Cognitive impairment in patients with symptomatic carotid artery occlusion

Floor Bakker

Bakker, Floor
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Cognitive impairment in patients with symptomatic carotid artery occlusion

Cognitieve stoornissen bij patiënten met een symptomatische occlusie van de arteria carotis

(met een samenvatting in het Nederlands)

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Floor Claire Bakker
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Promotor
Prof. Dr. L.J. Kappelle
(Department of Neurology, University Medical Center Utrecht, The Netherlands)

Co-promotores
Dr. C.J.M. Klijn
(Department of Neurology, University Medical Center Utrecht, The Netherlands)
Dr. A. Jennekens-Schinkel
(Sector of Neuropsychology, Wilhelmina Children Hospital, University Medical Center Utrecht, The Netherlands)

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Contents

1 General introduction

Obstructive carotid artery disease

Blood supply to the brain occurs through the carotid arteries (anterior circulation) and the vertebral arteries (posterior circulation). Atherosclerotic plaques in these cerebropetal arteries, whether partial ("stenosis") or complete ("occlusion"), may impair the blood supply to the brain and cause cerebral hypoperfusion. Whether regional cerebral blood flow (CBF) is maintained or not depends on compensatory processes such as vasodilitation to reduce cerebral vascular resistance, and development of collateral flow.[122]

Patients with obstructive disease of the carotid artery (CAD) are at increased risk of (recurrent) ischemic events. In patients with symptomatic occlusion of the internal carotid artery (ICA), the risk of recurrent stroke is approximately 5 to 6% per year.[64] Patients with symptomatic carotid artery occlusion and a compromised CBF have an even higher risk of recurrent stroke, in the order of 9 to 18% per year.[44,65] The cause of ischemic symptoms in these patients may be thrombo-embolism, i.e. occlusion of intracranial arteries by emboli originating from atherosclerotic plaques. In addition, hemodynamic disturbances as a result of chronic cerebral hypoperfusion have been suggested to play a role in patients with severe CAD.[65]

Treatment of patients with symptomatic carotid artery occlusion or stenosis is aimed at prevention of recurrent cerebral ischemia, and includes antithrombotic medication and modification of vascular risk factors such as hypertension, smoking, hyperlipidemia and diabetes mellitus. Furthermore, surgical revascularization procedures such as carotid endarterectomy or extracranial-intracranial (EC-IC) bypass surgery may be considered if the risk of recurrent stroke outweighs the risk of surgery.[65,67]

Cognitive impairment and obstructive CAD

Cognition may be broadly defined as the higher levels of perception, memory and the more central aspects of the control of action,[108] or as the information handling aspect of behaviour.[70] The international classification of functioning, disability and health (ICF) defines impairment of cognitive functioning as an abnormality in or loss of cognitive functions.[131] The impairment can be temporary or permanent, and can worsen or improve.

Cognitive impairment is a common consequence of cerebral ischemic stroke, its reported prevalence ranging up to 50% three months after the occurrence of the stroke.[53,93,115] Multiple or even single strokes on strategic locations in the brain can lead to vascular

dementia, a cognitive disorder with a far-reaching impact on daily life.[3,35,89,97,99] Little is known, however, about the prevalence and severity of cognitive impairment in patients with only transient or minor disabling symptoms of cerebral ischemia. For adequate counselling and care, it is relevant to know whether and to which extent cognitive impairment is to be expected in patients with obstructive CAD, also when the patient has no or only minor functional impairments.
Besides ischemic brain damage due to thrombo-embolism, chronic cerebral hypoperfusion has been suggested to cause or contribute to cognitive impairment in patients with severe stenosis or occlusion of the carotid artery.[65] If so, surgical interventions to improve the blood flow to the brain may halt or even reverse cognitive decline in these patients. Findings on the impact of carotid endarterectomy or EC-IC bypass surgery on cognitive functioning are contradictory, varying from deterioration to improvement of cognition after surgery.[73,112,114] Before conclusions can be drawn on the effectiveness of revascularization surgery in preventing (further) cognitive decline, knowledge is required on (prognostic indicators for) the course of cognitive functioning in patients with obstructive CAD who do not undergo revascularization surgery.

Purpose and design of the current study

The aims of the current study were the following:

1. To review the current state of knowledge on cognitive impairment in patients with obstructive CAD.
2. To determine the prevalence, nature, severity, and course of cognitive impairment in patients with a transient ischemic attack (TIA) or a minor stroke associated with obstructive CAD.
3. To find out whether quality of life (QoL) is affected in patients with symptomatic CAD, and whether cognitive impairment has an adverse effect on QoL in these patients.
4. To explore correlates of the presence and course of cognitive impairment in patients with symptomatic CAD, with a focus on cerebral ischemic damage, cerebral hypoperfusion, and impaired cerebral metabolism.

Having reviewed the existing literature, we investigated 113 consecutive patients with symptomatic occlusion of the left, the right, or both ICA(s), in a prospective follow-up study. We studied patients with symptomatic ICA occlusion, as this group may be

expected to suffer the most from chronic cerebral hypoperfusion and its consequences. Healthy spouses, and occasionally siblings, of the patients were asked to cooperate with the neuropsychological assessment, thus providing data on normal cognitive functioning and effects of re-testing.

Chapter two of this thesis provides a systematic review of the literature on cognitive impairment in patients with obstructive CAD. Chapters three and four address the prevalence, the nature and severity, and the neurological correlates of cognitive impairment in patients with a TIA associated with an ipsilateral ICA occlusion. In chapter five, both transversal and longitudinal data on cognitive functioning and health-related QoL are presented for patients with a TIA or a minor stroke attributable to an ipsilateral ICA occlusion. Chapter six addresses the impact of carotid endarterectomy for contralateral ICA stenosis on cognitive functioning in patients with symptomatic ICA occlusion. Finally, in chapter seven the overall results of this thesis are discussed.

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Cognitive disorders in patients with occlusive disease of the carotid artery: a systematic review of the literature

F.C. Bakker,
C.J.M. Klijn,
A. Jennekens-Schinkel,
L.J. Kappelle

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INTRODUCTION

Patients with occlusive disease of the internal carotid artery (ICA) are at risk of future transient or permanent neurological deficits. The major cause of cerebral ischemia in patients with occlusive disease of the ICA is intracranial arterial obstruction by thrombo-embolism. In addition, a compromised cerebral blood flow may play an important role in the recurrence of ischemic episodes in a sizeable proportion of patients, in particular in those with carotid occlusion.[65]

Although the detrimental influence of major ischemic stroke on cognition is well known,[92,115] the consequences of minor ischemic stroke or transient ischemic attacks (TIAs) are less well described.[31,47] Even less is known about the influence of chronic cerebral hypoperfusion on cognitive functioning.[65,85] The aim of this systematic literature review is to establish the current state of knowledge about prevalence, nature, severity, course and cause(s) of cognitive deficits in patients with stenosis or occlusion of the carotid artery that has not (yet) been surgically treated.

METHODS

Literature searches were carried out on Medline and Psychlit between 1980 and 1999 using a combination of neurovascular and neuropsychological key words. Neurovascular key words were atherosclerosis, carotid artery disease, embolism, hemodynamics, cerebral ischemia, amaurosis fugax, TIA, RIND, cerebral infarction, endarterectomy, cerebral revascularization or alternatives presented in the thesaurus of Medline and Psychlit. Neuropsychological key words were cognition, cognitive disorders, dementia, psychometrics, neuropsychology or alternatives presented in the thesaurus. Furthermore, relevant papers and books were checked for references. Studies published since 1980 written in English, German, French or Dutch and describing neuropsychological assessment of groups of patients (n>1) with carotid stenosis or occlusion were included. Papers focusing on cognitive changes after revascularization without description of pre-operative findings, and papers using cognitive dysfunction as an inclusion criterion were excluded. Twenty papers, all written in the English language, satisfied the inclusion criteria.[6,8,14,17,37,45,47,48,54,60,61,85,87,88,90,91,107,118,132,135] By consensus, two of these were dismissed[8,90]

because of overlap of patient groups and findings reported by the same authors.[6,91] We selected the papers with stronger emphasis on the neuropsychological findings,[6] and larger size of the patient sample and longer follow-up.[91]
Data on design (retrospective, prospective, cross-sectional, longitudinal, exclusion criteria), demographic characteristics of patients (age, gender), clinical diagnosis (no symptoms, TIA, stroke), carotid lesions (stenosis, occlusion, side), cerebral imaging (presence of infarct, location and size of infarct, presence of atrophy), psychological tasks and test batteries used, integration of test performances (specified according to number and nature of parameters of cognitive deficit [various separate parameters, general index of impairment]), interpretation of test results (ipsative, normative, controlled) and conclusions of authors (presence, nature and severity of cognitive deficits) were extracted from the papers and tabulated. Inventoried but not tabulated were criteria for inclusion of patients, education of patients, presence of pre-existing dementia, diagnostic criteria for ischemic symptoms, severity of stroke, location of symptoms (cerebral, ocular), number of ischemic episodes in patients, degree of stenosis, presence of white matter lesions, cerebral perfusion, time interval between latest ischemic episode and neuropsychological assessment, bandwidth of assessment procedures, and course of cognitive dysfunctioning.

