients with carotid artery disease and two patients with peripheral arterial disease) were accidentally lost in the hospital, and two samples (of two patients) appeared to be empty at the analysis of the saliva. These missing values were imputed using Expectation-Maximization estimation, which is considered an effective method to impute missing data points, because it uses all information in the available data.[40]

Before imputation, cortisol values were screened for outliers and normality.[41] Outliers (values above the standardized score of 3.29 on one or more cortisol values) existed for one patient with carotid artery disease and two patients with peripheral arterial disease, and those subjects were deleted from the analyses. In their notes, no underlying variable was found to be responsible for these outliers. After the deletion process, the skewness and kurtosis of the three cortisol measures, separately for the total patient group and healthy control group, were still relatively large (the skewness ranged 1.1 to 2.3 and the kurtosis from 2.2 to 7.4) and indicate that the values were not normally distributed. The cortisol variables were, therefore, logarithmically transformed.

Vascular patients and healthy controls were compared on age (univariate analysis of variance, ANOVA), gender ratio (Pearson Chi-square test), educational level (Mann-Whitney *U* test), and vascular risk factors (Pearson Chi-square test). Differences between the patient group and healthy control group (and post-hoc between the two patient subgroups) in cortisol levels and in cognitive test scores were examined with ANOVA. Linear relations between cortisol levels and test performance were examined with correlational analyses, within the patient group only. We determined a priori whether the correlations should be corrected for the influence of demographic characteristics or mood states as reported on the day before surgery. This was not the case, since none of these variables were significantly related to at least one cortisol variable and at least one cognitive variable. The alpha significance level was set on $p = .05$.

Results

After excluding the three patients with outliers in cortisol level, the study included 46 patients with carotid artery disease, 22 patients with peripheral arterial disease, and 45 healthy control subjects. Demographic and medical characteristics are shown in Table 1. The groups were comparable in age, sex ratio, and educational level ($p > .05$). But as expected, the total patient group included much more subjects with heart disease and vascular risk factors (such as hypertension, hypercholesterolemia, diabetes mellitus, and cigarette smoking) than the healthy control group.

Table 1. Characteristics of patients and healthy control subjects.

	All patients	Healthy subjects	*p*	Patients: carotid	Patients: peripheral	*p*
Age, y, mean ± SD	65.7 ± 7.4	66.7 ± 4.5	.42	65.9 ± 7.4	65.4 ± 7.5	.80
Males, %	84	80	.60	83	86	.69
Heart disease, %	59	11	<.001	54	68	.28
Hypertension, %	56	13	<.001	63	41	.09
Hypercholesterolemia, %	57	13	<.001	52	68	.21
Diabetes mellitus, %	12	2	.07	13	9	.64
Cigarette smoking, %	34	13	.02	30	41	.39

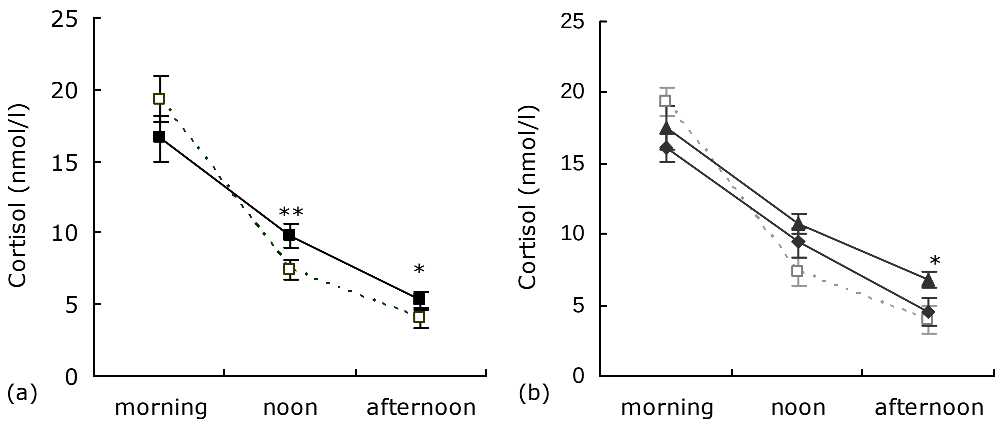

Fig 1. Diurnal course of salivary cortisol levels (a) in patients with vascular disease (n) and healthy control subjects (o), and (b) in patients with carotid artery disease (u) and patients with peripheral arterial disease (▲). Error bars are SEM. * $p < .05$, ** $p = .01$.