RESULTS

In fourteen papers (78%) the authors concluded that cognitive dysfunction was present (Tables 1-3 A), whereas in four studies (22%) no cognitive dysfunction was found (Tables 1-3 B). (To promote readability, we referenced in the text only those issues not tabulated.) The only study investigating the course of cognitive deficits in patients with TIA or stroke who did not undergo surgical intervention (n=14) did not find improvement or deterioration during a two-year follow-up.[91] Study design and characteristics of patient groups are summarised in Table 1.

Patient characteristics

The demographic features of the patient groups were roughly equal in the eighteen studies. On average, 75% of patients were male. The mean age varied between 50 and 65 years. Average number of years of education, reported in nine papers (50%), varied

Table 1 Design and patient characteristics of 14 studies finding cognitive deficits (A) and 4 studies denying cognitive deficits (B)

AUTHORS	STUDY DESIGN			PATIENTS		CLINICAL DIAGNOSIS		CAROTID ARTERIES			BRAIN TISSUE	
ordered according to year of publication	retro-/prospective	follow-up	exclusion criteria	age (m;sd)	sex (f/m)[a]	TIA[a]	stroke[a]	stenosis[a]	occlusion[a]	side (l/ r/ b)[ab]	cerebral infarct[a]	cerebral atrophy[a]
A.												
Hemmingsen[47]	P	pre/post CE	?	56	8/17	14	11	25	?	7/ 7/ 11	?	?
Baird[6]	R	no	relevant occlusive disease in both CAS and VAS	59	8/14	13	9[c]	13	9	?/ ?/ 10	?	?
Drinkwater[37]	P	pre/post bypass[d]	?	55 (11)	6/32	0	38	8	30	?/ ?/30	?	?
Hamster[45]	P	pre/post CE	stenosis <50%	61 (7)	4/29	22	6	33	?	?/ ?/19	8[ef]	?
Nielsen[87g]	P	pre/post bypass[d]	?	56 (5)	3/9	12	0	8	3	11[h]/ 1[h]/ ?	3[ei]	12[e]
Seidenberg[107]	R	no	?	60	2/44	?	?	?	?	?/ ?/ ?	?	?
Younkin[135]	P	pre/post bypass[d]	no cerebral symptoms, bilateral bypass, CE after bypass, post-operative complications	57	9/35	18	26	10	34	17[j]/ 27[j]/ ?	?	?
Hemmingsen[48]	P	pre/post CE	?	60	14/17	31	0	31	5	17[j]/ 14[j]/ ?	5[ef]	19[e]
Kelly[61]	P	no	psychiatric, other neurological disease, < 50 years old	65	12/27	39	0	35	4	12/ 10/ 17	?	?
Naugle[85]	R	no	stenosis <70%, other neurological disease	60 (5)	0/6	0	0	6	0	?/ ?/ ?	?	?

Nielsen[88k]	P	pre/post bypass[d]	?	52	7/ 26	0	33[c]	13	17	23[j]/ 10[j]/ ?	30[e]	?
Parker[91]	P	0-6-24 months[l]	- psychosis, organic brain syndrome, communicative disorders, alcohol abuse	60	?, ?	33	13	46	0	11[j]/ 11[j]/ 10[j]	?	?
Benke[14]	P	no	?	64 (32)	8/ 12	0	0	20	0	8/ 6/ 6	?	?
Yamauchi[132]	R	no	cortical infarctions, major head injury, alcohol abuse	64 (5)	3/ 9	1	8	1	11	4/ 8/ 0	9[fim]	?
B.												
Kelly[60]	P	pre/post CE	psychiatric, other neurological disease, acute physical distress	62 (8)	12/ 23	35	0	35	?	12[j]/ 13[j]/ 10[j]	?	?
Boeke[17]	P	pre/post CE	?	61	2/ 13	15	0	15	?	?/ ?/ 6	?	?
Van den Burg[118]	P	pre/post CE	psychiatric, other neurological disease	59	7/ 13	12	8	20	?	10[j]/ 10[j]/ ?	?	?
Iddon[54]	P	pre/post CE	stenosis <70%, dementia, depression	65 (9)	?, ?	30	0	30	?	?/ ?/ ?	?	?

CE= carotid endarterectomy CAS= carotid arterial system VAS= vertebral arterial system
a number of patients
b based on examination of arteries unless otherwise specified, l= left side, r= right side, b= both sides. query as entry: either no information or no information on asymptomatic side
c stroke or RIND
d extracranial-intracranial bypass
e according to CT-scan
f minor infarction
g one patient without any carotid lesion
h as derived from reported side of symptoms
i territorial or watershed infarction
j as derived from reported side of surgery
k three patients without any carotid lesion
l 32 patients with CE between 1st and 2nd evaluation
m according to MRI

between 7 and 13 years.[6,14,60,61,85,91,107,118,132] In seven studies, patients with concomitant psychiatric and/or neurological diseases were excluded.[54,60,61,85,91,118,132] Risk factors for carotid occlusive disease, such as diabetes mellitus and atherosclerotic cardiovascular disease, were reported to exist in the patient group of five studies.[14,60,91,107,132] In the other papers no information was given on concomitant disorders or diseases. Only four papers (22%) mentioned diagnostic criteria for ischemic symptoms.[45,48,54,118] In one study, ischemic episodes were labelled as TIAs, whereas the neurological deficits were reported to continue for 4 weeks and longer.[37] For the current survey, we considered these episodes as strokes. Five of the nine studies describing stroke patients included patients with minor strokes.[45,47,88,132,135] One study described both minor (25%) and major (15%) stroke patients,[118] and three papers did not provide information on the severity of stroke.[6,37,91] In two studies (11%) only patients with cerebral symptoms were included,[88,135] four studies (22%) included both patients with cerebral and ocular symptoms,[6,37,48,132] and in ten papers (56%) no information regarding the location of symptoms was presented.[17,45,47,54,60,61,87,91,107,118] The number of ischemic episodes and the time interval between the latest ischemic episode and the psychological assessment were mentioned in a minority of papers (22% and 33%, respectively); the number of episodes varied between 1 and at least 50,[47,48,87,135] and the interval varied between 3 days and at least 4 months.[47,48,87,88,132,135] In one study the mean degree of stenosis was 59%,[14] in five studies the degree of stenosis was at least 70%,[6,54,60,85,132] in one at least 60%,[61] and in another at least 50%.[45] The remaining papers (56%) did not mention the degree of stenosis.[17,37,47,48,87,88,91,107,118,135] Nine studies (50%) included patients with bilateral carotid obstruction. Eight studies (44%) did not provide information on uni- or bilaterality of carotid obstruction. The five studies that reported cerebral imaging found ischemic lesions and cerebral atrophy in varying proportions of stroke and TIA patients. Only one study assessed white matter lesions, and reported high intensity areas in all patients.[132]

No interpretable differences in patient characteristics were found between studies confirming and those denying cognitive deficits. As only a minority of papers provided information on neurovascular characteristics, such as the degree of carotid stenosis or the number and location of ischemic brain lesions, no conclusions can be drawn regarding the concordance in neurological features of the patient groups in the eighteen studies.

Table 2 Psychological tasks and test batteries used in 14 studies finding cognitive deficits (A) and 4 studies denying cognitive deficits (B)

AUTHORS ordered according to year of publication	PSYCHOLOGICAL TASKS OR TEST BATTERIES[a]
A.	
Hemmingsen[47]	Digit span, similarities, block design (WAIS), word pairs, story recall, visual gestalts, facial recognition, trailmaking, word fluency
Baird[6]	WAIS, Wechsler Memory Scale, Halstead-Reitan Battery, Wisconsin card sorting test
Drinkwater[37]	WAIS, Russell-Wechsler Memory Battery, Halstead-Reitan Battery
Hamster[45]	Digit symbol (WAIS), multiple choice vocabulary test, culture fair intelligence test, visual retention, attention set test, revision test, attention stress test, Vienna reaction timer, Freiburg personality inventory, scales for psychosomatic complaints
Nielsen[87]	information, arithmetic, similarities, digit span, block design, picture arrangement (WAIS), trailmaking, symbol digit modalities, 15 words learning, story recall, face recall, visual gestalts
Seidenberg[107]	WAIS, Wechsler Memory Scale (Russell), Halstead-Reitan Battery
Younkin[135]	Wechsler Memory Scale, trailmaking B, finger tapping, temporal orientation
Hemmingsen[48]	Digit span, digit symbol (WAIS), visual gestalts, word pairs, story recall, trailmaking
Kelly[61]	Wechsler Memory Scale, object memory, sentence production, picture vocabulary, picture absurdities, stereognosis, praxis, finger tapping, right-left discrimination
Naugle[85]	WAIS, Wechsler Memory Scale (Russell), grooved pegboard, trailmaking, category test, written word fluency
Nielsen[88]	information, arithmetic, similarities, digit span, block design, picture arrangement (WAIS), trailmaking, symbol digit modalities, 15 words learning, story recall, face recall, visual gestalts
Parker[91]	WAIS, Wechsler Memory Scale (Russell), Halstead-Reitan Battery, profile of mood states, Tennessee self-concept scale
Benke[14]	Block design (WAIS), verbal analogies, word list memory, lexical decision, word fluency
Yamauchi[132]	Digit span, arithmetic, picture arrangement, object assembly, block design, digit symbol (WAIS)
B.	
Kelly[60]	Wechsler Memory Scale, object memory, sentence production, word association, picture vocabulary, stereognosis, praxis, right-left discrimination, picture absurdities, hidden patterns, arithmetical reasoning, proverbs, state-trait anxiety, mini-mult
Boeke[17]	15 words, recurring faces, word fluency, reaction time, finger tapping, list of complaints, questionnaire on well-being
Van den Burg[118]	Groningen Intelligence Test, Raven Progressive Matrices, 15 words, recurring faces, word fluency, four choice reaction time, finger tapping, Minnesota rate of manipulation
Iddon[54]	National Adult Reading Test, pattern recognition, spatial recognition, spatial span, spatial working memory, attentional set shifting, paired associates learning, matching to sample, word fluency, mini mental state examination, depression inventory

WAIS= Wechsler Adult Intelligence Scale

a a detailed description can be found in the respective papers or in neuropsychological handbooks[70]

Study design

In fourteen studies (78%) the design was prospective. Two papers (11%) mentioned that patients were included consecutively.[48,61] In fifteen studies (83%), patients were referred to the surgical department of a hospital for (evaluation of) treatment of the carotid occlusive disease.[6,17,37,45,47,48,54,60,61,87,88,91,107,118,135] In three studies (17%), patients were seen in the neurological department, because of ischemic symptoms,[132] carotid bruits,[85] or unspecific complaints as headache and dizziness.[14] Twelve studies (67%) primarily addressed the outcome after surgery. The pre-operative findings of these studies were assessed in this review. In eight studies (44%) the number of patients was less than 30. No interpretable differences in study design were found between studies confirming and those denying cognitive deficits. The four studies denying cognitive deficits were prospective and longitudinal, and assessed mainly TIA patients. However, five other prospective and longitudinal studies did find cognitive deficits in TIA patients.[45,47,48,87,135]

Psychological assessment

We counted 79 different psychological assessment procedures in the eighteen studies (Table 2). Some of the procedures belong to a standard neuropsychological battery (e.g. Halstead-Reitan Battery) or a psychometric scale (e.g. Wechsler Adult Intelligence Scale). Thirty-seven procedures (47%) were used in only one study, whereas 13 (16%) were used in two studies, 19 (24%) in four to six studies and 10 (13%) in seven to fourteen studies. The bandwidth of psychological assessment varied between the studies, but did not discriminate between the studies finding and those denying cognitive deficits.

Integration and interpretation of test performances (Table 3)

Test performances can be quantified in separate test parameters or in a general index of impairment, which is based on performances on various tests. Interpretation of test performances can be ipsative, i.e. by comparison with premorbid level of functioning, or normative, i.e. by comparison with norms or control data.

Six studies (33%) employed a general impairment index, according to the scoring method of Russell et al.[100,101] In the studies using separate test parameters for statistics, the number of parameters varied between 1 and 30. Three studies[14,61,91] adjusted for multiple statistical comparisons by using a conservative level of statistical significance (0.002 or 0.01 instead of 0.05). No paper stated the percentage of patients with cognitive deficits. Instead, the means or medians of performances of the patient group were compared with

those of control persons or with norms. No interpretable differences appeared between the studies finding and those denying cognitive deficits in methods for integration and interpretation of test performances.

Type and severity of cognitive deficits (Table 3)

Six of the studies finding cognitive deficits (43%) did not specify the nature of cognitive impairment. Two studies (14%) concluded there was general impairment of cognitive functioning. In six studies (43%) specific domains of functioning were reported to be implicated, among which impairment of reasoning, memory and (psycho)motor skills were reported in more than two studies.

Seven of the studies finding cognitive deficits (50%) concluded mild impairment, three (21%) moderate or severe impairment, and in four (29%) the severity of impairment was not estimated. None of the studies mentioned criteria for severity.

Risk factors for cognitive deficits

Ten papers (56%) searched for determinants of cognitive deficits, such as side of carotid lesion, degree of carotid stenosis, vascular disease in other parts of the brain or body, type of ischemic event (ischemic stroke or TIA), recency of the ischemic event, presence of cerebral atrophy, and presence of white matter lesions. Patients with left, right or bilateral carotid stenosis did not differ in severity of cognitive impairment.[17,45,47,48,61,88] The only study assessing the influence of degree of carotid stenosis on cognitive functioning considered both as continuous variables and did not find significant correlations.[14] Degree of carotid occlusive disease was diagnosed by means of angiography,[47,48,61,88] Doppler sonography and angiography,[45] or Duplex sonography.[14] One study did not specify how the degree of stenosis was determined.[17] In one paper, interactive effects of atherosclerotic heart disease and cerebrovascular disease on cognitive functioning were mentioned.[107] Another study reported more severe cognitive impairment for stroke compared to TIA patients,[135] whereas two studies found a similar degree of cognitive impairment for TIA and stroke patients.[45,47] Time interval between stroke and neuropsychological assessment did not correlate with degree of cognitive impairment.[135] The two studies that assessed CBF by means of ^{133}Xenon-SPECT[48] or ^{133}Xenon-inhalation[135] did not correlate CBF and cognitive functioning prior to surgical intervention. Yamauchi et al.[132] found atrophy of the corpus callosum to be associated with cognitive impairment and with changes in hemodynamic parameters measured by ^{15}O-PET. The callosal atrophy

Table 3 Integration and interpretation of test results in 14 studies finding cognitive deficits (A) and 4 studies denying cognitive deficits (B)

AUTHORS	INTEGRATION OF TEST PERFORANCES		INTERPRETATION OF TEST RESULTS			CONCLUSIONS OF AUTHORS	
ordered according to year of publication	single test parameters (nr)	general index of impairment	ipsative	norms	control group	nature of deficits	severity of deficits
A.							
Hemmingsen[47]	13	no	no	yes	no	general	subnormal
Baird[6]	30	yes[a]	yes[b]	yes	no	no statement	mild
Drinkwater[37]	15	yes[ac]	no	yes	no	problem solving, motor skills, memory	severe
Hamster[45]	10	no	no	yes	no	memory, attention, psychomotor	considerable
Nielsen[87]	15	no	no	yes	non-cerebral outpatients[d]	tempo, general knowledge, arithmetic, memory, learning	slight
Seidenberg[107]	17	yes[a]	no	yes	no	no statement	mild to moderate
Younkin[135]	0	yes[c]	no	yes	no	no statement	no statement
Hemmingsen[48]	10	no	no	yes	patients with PVD[e]	no statement	slight
Kelly[61]	22	no	no	yes	patients with PVD[f]	memory	mild
Naugle[85]	13	yes[c]	no	yes	healthy persons, non-cerebral patients[f]	memory, manual dexterity, visual-spatial reasoning	no statement
Nielsen[88]	15	no	no	yes	non-cerebral patients[f]	sequential thinking, verbal repetition and learning, arithmetic	slight
Parker[91]	21	yes[a]	no	yes	non-cerebral patients[f]	no statement	no statement

Benke[14]	5	no	no	no	relatives, non-cerebral patients[f]	multimodal, non-focal	substantial
Yamauchi[132]	1[g]	no	no	yes	no	no statement	varied
B.							
Kelly[60]	15	no	no	yes	patients with PVD[f]	no deficits	no deficits
Boeke[17]	8	no	no	yes	non-cerebral patients[f]	no deficits	no deficits
Van den Burg[118]	18	no	no	yes	healthy persons[e], patients with PVD[f]	no deficits	no deficits
Iddon[54]	11	no	no	yes	healthy persons[h]	no deficits	no deficits

PVD= peripheral vascular disease
a average impairment rating[100,101]
b present versus estimated premorbid IQ
c impairment index[100,101]
d sex-,age-,education-matched
e age-matched
f age-, education-matched
g sum of six subtest scores
h age-, intelligence-matched

was hypothesised to reflect the severity of disconnection of cortical regions as caused by white matter lesions and cerebral atrophy due to ICA occlusive disease. According to these authors, cortical disconnection may be an important factor in the development of cognitive impairment in ICA occlusive disease without large cortical lesions.

DISCUSSION

Neuropsychological audit of TIA and stroke sequelae offers a framework for interpreting complaints on cognition and, hence, for adequate counselling and care. This review addresses cognitive functioning of patients with carotid occlusive disease who did not (yet) undergo surgery.

We found eighteen studies about cognitive functioning of asymptomatic, TIA or stroke patients with occlusive disease of the carotid artery. As almost no follow-up studies were performed in the population of patients who did not undergo surgery, information on the natural course of cognitive functioning is too scarce for conclusions.