Figure 1 shows the means and standard errors of the mean (SEM) of the cortisol levels at the three sampling points for patients and healthy control subjects. The total patient group had significantly higher noon and afternoon cortisol values than the healthy control group ($p = .01$ and $p = .03$, respectively), but the difference in morning cortisol values did not reach significance ($p = .70$). The mean cortisol value across the day did not differ either between the two groups ($p = .80$). Within the patient group, those with peripheral arterial disease had significantly higher afternoon cortisol values than those with carotid artery disease ($p = .02$).

Table 2 shows the performance of patients and healthy control subjects on the memory tests. The total patient group performed significantly worse than the healthy control group on all tests, except Digit Span backward (working memory) and the immediate recall of the Word Learning Test (verbal memory). The patients with carotid artery disease and those with peripheral arterial disease did not differ from each other on any of the cognitive tests (data not shown).

Correlations between the cognitive test scores and cortisol levels of the total patient group are also displayed in Table 2. Three correlations were significant and two of these were in line with our hypothesis: a lower score on Verbal Fluency categories was associated with a higher morning cortisol value and a lower score on Digit Span backward was associated with a higher cortisol value in the afternoon. Opposite to the prediction was the association between a *higher* score (better performance) on Verbal Fluency categories and a higher cortisol value at noon. Mean cortisol level across the day was not significantly associated with any of the cognitive test scores (data not shown, r ranged from −.14 to .13) and neither with a composed memory score (the mean of the eight standardized test scores) ($r = -.04$).

Table 2. Cognitive performance (mean ± SD) of patients and healthy control subjects, and correlation coefficients between cognitive scores and cortisol values within the patient group.

	Cognitive performance			Correlations with cortisol		
	Vascular patients	Healthy subjects	*p*	Morning	Noon	Afternoon
Digit Span						
forward	5.5 ± 1.0	6.0 ± 1.2	.02	-.01	.03	-.04
backward	4.1 ± 1.1	4.2 ± 1.5	.76	-.05	-.06	-.33**
Word Learning						
immediate recall	20.6 ± 5.4	22.3 ± 6.1	.11	.05	.04	.03
delayed recall	6.2 ± 2.6	7.6 ± 3.1	.009	-.08	.15	-.12
Doors Test						
part A	9.7 ± 1.5	10.6 ± 1.3	.001	-.07	.09	.08
part B	5.5 ± 1.7	7.1 ± 2.3	<0.001	-.22	.17	-.08
Verbal Fluency						
letters	11.7 ± 3.9	14.0 ± 5.0	.007	-.02	.31*	.05
categories	17.1 ± 3.9	20.3 ± 4.0	<.001	-.26*	.23	-.05

* $p < .05$, ** $p < .01$ (two-tailed).

Discussion

The aim of this study was to investigate whether cortisol levels are elevated in patients with severe atherosclerotic disease of the carotid or peripheral arteries, and whether there is a dose-response relationship between cortisol and memory function.

Noon and afternoon cortisol values were indeed higher in the total patient group compared to the healthy control group, but not morning values and the overall day value. Moreover, the difference in afternoon values could be largely attributed to the higher levels of patients with peripheral arterial disease compared to the levels of patients with carotid artery disease.

The total patient group performed significantly worse than the healthy control group on almost all memory tests, whereas the two different patient groups did not differ from each other. These findings are in agreement with previous studies reporting memory impairment in various clinical manifestations of atherosclerotic disease.[1-6]

Within the total patient group, only three cognitive test scores were significantly associated with cortisol. Two of these associations were in the predicted direction (a lower score on Verbal Fluency categories was associated with a higher morning value and a lower score on Digit Span backward was associated with a higher afternoon value), whereas the other was not (a higher score on Verbal Fluency categories was associated with a higher cortisol value around noon). The findings, thus, do not convincingly support the hypothesis that elevated cortisol levels are responsible for the memory impairment that can be observed in patients with severe atherosclerotic disease.

Assessment of patients took place one day before surgery. Although anticipatory stress may have contributed to the somewhat higher noon and afternoon cortisol levels observed in the patient group, it probably did not influence the relationship between cortisol and memory, since preoperative stress is likely to affect *both* cortisol and memory function within a subject. In addition, mood is hardly associated with reduced cognitive performance before vascular surgery.[2,42-44]

Patients with a history of stroke were explicitly excluded to decrease the possibility that substantial brain damage would account for cognitive impairment. It is possible, however, that silent infarcts or other brain abnormalities, such as atrophy or paraventricular white matter lesions, were present and accounted for the memory disorders observed in our patient group.[45-47] Unfortunately we had no data on this, but the fact that other cognitive functions are affected as well,[2] supports this possibility. We do not think that the reduction in cerebral blood supply is responsible for impaired brain function, since restoration of the blood flow does not improve cognitive functioning.[7]

In the present study, we could not confirm our idea that elevated cortisol might play a role in cognitive (or at least memory) impairment. Though patients with severe atherosclerosis showed elevated noon and afternoon cortisol levels, this was not related to memory impairment. This leaves the explanation that silent brain infarcts and other brain abnormalities, as associated with atherosclerotic disease, may be responsible for the cognitive impairments that can be observed in these patients.