Transversal results on cognitive functioning of patients varied from no deficits to obvious cognitive impairment. Patient characteristics, study design, neuropsychological assessment procedures and interpretation varied widely between the eighteen studies. However, when comparing the fourteen studies reporting cognitive deficits and the four studies reporting uncompromised cognition, we could not detect systematic biases explaining the difference in study results. As the majority of studies did not report on relevant neurovascular variables, such as cerebral infarction or hypoperfusion, it remains uncertain whether heterogeneity in the neurological condition of patients caused the difference in study results.

Seven of the eleven studies (64%) analysing the performances of TIA patients concluded that cognitive deficits were present.[6,45,47,48,61,87,135] Furthermore, all three studies assessing asymptomatic patients with carotid obstruction found cognitive deficits.[14,45,85] Hence, the absence or disappearance of neurological signs does not guarantee undisturbed cognitive functioning in patients with carotid obstruction.

None of the studies distinguished patients with cognitive deficits from those without by individual estimation of dysfunctioning. Therefore, the literature offers no information on the prevalence of cognitive impairment in the patient population with carotid occlusive disease.

Of the eight studies specifying the nature of cognitive deficits, two concluded global impairment and six specific deficits in, for example, memory, reasoning or (psycho)motor skills. However, in neuropsychology one should beware of deriving the nature of impairment from the measurement pretension of the test, based on psychometric research in a healthy population.[25] None of the studies addressed this topic.

The majority of papers estimating severity of cognitive impairment concluded mild impairment (70%), presumably based on clinical impression as none of them mentioned the criteria for severity of impairment. To avoid subjective evaluation, a principled estimation should be made.

Another point of interest concerns the vascular risk factors of cognitive dysfunctioning. Subgroups of patients at risk of cognitive impairment may exist. Although some papers searched for risk factors, various clinical subgroups and possible causative factors are not examined yet. Some relevant variables concerning the existence of structural brain pathology are the nature and location of the symptoms (TIA or stroke, cerebral or ocular), and the size and location of infarcts. Besides structural brain pathology, chronic cerebral hypoperfusion may be a risk factor for cognitive deficits. Degree of the carotid obstruction, uni- or bilaterality of the carotid obstruction, presence of atherosclerotic disease in other brain arteries (e.g. in the vertebrobasilar arterial system), and presence of collateral circulation do affect the vascular supply of the brain. A comprehensive assessment of risk factors, by means of a multiple regression analysis including various neurological and demographic factors or by delineating well defined clinical subgroups, has yet to be accomplished.

Most likely, a nonrepresentative portion of the patient population with occlusive disease of the carotid artery has been sampled so far. Twelve studies (67%) were designed to address the outcome after surgery and, hence, included only patients suitable for surgery. As the indications and contra-indications for operation were mentioned in only two of these papers,[60,118] the nature of the selection bias remains unknown. Furthermore, although the design of most studies was prospective, only two papers mentioned that patients were included consecutively. Only a principled and consecutive inclusion can prevent biases in the patient sample.

To get a clear picture of the influence of carotid occlusive disease on cognition, patients should be screened for concomitant disorders, e.g. depression or anxiety, that might affect cognitive functioning. Disentangling causes of demonstrated cognitive deficits is hampered by the co-existence of other neurological diseases affecting cognitive func-

tioning. As only a minority of the studies discussed in this review (39%) stated that patients with concomitant psychiatric and/or neurological diseases were excluded, we can not be sure that the cognitive deficits described are caused by the carotid occlusive disease.

We conclude that the majority of the current papers indicate a detrimental influence of carotid occlusive disease on cognition, but unbiased evidence has yet to be assembled. Apparently, the cognitive impairment is of a global, diffuse nature and mild to moderate in severity. Further research is needed to describe cognitive functioning in a representative sample of the patient population with carotid occlusive disease. We propose a prospective study with consecutive and principled inclusion of patients to prevent biases in sample selection. To assess natural course of cognitive functioning, a follow-up study is necessary. Since there are no indications that cognitive impairment is confined to a specific cognitive domain, a broad range of cognitive skills should be assessed. A consensus on the methods for neuropsychological assessment, such as recently was accomplished for the assessment of neurobehavioral outcomes after cardiac surgery,[84] would promote adequate assessment. To ascertain the causative factors of cognitive deficits, clinical subgroups of patients should be delineated and both structural and hemodynamic components of brain functioning should be assessed.

3 Cognitive impairment in patients with carotid artery occlusion and ipsilateral transient ischemic attacks

F.C. Bakker,
C.J.M. Klijn,
A. Jennekens-Schinkel,
I. van der Tweel,
C.A.F. Tulleken,
L.J. Kappelle

Submitted for publication

INTRODUCTION

In patients with transient ischemic attacks (TIAs) associated with stenosis or occlusion of the carotid artery, by definition no neurological signs of the TIA remain after 24 hours. Yet, subtle cognitive deficits have been reported up to months after the event.[9] These deficits may be caused by structural brain damage or by chronic compromise of the cerebral blood flow.[65,114]

There is controversy with respect to the occurrence and, if present, the extent of cognitive impairment in patients with carotid occlusive disease.[9] Insufficient information about the neurological deficits of patients and methodological flaws preclude a conclusion to this debate. Most studies did not give information about the degree of stenosis, or the number and location of ischemic brain lesions. Moreover, cognitive functioning has been examined mainly in a selection of patients with carotid occlusive disease, i.e. patients suitable for carotid endarterectomy or extracranial-intracranial (EC-IC) bypass surgery.[9]

The aim of the current study was to assess the prevalence, nature and severity of cognitive impairment in patients with carotid artery disease who have suffered from a TIA. In addition, we investigated which illness characteristics were associated with cognitive impairment. We sampled patients with a symptomatic occlusion of the carotid artery, as these may be at the highest risk of a compromised cerebral blood flow.

SUBJECTS AND METHODS

Patients

Thirty-nine patients with symptoms of transient (lasting less than 24 hours) ischemia attributable to an occlusion of the carotid artery were recruited from consecutive patients referred to the outpatient clinics of the departments of Neurology or Vascular Surgery of the University Medical Center Utrecht, The Netherlands. Symptoms should have occurred within six months prior to inclusion in the study. All patients received angiography to confirm the carotid artery occlusion. Excluded were patients with a stroke within six months prior to inclusion, and patients with a modified Rankin grade[12] of more than three.

The degree of stenosis in the contralateral carotid artery was measured on digital subtraction angiograms according to the NASCET criteria.[40] All patients underwent magnetic resonance imaging (MRI) to assess the presence of infarcts and ischemic white matter lesions[123] in the symptomatic and asymptomatic hemisphere (1.5-Tesla whole body system, ACS/NT-15 model, Philips Medical Systems, Best, The Netherlands, sagittal T1-weighted spin-echo sequence and T2-weighted spin echo) and were interviewed and investigated for the presence of vascular risk factors. Handicap was assessed by means of the modified Rankin scale.[12]
The median time interval between the last ischemic event and the MRI and neuropsychological examinations was 50 and 54 days, respectively (range: two days to six months, 13 patients with symptoms less than 3 months ago). In each patient, all investigations were done within a few days.

Controls

Spouses, and occasionally siblings, of the patients were asked to cooperate with the study, thus providing a healthy control group. Excluded were persons with neurological or psychiatric diseases.

Neuropsychological assessment

Patients and controls underwent an identical, comprehensive neuropsychological assessment. The tests, ordered according to the measurement pretensions, and the parameters used for data analysis are listed below. Patients were screened for the presence of dysphasia, agnosia or apraxia. Signs of these disorders in executing the tests, in making conversation, or in moving around were recorded and, if present, further explored by means of a picture-naming and a writing task in case of dysphasia, and a drawing task in case of unilateral neglect.[113] Patients' spouses were interviewed with respect to changes in patients' everyday cognitive functioning.

General Intelligence

Nonverbal intelligence was assessed with the Standard Progressive Matrices (SPM).[94] We used a time limit of twenty minutes, and scored the number of correct answers (maximum=60). In addition, we performed the Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS)-Revised,[128] which is relatively insensitive to brain damage,[136] and yields an indication of premorbid verbal intelligence. The maximum score is 70.

Learning and Memory

Of the Wechsler Memory Scale Form 1 (WMS),[127] we used the raw score with a maximum of 97. The Verbal Learning and Memory Test (VLMT),[82] is the recently developed Dutch version of the California Verbal Learning Test.[32] The reproductions of a list of sixteen orally presented nouns were summated over five trials (maximum=80). Of the Visual Retention Test part C, administration A (VRT),[109] we scored the number of errors.

Executive function

Of the Trail Making Test (TMT),[96] we used the number of errors (part A and B) and the increase in execution time from part A to part B. Of the Modified Card Sorting Test (MCST),[86] we scored the number of errors. In the Word production according to lexical rules (UNKA-test),[57] a production time of 60 seconds per phoneme was used and the total number of correct words was counted.