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Chapter 8

Summary and general discussion

Carotid endarterectomy (CEA) is a surgical procedure to remove atherosclerotic plaque from the carotid arteries. Its intention is to reduce the risk of stroke.[1-4] The main aim of this thesis was to investigate the possible beneficial function of CEA on cognitive functioning and on perceived health. Several potentially confounding factors on task performance, such as mood and nonspecific effects from practice and surgery, were taken into account. This concluding chapter will summarize and discuss the main findings of this thesis. In addition, methodological considerations will be discussed and recommendations for future research will be given. The thesis ends with the clinical relevance of the study.

Cognitive functioning before CEA

Cognitive improvement due to the restoration of adequate cerebral blood flow presumes the existence of subnormal levels of cognitive functioning before surgery. In Chapter 2 of this thesis we examined a wide range of cognitive functions in patients with severe atherosclerotic disease, but without history of stroke. The patients performed significantly worse than healthy control subjects on most tests, even with preoperative mood taken into account. Impairments were present in the domains of attention, verbal and visual memory, verbal fluency, psychomotor speed, and executive functioning. As described in Chapter 3, patients with peripheral vascular disease (of their legs) performed very similarly. Simple motor skills and visuospatial performance (in both vascular groups) were not affected, implying that the impairments on the other cognitive tasks cannot be attributed to a reduced motor speed of the patients. The findings are largely in agreement with earlier reports, in which particularly reductions in verbal and visual memory, executive functioning (including verbal fluency), and more complex psychomotor skills in patients with atherosclerotic disease of the carotid artery before CEA were detected.[5-8]

The study described in Chapter 2 is relatively unique in further discriminations within the patient group with carotid artery disease, for example, separating those with unilateral versus bilateral stenosis of the carotid arteries, and those with versus without symptomatic history. This information could be useful in predicting who may eventually profit most from CEA with respect to cognitive functioning. Nevertheless, we observed only marginal differences between patients grouped according to the severity of the contralateral stenosis, or to the presence and type of previous ischemic symptoms. Medical risk factors, such as hypertension, hypercholesterolemia, diabetes mellitus, and heart disease, were not consistently associated with cognitive performance either. Accordingly, the findings do not clearly support the necessity of a distinction of subgroups in investigating the cognitive effects of CEA.

Cognitive changes following CEA

As described in Chapter 3 of this thesis, an issue that has often been ignored in previous longitudinal research on the effects of CEA on cognitive functioning is: accounting for potential confounding effects, such as positive effects from practice caused by repeated testing and the negative influence of surgery and anesthesia. A varying influence of these confounders may have contributed to the very mixed results that can be observed in the literature, namely improvement, no change, and even decline of cognitive functions.[8-18] An attempt was made to take the influences of these nonspecific effects into account by including patients with symptomatic femoropopliteal occlusive disease before endarterectomy of the superficial femoral artery (remote endarterectomy: REA) as a control group. These subjects were highly similar to patients with carotid artery disease with regard to demographic and medical characteristics, and, therefore, it may be assumed that possible practice effects are the same. Moreover, because the two vascular operations were highly comparable in procedure, except for its locus, we were also able to control for the possible negative influence of surgery and anesthesia (or perhaps positive with respect to relief from uncomplicated surgery) on cognitive outcome.

Significant improvements up to 1 year after surgery were demonstrated for both types of vascular patients in delayed verbal memory, the planning speed of movement, executive functioning, and motor skills with the dominant hand. However, no significant effect of the type of surgery was observed. This indicates that a *specific* effect of CEA (thus after correcting of a practice effect and nonspecific surgical effects) on cognitive functioning could not be demonstrated. Furthermore, controlling for the postoperative decrease in feelings of tension eliminated one of the previous significant time effects (i.e. the planning speed of movement). Because we cannot think of any physiological explanation why patients after *REA* would improve in cognitive functioning, we attributed the overall improvements to practice and to relief from surgery.

Cognitive laterality

The laterality hypothesis, addressed in Chapter 4, assumes ipsilateral effects on cognitive performance after CEA. Only right-handed male subjects were selected to test this hypothesis, because hemispheric specialization manifests itself most pronounced and reliable in right-handed males.[19] In addition, tasks sensitive to hemispheric specialization were included. Three months after CEA, performance increased only in left hand motor skills, irrespective of the side of surgery. Because this effect was comparable to that observed in the healthy control group, we attributed it to practice. Thus, although instruments and sample characteristics were optimal in studying hemispheric functional asymmetry, predominantly ipsilateral effects on cognitive functioning after CEA were not demonstrated. In line with the results of Chapter 3, this supports our observation that the preoperative cognitive impairments are not reversed by CEA.

Perioperative embolism
In Chapter 5 we investigated whether perioperative embolism accounted for possible cognitive decline after CEA. We indeed detected intraoperative and immediate postoperative emboli in a large majority of patients, most often after the surgical phase of clamp release, though the total number per patient was generally low. The latter, and the relatively large postoperative interval of 3 months, may explain why no significant association between embolic load and cognitive change following surgery was shown. The absence of a relation does, however, not preclude an effect of a specific type of emboli (particulate or air) on postoperative cognitive functioning. Unfortunately we had no information on this aspect.

Subjective aspects and cognitive functioning

Mood may affect the motivation and energy to perform a task to the best. This stresses the importance of taking mood factors into account in cognitive research.[9,10] Furthermore, performance on tests often does not run parallel to patients' own evaluations of their cognitive capabilities.[20-23] This subjective aspect has generally been ignored in research evaluating the effects of CEA, which is remarkable since it is this aspect that is specifically of concern to the patient.[24]

Mood
Before CEA, patients reported significantly less vigor and more fatigue, tension and depression than healthy control subjects. Correction for the potential negative effect of mood did, however, not affect differences in task performance (Chapter 2). After surgery, patients reported significantly less tension. Controlling for this change considerably reduced the time effect on one of the four cognitive tests previously showing an improvement (Chapter 3), and indicates the importance of taking mood factors into account.

Cognitive failures in daily life
The number of cognitive failures in daily life reported before CEA was very similar to that reported by our healthy control subjects (data not shown). Within the patient group, there were also no changes on this variable during the year after CEA (Chapter 6). Perhaps, the cognitive impairment as assessed with objective tests (Chapter 2) is rather subtle and does not (yet) cause cognitive complaints in daily life.

Perceived health

Patients with severe carotid artery disease are faced with the risk of developing stroke. Most probably, a number of them already suffered from ischemic symptoms, such as temporary monocular blindness (amaurosis fugax) or a hemispheric transient ischemic attack, which comprises of symptoms like temporal paralysis or language problems. Comorbid medical conditions, such as hypertension and hypercholesterolemia, are frequently found in this patient group as well.

It has been suggested that CEA improves the perception of health. The few studies on this topic, however, varied greatly in their outcomes.[7,18,25-29] In addition, evaluation of both physical and mental aspects of health perception in the same study is the exception rather than the rule.[18,28] Effects of CEA on perceived health in the long run received minor attention too.[7] Therefore, we assessed patients before and at 3 months and 1 year after CEA with the widely used Short Form 36 Health Survey (Chapter 6).

Patients preoperatively reported significant but small deviations from the population norm in physical function, general health, and vitality. In fact, we had expected a worse evaluation of health before CEA, at least in view of the life-threatening nature of the disease and the comorbid conditions. Perhaps patients are not fully aware of the risks they run. The exclusion of those with a history of stroke (possibly suffering from residual neurological deficits) may also explain why both physical and mental health aspects were evaluated as relatively well.

The small preoperative deviations from the population norm leave little room for improvement after CEA. Nevertheless, small but significant improvements in perceived health up to one year after surgery were observed, being significant in physical role function, general health, vitality, and mental health. Patients also retrospectively noted a slight worsening of health in the year before surgery and some improvement after surgery. We argue that the small deviations from the norm before CEA are due to an increase in distress before an operation, and that the improvements can be attributed to a postoperative decrease in anxiety due to the knowledge of the reduced stroke risk and relief after uncomplicated surgery. The two earlier studies with a multidimensional approach, nevertheless, did not find specific improvements in health perception following CEA.[18,28] The inclusion of stroke patients possibly contributed to the somewhat more negative outcomes of these studies.

Methodological considerations

As mentioned, the possible restorative role of CEA with respect to cognitive functioning has frequently been a topic of investigation. The main strength of the study described in Chapter 3 was the methodological more strict design in comparison to previous studies. In the first place, the existence of cognitive deficits prior to the intervention was ascertained (see also Chapter 2) in order to assess the room for improvement after the procedure. Secondly, we accounted for several confounding variables, such as mood, practice effects, and nonspecific surgical influences. Other methodologically important considerations involve the inclusion of patients and controls, the timing of preoperative and postoperative measurements, and the type of data analysis. These issues will be briefly discussed in this section.