Reaction speed

In the "simple" conditions of the Vienna reaction apparatus,[106] sequences of single stimuli were presented (a yellow light and a tone, respectively). The third and fourth conditions were of the go-no go type; combinations of stimuli were presented among irrelevant signals that had to be ignored. In each condition, the median reaction time (msec) was calculated, and its components (median decision and median motor time).

Motor speed

The Tapping task[106] is a measure of motor speed, and is as such not a cognitive task. Nonetheless, this task is useful for the interpretation of performances on other tasks. Manual paresis or clumsiness, as observed on the tapping task, can have an adverse impact on the manual responses in the execution of cognitive tasks. The number of taps was counted for each hand.

Mood

The VROPSOM[4] is the Dutch version of the Depression Adjective Check Lists,[72,124] which screen for the presence of depressive affect. The score was the sum of dysphoric items ticked and euphoric items not ticked.

Data analysis

The characteristics of patients, controls and subgroups of patients were compared with an analysis of variance (ANOVA) (age), the Mann-Whitney U test (education, profession[110]) and the Chi-square or Fisher's exact test (sex, presence of vascular risk factors, angiographic and MRI findings).

Case-by-case

To determine whether cognitive impairment was present on an individual level, we used a cut-off point for impairment on each task. In choosing the cut-off points, we relied as much as possible on psychometrically established and published norms.[4,20,56,82,128,134,137] These norms had been adjusted for age,[4,20,82,128,134] sex,[4,20,82] and education or estimated premorbid intelligence,[4,20,56,134] and/or the norms had been established in groups similar to our patient group with respect to demographic characteristics,[56,137] and/or the impact of demographics on the results had been examined and found to be negligible.[82,134] If no adequate norms were available (Trail Making Test, reaction speed tasks), the cut-off points for male and female patients were set at two standard deviations from the mean of our male, respectively female controls. Cognitive impairment was considered to be present when a patient exceeded the cut-off point in two or more tasks.

Statistical analysis

Patients were grouped by presence of brain lesions on MRI and location of ischemia (cerebral or retinal), and were compared with controls. ANOVA was used for the group-wise comparison of the raw scores on the cognitive and motor tasks and on the checklist for depressive affect. The raw scores on the Trailmaking Test were loglinear transformed before entering them into the model because of large and unequal standard deviations. Univariate significant ($p \leq 0.05$, two-sided) or tending to significance ($0.05 < p \leq 0.10$, two-sided) test outcomes were jointly analyzed (multivariate ANOVA) to determine their independent contribution to the group differences.

When comparing patients with controls, we corrected for the difference in sex distribution between the two groups by entering sex as an independent variable in the model. We used the Bonferroni post-hoc correction in examining the pair-wise differences between subgroups of patients and controls.

By means of stepwise linear regression analysis, we examined whether illness characteristics predicted the raw scores on the cognitive and motor tasks, or on the cognitive impairment score. In calculating the cognitive impairment score, raw scores on the cognitive tasks were converted to standardized z-scores by comparison to the normative data used for the case-by-case analysis (mean of normative data minus patient's score, divided by the standard deviation of normative data), and z-scores were summed.

All statistical analyses were performed with SPSS for Windows, version 8.0.

The Institutional Review Board of the University Medical Center Utrecht approved the study protocol and informed consent was obtained from all patients and controls.

RESULTS

Demographic variables, level of education and prestige level of profession of patients and controls are summarized in Table 1. Except for the larger proportion of males in the patient group, for which we corrected in the statistical analysis, we found no differences in any of the variables between patients and controls. Twenty-two of the 39 patients had had transient symptoms of cerebral ischemia, and 17 had suffered isolated transient monocular blindness (TMB).

Table 2 summarizes the patient characteristics with respect to vascular risk factors, angiographic findings and MRI findings, comparing patients with symptoms of cerebral ischemia to those with isolated TMB. The groups differed on various characteristics, although only significantly on smoking: there were more smokers in the group of patients with cerebral TIAs than in the group with TMB. Thirteen patients had 1, four had 2 and five had 3 infarcts, either symptomatic (n=16) or asymptomatic (n=20). Eighteen patients had modified Rankin grade 0, eleven had grade 1, eight had grade 2 and two had grade 3. In four patients, disability was determined by other causes than cerebral ischemia; e.g. peripheral vascular disease, leg amputation, sensory polyneuropathy or lower back pain.

Table 1 Demographic characteristics of patients and controls

	Patients (n=39)	Controls (n=46)	*p*-value
Age, mean (sd, range)	62 (8.7, 44-78)	59 (8.3, 40-77)	0.150
Sex, m/f (%)	32/7 (82/18)	18/28 (39/61)	<0.001
Level of education			0.192
lower, n (%)	34 (87)	35 (76)	
middle-higher, n (%)	5 (13)	11 (24)	
Prestige level of profession			0.950
lower, n (%)	24 (62)	28 (61)	
middle-higher, n (%)	15 (38)	18 (39)	

n, number; sd, standard deviation; m, male; f, female

Table 2 Vascular risk factors, angiographic findings, and MRI findings in patients with cerebral TIAs and those with TMB

	Cerebral ischemic symptoms (n=22) n (%)	Isolated TMB (n=17) n (%)	*p*-value
hypertension	14 (64)	8 (47)	0.301
diabetes mellitus	7 (32)	1 (6)	0.106
hyperlipidemia	20 (91)	16 (94)	1.000
history of minor ischemic stroke	6 (27)	7 (41)	0.361
history of ischemic heart disease	10 (46)	10 (59)	0.408
history of peripheral vascular disease	6 (27)	6 (35)	0.590
current cigarette smoking	18 (82)	7 (41)	0.009
Angiography			
side of symptomatic carotid occlusion (L/R)	11/11 (50/50)	12/5 (71/29)	0.195
contralateral carotid stenosis 70%-99%	4 (18)	3 (18)	1.000
contralateral carotid occlusion	2 (9)	4 (24)	0.374
MRI			
presence of ischemic lesions	15 (68)	10 (59)	0.546
cerebral infarction	14	8	
territorial	3	2	
lacunar	2	1	
border zone	2	3	
combination of the 3 infarction types	7	2	
white matter lesions[a]	1	2	

[a] grade 1[123]

TIA, transient ischemic attack; TMB, transient monocular blindness; n, number of patients; L, left; R, right; MRI, magnetic resonance imaging

In none of the patients, pre-existing dementia was apparent by history. Apart from two patients with slight word-finding difficulty and one with slight hemispatial neglect, no patient had dysphasia, agnosia or apraxia. Compared to controls, the mean performances of the 39 patients were significantly worse in six of the nine cognitive tasks and in the motor task (Table 3). The differences in reaction times were mainly caused by long deci-

sion times in patients. Almost no differences were found in motor times (data not shown). Jointly analyzed, all tasks except the UNKA word fluency did independently contribute to the overall difference between patients and controls (MANOVA, p=0.001). Significant interaction effects between sex and group (patient or control subject) appeared on the "simple" reaction time task (p=0.03 for "light stimulus", p=0.01 for "tone stimulus"), and on the tapping task (p=0.04 for "right hand", p=0.00 for "left hand"), female patients performing more slowly. The absence of a significant difference between patients and controls on the Vocabulary task (Table 3) is supportive of a good match between the two groups in level of premorbid cognitive functioning.

As the presence of ischemic brain lesions (a recent or old infarct or white matter lesions in the symptomatic or asymptomatic hemisphere) and the location of ischemia (cerebral versus retinal) did not interact in their effects on cognitive or motor performances, their main effects were examined separately (Table 3). Cognitive impairment was more severe in patients with brain lesions and in patients with cerebral ischemia, although the differences were not large and not statistically significant, except one (Table 3).

Linear regression analysis did not reveal any patient characteristic as listed in Table 2 that was consistently associated with the cognitive or motor performances of patients. Nor did the number of infarcts or the time interval between the last ischemic event and the neuropsychological assessment influence the results. Degree of stenosis of the carotid artery contralateral to the symptomatic hemisphere tended to correlate with the cognitive impairment score (Spearman's r, 0.29; p=0.077). All the other patient characteristics, including the presence of diabetes or ischemic heart disease, correlated less than 0.2 with the cognitive impairment score.

On a case-by-case basis, twenty-one patients (54%) and four controls (8%) were classified as cognitively impaired. The specificity of the used criterion for cognitive impairment was 0.91 (42/46), the predictive value was 0.84 (21/25). Cognitive impairment, if present, was mild, as only five patients obtained a cognitive impairment score that was more than three standard deviations worse than the norm mean. The Standard Progressive Matrices and the reaction time tasks were the most sensitive, revealing deficits in sixteen and ten patients respectively. The other cognitive tasks except the Vocabulary subtest (WAIS-R) revealed deficits in four to nine of the 21 patients. Of the ten patients exceeding their cut-off scores in the reaction times, five had normal scores in the tapping task.