Inclusion of subjects

Consecutive inclusion of patients seems to be the best way to achieve a representative research sample. This may be feasible in studies evaluating the effects of a surgical procedure on morbidity and mortality, but less so in cognitive research.[18] In addition to the requirement of being mentally and physically able to perform the tasks, assessment of cognitive functions appeals much to time, motivation, and energy of the patients, and also of the hospital staff. Although many efforts were made to recruit patients consecutively, a number of situations indeed occurred in which patients or staff could not cooperate. This may have restricted the representativeness (and size) of our patient sample, but unfortunately seems to be inevitable in cognitive research.

To ascertain preoperative impairment prior to CEA, the performance on cognitive tests of patients and healthy subjects with similar demographic characteristics were compared (Chapter 2). In both groups, tests were presented in exactly the same order and with exactly the same instructions to standardize the assessment procedure as much as possible. We think this way of obtaining reference performance criteria is more reliable, at least in scientific research, than the use of norms reported in the literature (if available anyway). However, recruitment of healthy subjects through an advertisement in a local newspaper can also produce bias, since the healthiest and most motivated subjects may feel attracted to an assessment of cognitive functions. This possibility crossed our mind when we observed that our healthy subjects had significantly higher scores than the population norm on all health-related aspects of the health questionnaire (SF-36), except for the mental health scale (data not shown). For this reason, we compared patients before and after CEA to the population norm rather than to the healthy control group on quality of life aspects (Chapter 6). Nevertheless, with respect to cognitive functions, we maintain to believe that a healthy control group assessed in a standardized situation is the better option.

The question of what constitutes an appropriate control group in the study of cognitive changes following CEA was asked already by Asken and Hobson in their review on intellectual change after CEA of 1977.[29] According to their view, the selection of another class of surgical patients with equal anesthesia insures equivalence of the demand characteristics of the test situation: being hospitalized, awaiting surgery, postoperative relief, and expectations of success. A more recent review rather preferred equality in medical and arteriographic characteristics.[10] We selected patients with peripheral vascular disease undergoing REA as a control group (Chapter 3). These subjects were highly similar to patients before CEA in both demographic and medical characteristics, and therefore, possible practice effects were assumed to be the same. Since CEA and REA are highly comparable in vascular procedure, except for its locus, we were able at the same time to control for the possible nonspecific negative influence of (awaiting) surgery and anesthesia on cognitive outcome.

Most notable was our finding of similar cognitive performance before CEA and REA (Chapter 3). In fact, this was also reported by two other studies that exclusively included peripheral vascular surgery patients as control subjects,[30,31] and perhaps indicates either the high prevalence of carotid artery stenosis in peripheral vascular disease[32-35] or the common underlying disease of generalized atherosclerosis.[30] Generalized atherosclerosis may be associated, for example, with structural brain abnormalities arising from chronic hypoperfusion caused by accumulating atherosclerotic plaque in other intracerebral arteries or from occlusion of blood vessels by series of microemboli. Unfortunately, the degree of carotid artery stenosis in our REA group and signs of brain damage with imaging techniques in both the CEA and REA group, were not assessed.

Since decreased memory function is associated with increased cortisol levels, we explored whether an elevation of cortisol might be the common mechanism underlying the cognitive impairment in patients with severe atherosclerotic disease. Patients indeed showed elevated noon and afternoon cortisol levels, but this was not related to memory impairment (Chapter 7). This finding further supports the view that silent brain infarcts and other brain abnormalities, as associated with atherosclerotic disease, may be responsible for the cognitive impairments.

Preoperative assessment

To avoid the influence of being hospitalized and awaiting surgery, and to reduce time costs in the hospital, the questionnaires concerning quality of life and cognitive failures in daily life were sent to the homes of patients, as soon as we recruited them from the waiting list (Chapter 6). Generally this was several weeks before surgery. In contrast, neuropsychological testing of patients before CEA and REA was performed in the hospital 1 day before surgery (Chapter 2). The fact that patients were hospitalized and awaited surgery may have influenced cognitive test performance.[29] However, due to time limitations and for practical reasons it was not possible to perform all the assessments in the home situation some time before surgery. On the other hand, testing of cognitive functions in a quiet hospital room (or in the case of healthy controls in the department lab) promoted standardization and enabled control of the researcher over the testing situation. As mentioned, we attempted to reduce the potential effect of preoperative anxiety on cognitive performance as much as possible by including mood states as covariates in the statistical analyses (Chapter 2, Chapter 3). Moreover, our control group with peripheral vascular disease was also hospitalized and anticipated surgery (Chapter 3).

Postoperative assessment
At the start of the project, we planned postoperative assessments at the day of discharge from the hospital (most often the third day after surgery) and at 3 months and 1 year after surgery to investigate the immediate, short-term, and long-term effects of CEA on cognitive functioning. Negative effects from surgery, for example, might be more pronounced shortly after surgery, whereas positive effects might need some time to become apparent.[9,10] However, our patients found the early postoperative measurement to be very uncomfortable and fatiguing. Since we felt that the cognitive achievements were likely to be influenced by this discomfort and we were afraid of losing patients for this reason in the follow-up assessments, we abandoned this measurement, and focused on the more stable and clinically more relevant measurements at 3 and 12 months after the operation.[36]

Data analysis
Research on cognitive functioning after coronary artery surgery usually focuses on the incidence of cognitive decline. Moreover, incidence analysis (by single-case definitions) rather than group mean analysis is recommended in the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery.[36,37] Although this technique, focusing on individuals, has not been applied (yet) in the assessment of cognitive changes after CEA, because of similarities with the area of coronary artery research, I would like to consider several of its drawbacks, as addressed by Keizer.[38] The main criticism on incidence analysis perhaps is that the incidence of cognitive decline strongly depends on the definition of cognitive decline. Examples are a 20% decrease in at least 20% of the tests, a decrease of 1 standard deviation (SD) on at least two tests, and change according to the 'reliable change index'. Other issues involve the ignorance of the magnitude of changes if continuous test scores are reduced to dichotomous outcome measures, and the statistical phenomenon of regression to the mean.[38] Moreover, patients classified as showing decline (for example a decrease of 1 SD in at least two tests) may demonstrate improvement as well (namely an increase of 1 SD in two other tests). This possibility has generally been disregarded in the previous cardiac studies.[38] For all these reasons, like Keizer we prefer group and subgroup mean analysis instead of individual analysis.

Future research

Although the studies presented in this thesis have shown no restorative effect of CEA on cognitive functioning, the removal of the stenosis may have a protective value against cognitive decline in the future. This can only be reliably examined in a large longitudinal trial in which patients with severe atherosclerotic disease of the carotid artery are randomly assigned to optimal medical care alone or to optimal medical care plus CEA.[39] However, since the efficacy of the operation in reducing the risk of stroke in patients with high-grade stenosis has been clearly demonstrated already in 1991,[1,2] such a design would ethically be controversial nowadays, even for asymptomatic patients.[3,4]

We established impairment in several cognitive domains in patients with severe carotid artery disease. Cognitive functions in patients with peripheral vascular disease were impaired to about the same extent, suggesting an effect of the common underlying (chronic) disease of generalized atherosclerosis. It would be interesting and clinically relevant to compare the cognitive functions of patients with various clinical manifestations of atherosclerotic disease, and to focus on common abnormalities in brain structure or neuronal metabolism. Future research should also reliably investigate the contribution of vascular risk factors and medication use on cognitive impairment. Disentangling the complex relations between atherosclerosis, brain abnormalities, vascular risk factors, and cognitive functions certainly is a difficult but challenging task.

Clinical relevance

Demonstration of cognitive improvement due to CEA could have been of supplementary value in the decision to perform the surgical intervention. However, the present thesis found neither improvement nor decline in cognitive functions after CEA. Prevention of future complications, like stroke, thus remains as the basis for the decision. On the other hand, our findings are useful to reassure patients who report concerns with respect to cognitive changes due to the operation.

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Samenvatting

Patiënten met een vernauwing van de halsslagader hebben een verhoogd risico op een herseninfarct. De preventieve maatregelen die hiertegen kunnen worden genomen zijn het gebruik van medicijnen, zoals aspirine, en het bestrijden van risicofactoren van atherosclerose, zoals een hoge bloeddruk, een verhoogd cholesterolgehalte, diabetes mellitus en roken. Een carotis endarteriëctomie (CEA) kan worden uitgevoerd als er sprake is van een ernstige vernauwing van de halsslagader. Bij deze operatie wordt de vernauwing, door atherosclerose ontstaan, opgeheven.

In het verleden is veel onderzoek gedaan naar de vraag of de hersenen na een CEA beter kunnen gaan functioneren. Deze vraag is gebaseerd op de observatie dat patiënten met een belemmerde bloedtoevoer naar de hersenen cognitieve stoornissen vertonen en ná de operatie in het cognitief functioneren verbeteren. Pogingen om alternatieve verklaringen voor een dergelijke verbetering uit te sluiten zijn echter onvoldoende ondernomen. Bovendien is in eerder onderzoek nauwelijks nagegaan of er vóór de operatie inderdaad wel sprake is van een verminderd cognitief functioneren.