Cognitive impairment was not restricted to patients with cerebral ischemia, as seven of the patients with isolated retinal ischemia (41%) had cognitive deficits. Similarly, it was

Table 3 Cognitive performances, motor speed, and depressive affect in patients, subgroups of patients and controls

TEST	OVERALL		SUBGROUPS			
	patients (n=39)	controls (n=46)	symptoms cerebral ischemic symptoms (n=22)	TMB only (n=17)	ischemic abnormalities on MRI yes (n=25)	no (n=14)
	mean (sd)	mean (sd)	mean (sd)	mean (sd)	mean (sd)	mean (sd)
Cognitive performances						
SPM	29.5 (9.0)***	37.7 (6.8)	28.2 (8.3)***	29.5 (9.0)*	28.4 (8.4)***	31.6 (10.0)*
vocabulary	36.6 (9.1)	38.4 (8.0)	35.4 (8.1)	38.1 (10.4)	35.2 (9.1)	38.9 (9.1)
WMS	55.3 (7.8)	58.6 (6.7)	55.3 (8.3)	55.4 (7.4)	55.8 (8.1)	54.6 (7.3)
VLMT	43.1 (8.2)**	51.2 (9.8)	43.8 (7.2)**	42.1 (9.6)***	44.4 (8.5)**	40.8 (7.5)***
VRT	8.3 (3.5)*	6.3 (2.6)	8.7 (3.7)**	7.7 (3.2)	8.5 (2.9)*	7.9 (4.4)
MCST	10.7 (8.6)	7.7 (7.9)	12.1 (9.0)	9.1 (8.1)	11.5 (7.2)	9.4 (10.8)
TMT[a]	85.2 (28-334)***	46.9 (8-120)	88.6 (28-334)***	80.7 (34-281)*	86.5 (28-281)***	83.1 (34-334)*
UNKA	36.1 (11.2)*	42.2 (12.1)	36.3 (12.1)	35.8 (10.1)	34.3 (9.9)*	39.0 (12.9)
RT light	547.3 (131.7)***	488.8 (73.7)	558.3 (136.9)*	533.1 (127.5)	540.4 (98.2)	559.6 (180.8)†
RT tone	447.8 (122.2)***	402.4 (70.8)	473.5 (144.1)**‡	412.6 (74.0)	450.8 (110.3)	442.1 (147.2)
RT light-light	619.1 (107.8)**	573.4 (103.3)	619.8 (114.8)	618.4 (102.0)	627.2 (112.7)	603.6 (100.3)
RT light-tone	691.0 (109.1)*	650.2 (91.5)	704.7 (124.1)	673.1 (86.2)	720.2 (113.8)*††	630.1 (68.6)
Motor speed						
tapping right hand	177.8 (24.9)***	190.8 (20.2)	175.1 (23.5)*	181.5 (26.9)	178.8 (26.2)†	176.0 (23.0)
tapping left hand	157.3 (20.1)***	166.9 (19.6)	154.7 (19.7)*	160.5 (20.8)	156.5 (21.5)†	158.9 (18.0)
Depressive affect						
VROPSOM	10.3 (5.8)	11.0 (5.2)	10.8 (6.5)	9.6 (5.0)	11.8 (5.8)‡‡	7.6 (5.0)

[a] geometrical mean (range)
patients versus controls: † p<0.10, * p<0.05, ** p<0.01, *** p<0.001
patients with cerebral versus those with ocular signs: ‡ p<0.10
patients with versus those without ischemic abnormalities on MRI: †† p<0.05, ‡‡ p<0.10

n, number; MRI, magnetic resonance imaging; TMB, transient monocular blindness; sd, standard deviation; SPM, standard progressive matrices; WMS, Wechsler memory scale; VLMT, verbal learning and memory test; VRT, visual retention test; MCST, modified card sorting test; TMT, trailmaking test; UNKA, word production test; RT, reaction time; VROPSOM, checklist for depressive affect

not restricted to patients with visible brain damage on MRI, although the proportion of cognitively impaired patients tended to be higher in the group with brain damage (64%) than in the group without lesions on MRI (36%) (p=0.089, Chi-square test). Of the seven patients with isolated TMB and without abnormalities on MRI, two were cognitively impaired.

Patients and controls could not be distinguished on the VROPSOM checklist for depressive affect (Table 3). Three patients and three controls had VROPSOM scores in the clinical range of depressed mood. On average, there were no differences on the VROPSOM between patients with and those without cognitive impairment (p=0.868; 95% confidence interval for mean difference, -4.2 to 3.5). When co-varying for mood, the finding of worse cognitive performances of patients compared to controls still held true.

DISCUSSION

This study shows that around half of the patients with carotid artery occlusion who had suffered from an ipsilateral TIA was cognitively impaired, based on both group-wise comparison with healthy controls and on individual comparison with their estimated premorbid level of cognitive functioning.

In contrast to most studies in this area, we included patients regardless of suitability for carotid endarterectomy or EC-IC bypass surgery, thereby preventing the selection bias affecting most previous studies.[9] To the best of our knowledge, this is the first report on cognitive functioning in patients with carotid obstruction in which a distinction was made between patients with transient symptoms of cerebral ischemia and those with temporary loss of vision only, and in which was controlled for MRI acknowledged cerebral damage.

Previous reports on cognitive functioning of patients with carotid occlusive disease and TIAs concentrated on patients with cerebral symptoms. Most studies concluded that patients had cognitive deficits[6,45,47,48,61,87,135] but others[17,54,60,118] could not confirm this. Some of the studies finding deficits examined the relationship between the side of the carotid obstruction and the presence of cognitive impairment: in accordance with our results, no association was found.[45,47,48,61] None of the studies examined whether other patient characteristics, such as the presence or absence of cerebral infarcts, were related to cognitive functioning.[9]

We searched for explanatory non-cognitive effects of variables such as mood depression and decreased manual dexterity. Depressive feelings are thought to be associated with (reversible) cognitive impairment.[5, 63] For two reasons we do not consider depressed mood to explain the cognitive deficits. Firstly, patients and controls indicated on average the same mood state and the proportion of persons with a depressed mood did not differ between patients and controls. Secondly, mood state did not differentiate patients with from those without cognitive impairment. Impaired manual dexterity is another possible confounder, as performances on cognitive tasks which require a motor action (i.e. writing response in the SPM, pushing a button in the reaction time task) may be hampered by motor slowness or clumsiness. Only two patients had a slight unilateral paresis of the preferred hand as the result of an ischemic stroke in the past, and it only had a minor influence on the execution of the cognitive tasks. In the reaction speed tasks, the differences between patients and controls were not caused by a reduction of motor speed, but by a reduction of speed in decision making. Hence, it is unlikely that paresis or clumsiness of the arm explains the subnormal performances of patients.

Having excluded non-cognitive effects, we conclude that the cognitive deficits most probably reflect cerebral dysfunction. The degree and nature of cognitive impairment did not justify a diagnosis of vascular dementia, for which multiple cognitive deficits, each causing a significant impairment in social or occupational functioning are a prerequisite (DSM-IV).[3] Instead, as was evident from the anamnesis (data not shown) and the test results, the impairment can be characterized as a mild neurocognitive disorder, in which the degree of cognitive impairment is such that it can be partially compensated for in everyday functioning.[3]

The fact that deficits appeared in the entire range of tests and that there was heterogeneity in the pattern of deficits between patients argues against a vulnerability of specific cortical functions. Sixty-two percent of the patients had significant stenosis or an occlusion of the carotid artery contralateral to the symptomatic hemisphere, or had ischemic lesions in the contralateral hemisphere. This may explain why the side of the symptomatic hemisphere had no effect on the cognitive performances.

Co-existing diseases in our patient group such as diabetes mellitus and cardiac disease can have adverse effects on cerebral functioning.[43,62,79] However, as far as the statistical power was sufficient to demonstrate, these factors did not predict cognitive impairment in our patient group. Attempting to obtain some idea of the mechanism(s) that may have caused the cognitive impairment, we compared the performances of patients with

ischemic symptoms of the brain with those of patients with isolated retinal symptoms, and the performances of patients with ischemic abnormalities on MRI with those of patients with a normal MRI. If cognitive impairment would be a direct consequence of the cerebral transient ischemic attack, patients with isolated retinal symptoms would not be cognitively impaired. Yet, cognitive deficits were detected in 41% of these patients. With regard to the effect of previous structural brain damage, relatively more patients with ischemic lesions on MRI had cognitive deficits, but ischemic lesions were no prerequisite for cognitive impairment. Thus, besides cerebral lesions, other variables probably have had a detrimental influence on cognitive functioning.