Het doel van dit proefschrift was om de effecten van een operatie aan de halsslagader op het cognitief functioneren te bestuderen. Getracht is om alternatieve verklaringen voor een eventuele verbetering (of verslechtering) uit te sluiten. Ook is nagegaan of er veranderingen optreden in de gezondheid, zoals waargenomen door de patiënt.

In Hoofdstuk 2 van dit proefschrift wordt het cognitief functioneren van patiënten met een ernstige vernauwing van de halsslagader vóór een CEA beschreven. Patiënten die reeds een herseninfarct hebben gehad werden van het onderzoek uitgesloten omdat cognitieve stoornissen bij deze mensen (mede) verklaard zouden kunnen worden door structurele hersenschade. De controlegroep bestond uit gezonde vrijwilligers met dezelfde demografische kenmerken. De patiëntengroep presteerde minder goed dan de controlegroep op tests die de aandacht, het verbale geheugen, het visuele geheugen, de taalvaardigheid, de psychomotorische snelheid en het uitvoerend functioneren pretenderen te meten. Correctie voor stemming beïnvloedde deze resultaten niet. De eenvoudige motorische functies en het visueel-ruimtelijke vermogen waren gelijk in de twee groepen. Wanneer de patiëntengroep werd ingedeeld op de aanwezigheid en het type (cerebraal of retinaal) van eerdere klinische symptomen of op ernst van de vernauwing aan de contralaterale zijde werden slechts minimale verschillen tussen de subgroepen gevonden.

In Hoofdstuk 3 wordt onderzocht of een CEA een positief effect heeft op het cognitief functioneren. In onze studie is onder meer gecorrigeerd voor leereffecten die kunnen optreden bij herhaald testen en voor non-specifieke effecten van een operatie, zoals stress voor het ondergaan van een operatie en opluchting na een geslaagde operatie. Dit gebeurde door het opnemen van een controlegroep bestaande uit patiënten met een afsluiting van de beenvaten die eveneens een operatie ondergingen. Deze beenoperatie is wat betreft duur, narcose en verwachte hersteltijd gelijk aan een CEA en ook bestaan er overeenkomsten in de medische achtergrond van beide patiëntgroepen. Wederom werden patiënten met een eerder opgetreden herseninfarct van het onderzoek uitgesloten. Verbetering in deze groep zou immers ook door herstel van het letsel kunnen worden verklaard, terwijl de afwezigheid van een effect te wijten zou kunnen zijn aan het bestaan van permanente hersenschade. Vóór de operatie werden geen verschillen in testprestaties gevonden tussen patiënten met een vernauwing van de halsslagader en patiënten met een afsluiting van de beenvaten. Beide groepen presteerden echter wel minder goed dan een gezonde controlegroep. Tot een jaar na de operatie waren verbeteringen zichtbaar in het verbale geheugen, het uitvoerend functioneren, de planning van een beweging en de motorische vaardigheden met de voorkeurshand. Een verschil hierin tussen de twee patiëntgroepen werd echter niet gevonden. Een specifiek verbeterend effect van een CEA op het cognitief functioneren kon in dit onderzoek dus niet worden aangetoond.

Hoofdstuk 4 heeft betrekking op de lateraliteitshypothese. Deze hypothese stelt dat een CEA een gunstiger effect heeft op de cognitieve functies die worden gemedieerd door de hersenhelft aan de kant van de operatie. Aldus mogen verbeteringen in de verbale en taalfuncties verwacht worden na een operatie aan de linker halsslagader en verbeteringen in het nonverbale of visueel-ruimtelijke functioneren na een operatie aan de rechter halsslagader. De motorische functies van de lichaamszijde tegengesteld aan die van de operatie kunnen volgens deze hypothese overeenkomstig verbeteren. Omdat een dergelijke lateraliteit van hersenfuncties het meest uitgesproken is bij rechtshandige mannen zijn alleen zij in dit onderzoek geïncludeerd. Tevens is gekozen voor tests die de betrokkenheid van de linker of rechter hersenhelft min of meer zuiver meet, zoals een dichotische luistertaak, een motorische reactietaak en een test voor vingervlugheid. Drie maanden na de operatie trad enkel een verbetering op in de motorische vaardigheid van de linkerhand, ongeacht de operatiezijde. Omdat een dergelijke verbetering ook werd geconstateerd in de gezonde controlegroep, werd deze toegeschreven aan een leereffect.

Hoewel een CEA de kans op een toekomstig herseninfarct verkleint, bestaat er tijdens de operatie een licht verhoogd risico op complicaties. Deeltjes van de aanslag aan de binnenkant van de halsslagader kunnen bij het verwijderen namelijk losraken en, bij het herstel van de bloedtoevoer, verderop gelegen vaten afsluiten. De losgeraakte deeltjes worden ‘embolieën’ genoemd en deze kunnen in de middelste halsslagader middels zogeheten transcraniële Doppler (TCD) ultrasonografie geregistreerd worden. In Hoofdstuk 5 wordt nagegaan of er een verband bestaat tussen enerzijds de mate van embolisatie tijdens en/of direct na een CEA en anderzijds het cognitief functioneren drie maanden na de operatie. Microembolisatie kwam voor bij het merendeel van de patiënten, doch het aantal geregistreerde deeltjes (bestaande uit vaste deeltjes óf lucht) was over het algemeen laag. Dit gegeven, en het relatieve lange postoperatieve interval van drie maanden, verklaart wellicht waarom een verband tussen embolisatie en cognitieve verandering na een CEA niet werd gevonden.

Er is nog maar weinig onderzoek gedaan naar de beoordeling van het cognitief functioneren door CEA patiënten zelf. Dit is opvallend omdat patiënten met een vernauwing van de halsslagader zich juist hierover vaak zorgen maken. Hoofdstuk 6 gaat in op dit onderwerp en beschrijft tevens de fysieke en mentale gezondheid zoals deze door de patiënt voor en na een CEA wordt waargenomen. Kleine verbeteringen tot een jaar na de operatie werden gevonden op de gezondheidsschalen fysiek rolfunctioneren, algemene gezondheid, vitaliteit en mentale gezondheid. Daarnaast meldde ongeveer 70% van de patiënten na de CEA dat hun gezondheid gedurende het afgelopen jaar gelijk was gebleven of enigszins was verbeterd. Het aantal cognitieve klachten was niet veranderd drie maanden en een jaar na de operatie. Verschillen tussen subgroepen op basis van bijvoorbeeld demografische kenmerken en symptomatische achtergrond waren ook niet aanwezig.

Ten slotte wordt in Hoofdstuk 7 een exploratief onderzoek beschreven naar de mogelijke samenhang tussen cortisol en geheugen bij patiënten met ernstige atherosclerose. Het hormoon cortisol wordt door de bijnier afgegeven na activatie van de zogeheten HPA-as in reactie op fysiologische of psychologische stress. Een verhoging van cortisol wordt vervolgens geïnhibeerd door de koppeling van cortisol aan receptoren die zich onder andere in de hippocampus bevinden. Wanneer mensen ouder worden, neemt de regulatie van deze homeostase af, met continu verhoogde cortisolwaarden tot gevolg. Dit kan schade veroorzaken aan de hippocampus. Omdat de hippocampus ook betrokken is bij leren en geheugen, zijn zelfs geheugenstoornissen als gevolg daarvan mogelijk. In Hoofdstuk 7 wordt nagegaan of een vermindering van geheugenfuncties, zoals geconstateerd bij patiënten met verschillende uitingen van de ziekte atherosclerose (in de beenvaten of in de halsslagader), samenhing met cortisol. Cortisol werd uit speeksel bepaald dat op drie momenten van een dag was verzameld, namelijk direct bij het opstaan, vlak voor het middageten en vlak voor het avondeten. Hoewel het cortisolniveau van patiënten in vergelijking met gezonde vrijwilligers met name in de middag verhoogd was, bleek er geen relatie te bestaan met de prestaties op verschillende geheugentests.

Concluderend laten de resultaten van dit proefschrift zien dat een CEA geen specifiek verbeterend effect heeft op het cognitief functioneren. Er is echter ook geen sprake van een verslechtering van de cognitieve functies na de operatie. Het voorkómen van een herseninfarct blijft dus de enige reden om een CEA uit te voeren. Opvallend was dat patiënten met een afsluiting van de beenvaten nagenoeg hetzelfde presteerden als patiënten met een vernauwing in de halsslagader, doch dat deze prestaties beneden het niveau van een gezonde groep lagen. Wellicht dat de algemene ziekte atherosclerose aan deze cognitieve afwijkingen ten grondslag ligt. Atherosclerose kan worden geassocieerd met structurele hersenbeschadigingen die ontstaan zijn door een vernauwing of afsluiting van bloedvaten in de hersenen als gevolg van opeenhoping van aanslag of embolisatie. Vervolgonderzoek zou zich vooral moeten richten op de relatie tussen deze (subtiele) hersenbeschadigingen en cognitief functioneren.

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Curriculum Vitae

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