Possibly, the cognitive impairment reflects a state of chronic hemodynamic compromise caused by the carotid occlusion combined with an insufficient collateral circulation. Sensitive measures of cerebral perfusion and metabolism may clarify this issue. Some patients may be at a pre-clinical stage of vascular dementia or even Alzheimer disease, as vascular risk factors and vascular disease increases the risk of both types of dementia.[22,49]

Our study has some limitations. Firstly, patients were not neuropsychologically examined before the documentation of carotid artery occlusion and the occurrence of TIAs. Therefore, we could not directly compare their present with their premorbid level of cognitive functioning. To determine whether cognitive decline was present in the individual patient, we had to rely on norm scores and employ an inevitably arbitrary criterion for cognitive impairment. However, the decisions were based on norms that take into account markers of premorbid level of cognitive functioning, such as education and sex. Although it has been argued that test scores of patients should not be corrected for markers of premorbid functioning as severe brain damage would obliterate their effect on neuropsychological test results[95], we chose to use corrected norms because the brain damage in the studied patients was relatively mild. As any cognitive impairment in this group of patients without major brain disease would be mild in severity, we used a criterion for cognitive impairment that enabled revealing subtle cognitive deficits. Nonetheless, the specificity and predictive value of the used criterion turned out to be high. A second limitation of our study is the unequal distribution of males and females between patients and controls. We took account of this by incorporating the variable sex in our statistical models, thus correcting for its influence on the results. Furthermore, this limitation does not apply that much for our criterion-based findings on cognitive impairment, as we made use of sex-specific norms in determining the criterion. Both the comparison of patients' performances with those of the control group and the compari-

son with norms adjusted for demographic characteristics, showed cognitive impairment in patients. Lastly, the number of patients in our study is relatively small, which may cause existing effects to go unnoticed because of lack of statistical power. However, we were mindful of statistical trends and were cautious with interpreting lack of statistical difference as lack of effect.

We conclude that patients with carotid artery occlusion who have suffered from an ipsilateral TIA can have lasting cognitive deficits, which are mild in severity and non-specific in nature. This also holds true for patients with a normal MRI and for patients with isolated retinal symptoms of ischemia. The pathophysiological processes underlying the cognitive impairment remain to be elucidated.

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4

Cognitive impairment is related to cerebral lactate in patients with carotid artery occlusion and ipsilateral transient ischemic attacks

F.C. Bakker,
C.J.M. Klijn,
A. Jennekens-Schinkel,
I. van der Tweel,
J. van der Grond,
A.C. van Huffelen,
C.A.F. Tulleken,
L.J. Kappelle

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INTRODUCTION

Patients with obstructive disease of the carotid artery who have suffered a transient ischemic attack (TIA) can have lasting cognitive impairment, despite the recovery of focal neurological deficits.[9] This holds even for patients without ischemic lesions on magnetic resonance imaging (MRI) or history of stroke. The cause of this cognitive impairment has not been elucidated yet. Thrombo-embolism, but also chronic cerebral hypoperfusion have been suggested to play a role.[65,114]

The association between hemodynamic compromise and cognitive impairment has not been examined in patients with TIAs, but correlations have been reported in patients with acute stroke,[52] vascular dementia[80,81] or cerebral microangiopathy.[103,104]

One indication of hemodynamic compromise is an exhausted cerebral autoregulation of the cerebral blood flow (CBF), as can be demonstrated by the inability to respond to vasodilatory stimuli.[76] Also, cerebral metabolic changes found on ^{1}H-MR spectroscopy in combination with low blood flow have been suggested to indicate compromised CBF.[120]

The purpose of the current study was to assess whether cognitive impairment in patients with carotid artery occlusion and ipsilateral TIAs is associated with a poor hemodynamic or metabolic state of the brain, as measured by 1) Transcranial Doppler CO_2-reactivity (TCD); and 2) metabolic measurements by ^{1}H-MR spectroscopy (^{1}H-MRS).

SUBJECTS AND METHODS

Patients

Thirty-nine consecutive patients with symptoms of transient (lasting less than 24 hours) ischemia associated with an angiographically proven occlusion of the internal carotid artery (ICA), were investigated at the University Medical Center Utrecht, The Netherlands. In all patients, symptoms had occurred at most six months prior to inclusion in the study. Excluded were patients with a stroke within six months prior to inclusion, and patients with a modified Rankin grade[12] of more than three.

Twenty-two of the 39 patients had suffered symptoms of cerebral ischemia, and 17 had experienced only transient monocular blindness. Cerebral symptoms had consisted of facial or limb weakness (21 patients), sensory disturbances (12 patients) and cortical

deficits, like homonymous hemianopia and dysphasia (10 patients). The symptomatic ICA occlusion was on the left side in 23 and on the right side in 16 patients. Thirteen patients also had a contralateral carotid occlusion (n=6) or a contralateral stenosis of at least 70% (n=7) (according to the NASCET criteria).[40] Volume blood flow in the middle cerebral artery (MCA) ipsilateral to the symptomatic ICA occlusion, as measured with magnetic resonance angiography,[121] was decreased in patients, with a mean of 80 ml/min (standard deviation 28). Thirteen patients had a history of a minor ischemic stroke that had occurred 7 months to 17 years ago (median time: 3 years).
All patients underwent neuropsychological assessment, MR investigations and TCD ultrasonography, as described below. The median time intervals between the last ischemic event and the neuropsychological, MR and TCD investigations were 54, 50 and 47 days, respectively (range: two days to six months). In each patient, all investigations were done within a few days.

Controls

Spouses, and occasionally siblings, of the patients were asked to cooperate with the neuropsychological assessment, thus providing a healthy control group. Excluded were persons with neurological or psychiatric diseases.
The control group for the MR investigations (MRI,^{1}H-MRS) consisted of subjects who were treated in the departments of Neurology or Urology for other than intracranial disease. None of the control subjects had a history of ischemic neurologic deficits, and none showed abnormalities on MRI of the brain. The TCD control group consisted of subjects who were investigated before implantation of an internal cardioverting defibrillator. These subjects all had a normal cardiac output function and no history of ischemic neurologic deficits.

Neuropsychological assessment

The tests and the parameters used for data analysis are listed below. Patients were screened for the presence of dysphasia, agnosia or apraxia. Signs of these disorders in executing the tests, in making conversation, or in moving around were recorded and, if present, further explored by means of a picture-naming and a writing task in case of dysphasia, and a drawing task in case of unilateral neglect.[113]

General Intelligence

Nonverbal intelligence was assessed with the Standard Progressive Matrices (SPM).[94] We used a time limit of twenty minutes, and scored the number of correct answers (maxi-

mum=60). In addition, we performed the Vocabulary subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R),[128] which is relatively insensitive to brain damage,[136] and yields an indication of premorbid verbal intelligence. The maximum score is 70.

Learning and Memory

Of the Wechsler Memory Scale Form 1 (WMS),[127] we used the raw score (maximum=97). The Verbal Learning and Memory Test (VLMT) [82] is the recently developed Dutch version of the California Verbal Learning Test. The reproductions of a list of sixteen orally presented nouns were summated over five trials (maximum=80). Of the Visual Retention Test part C, administration A (VRT),[109] we scored the number of errors.

Executive function

Of the Trail Making Test (TMT),[96] we used the number of errors (parts A and B) and the increase in execution time from part A to part B. Of the Modified Card Sorting Test (MCST),[86] we scored the number of errors.

In Word production according to lexical rules (UNKA-test),[57] a production time of 60 seconds per phoneme was used and the total number of correct words was counted.

Reaction speed

In one of the "go-no go" conditions of the Vienna reaction apparatus,[106] combinations of stimuli ("light-light") were presented among irrelevant signals that had to be ignored. The median reaction time (msec) was calculated and used as parameter.

Mood

The VROPSOM[4] is the Dutch version of the Depression Adjective Check Lists,[72] which screen for the presence of depressive affect. The score was the sum of dysphoric items ticked and euphoric items not ticked.

We obtained an overall measure of cognitive impairment ("cognitive impairment score"), by converting raw scores on all cognitive tasks except Vocabulary to standardized z-scores (mean of normative data minus patient's score, divided by the standard deviation of normative data), and summing these z-scores. A higher impairment score indicates worse cognitive functioning. The normative data consisted of psychometrically established norms, adjusted for age, sex, and education or estimated premorbid intelligence. In the absence of adequate norms (Trail Making Test, reaction speed task), the performances of the male and female control groups were used.

Magnetic Resonance Imaging

MR studies (MRI,^{1}H-MRS) were performed on a 1.5-Tesla whole body system (ACS/NT-15 model; Philips Medical Systems, The Netherlands). MRI investigations consisted of a sagittal T1-weighted spin-echo sequence (repetition time [TR], 545 ms; echo time [TE], 15 ms; slice thickness, 4 mm with a 0.6-mm interslice gap; field of view [FOV], 225 mm; 256x256 matrix) and a transaxial T2-weighted spin echo sequence (TR, 2000 ms; TE, 20 and 100 ms; slice thickness, 7 mm with a 1.5-mm interslice gap, FOV, 225 mm; 256x256 matrix). All MRI scans were reviewed independently by 2 investigators (C.J.M.K., L.J.K.) for the presence of infarcts or white matter lesions. White matter lesions were graded according to the method of Van Swieten et al.[123]

^{1}H-Magnetic Resonance Spectroscopy

^{1}H-MRS was performed with a single voxel technique (TR, 2000 ms; TE, 136 ms; 2000-Hz spectral width; 2048 time domain data points; 64 signals acquired). In each subject a volume of interest (VOI) (typically 70x35x15) was selected in the centrum semi-ovale of the hemisphere ipsilateral to the symptomatic ICA occlusion, thus containing primarily white matter. The anterior-posterior and left-right dimensions of the VOIs were chosen such that regions containing subcutaneous lipid were excluded. Areas of grey or white matter hyperintensities were excluded from the VOI with a margin of 2 cm, thus reducing the VOI in size.

After selection of a VOI, the 90° pulse length was determined. To minimize eddy currents and to maximize the water echo signal, spectroscopy was first performed without water suppression for adjustment of the gradients. Subsequently, a localized automatic shimming of the VOI was performed, resulting in a water resonance line-width of 6 Hz or less (full width at half-maximum).

Water suppression was performed by selective excitation (60 Hz bandwidth), followed by a spoiler gradient. After zero-filling of the time-domain data points to 4096 data points, gaussian multiplication of 5 Hz, exponential multiplication of -4 Hz, fourier transformation, and baseline correction, the *N*-acetyl aspartate (NAA, referenced at 2.01 ppm), total creatine and lactate peaks were identified by their chemical shifts. To distinguish lactate resonances from lipid resonances at a TE of 136 ms, lactate was defined as an inverted resonance at 1.33 ppm with a signal-to-noise ratio larger than two and a clearly identifiable 7 Hz J-coupling.

Since it was not possible to calculate absolute concentrations, data were expressed as ratio of peak intensities of NAA and creatine, and as presence or absence of lactate.

TCD CO_2-reactivity

The TCD sonography was performed with a Multi-Dop X device (DWL, Sipplingen, Germany). CO_2-reactivity was measured in the MCA ipsilateral to the symptomatic ICA occlusion with a 2-MHz Doppler probe with the subject in the supine position. The TCD probe was fitted in a light metal frame, which was firmly fixed to the head with two ear pieces and an adjustable nose saddle. After a 2-minute baseline period, subjects inhaled a gas mixture of 5% CO_2 and 95% O_2 (carbogene) for the next two minutes. The carbogene was inhaled through a mouthpiece connected to a respiratory balloon, and the use of a nose clip ensured proper inhalation. The CO_2 content of the breathing gas was monitored continuously with an infrared gas analyser. A spectral TCD recording of 5 seconds was made after 1 minute during the baseline period and after 1.5 minutes of carbogene inhalation. The CO_2-reactivity was expressed as the relative change in blood flow velocity (BFV) after 1.5 minutes of carbogene inhalation, according to the equation $[(BFV_{CO2}\text{-}BFV_{baseline}) / BFV_{baseline}] \times 100\%$. The mean of the maximal BFV values during the spectral TCD recordings was used in this calculation.

Data analysis

Patients were compared with controls on demographics (age: analysis of variance [ANOVA]; sex: Chi-square test; education: Mann-Whitney U test) and on their performances on the cognitive tasks and the checklist for depressive affect (ANOVA). We corrected for the difference in sex distribution between the two groups by entering sex as an independent variable in the model.

Subsequently, CO_2-reactivity and the NAA/creatine ratio, both ipsilateral to the symptomatic ICA occlusion, were compared between patients and controls (Student's t-test and Mann-Whitney U test, respectively). In patients, associations of CO_2-reactivity and the NAA/creatine ratio with the cognitive impairment score were examined (Pearson correlation). Patients with and without lactate were compared on the cognitive impairment score (Student's t-test). Furthermore, we examined whether the pattern of performances across the cognitive tasks discriminated patients with lactate from those without (Discriminant analysis, stepwise).

Two-tailed *p*-values less than or equal to 0.05 were considered to reflect a statistically significant result. If the *p*-value was between 0.05 and 0.10, a tendency to significance was presumed and reported. All statistical analyses were performed with SPSS for Windows, version 8.0.

The Institutional Review Board of the University Medical Centre Utrecht approved the study protocol and informed consent was obtained from all patients and controls.

RESULTS

The patient and control groups did not differ in age, level of education or proportion of males, except for a lower proportion of males in the control group for neuropsychological examination, for which we corrected in the statistical analysis (Table 1). Fourteen patients had no lesions according to MRI scanning. Twenty-two patients had cerebral infarcts and three had mild (grade 1) ischemic white matter lesions in one or both hemisphere(s). Twelve patients had border zone infarcts, eight had territorial infarcts, and eleven had lacunar infarcts. Nine patients showed two types of infarction. Apart from two patients with remaining mild word-finding difficulty and one with remaining mild hemispatial neglect, no patient had full-blown dysphasia, agnosia or apraxia.

Table 1 Demographic characteristics of patients and control groups

	Patients (n=39)	Control groups NPA (n=46)	MR (n=28)	TCD (n=29)
Age, mean (sd, range)	62 (8.7, 44-78)	59 (8.3, 40-77)	59 (10.5, 40-73)	59 (10.5, 40-78)
Sex, m/f	32/7	18/28*	22/6	24/5
Level of education				
lower, n	34	35	-	-
middle-higher, n	5	11	-	-

* patients versus controls, $p<0.001$
NPA=neuropsychological assessment, MR=magnetic resonance imaging, TCD=transcranial Doppler sonography, sd=standard deviation, m=male, f=female, n=number

Table 2 Cognition and depressive affect in patients and controls

	Patients (n=39) mean (sd)	Controls (n=46) mean (sd)	*p*-value
*Cognition**			
vocabulary (raw score)	36.6 (9.1)	38.4 (8.0)	0.690
cognitive impairment score	5.6 (5.9)	-0.1 (4.0)	<0.001
*Depressive affect**			
VROPSOM (total dysphoric)	10.3 (5.8)	11.0 (5.2)	0.467

* the test(s) and their parameters are described in the Subjects and Methods section
sd=standard deviation

As a group, patients were cognitively impaired. The mean cognitive impairment score in patients significantly deviated from the norm score, i.e. from zero, and from that of control subjects (Table 2). The absence of a significant difference between patients and controls on the Vocabulary task, is supportive of a good match between the two groups in

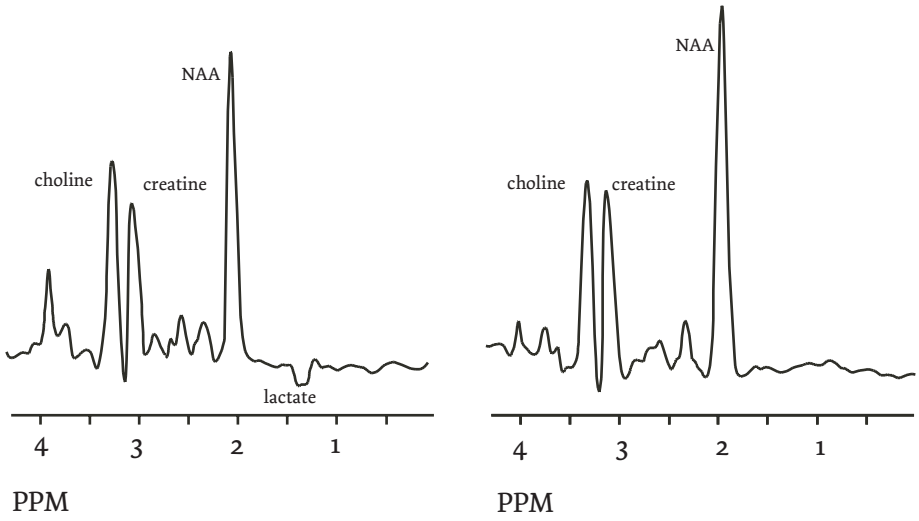

Figure 1. *^{1}H-MR spectra of the centrum semi-ovale ipsilateral to the symptomatic ICA occlusion, in a patient with lactate (left spectrum) and one without lactate (right spectrum). The chemical-shift axis in parts per million (PPM) is positioned below each spectrum.*

Table 3 CO2-reactivity and metabolic ratio in patients and controls

	Patients mean (sd)	Controls mean (sd)	*p*-value
CO_2-reactivity, % BVF change			
ipsilateral* MCA	16 (19)	51 (13)	<0.001
Metabolic ratio, centrum semi-ovale			
NAA/creatine, ipsilateral*	1.88 (0.24)	2.01 (0.34)	0.008†

* ipsilateral=ipsilateral to the side of the symptomatic ICA occlusion
† Mann-Whitney U test
sd=standard deviation, MCA=middle cerebral artery, BVF=blood volume flow, ICA=internal carotid artery

level of pre-morbid cognitive functioning. Patients and control subjects did not differ in depressive affect, according to the VROPSOM checklist (Table 2). Also, the proportion of persons with VROPSOM scores in the clinical range of depressed mood did not differ between patients and controls (respectively, 8% and 7%; Fisher's exact test, p=1.000). Thus, the worse cognitive performances in patients, compared to controls, could not be explained out of a depressed mood.

Mean CO_2-reactivity and mean NAA/creatine ratio in the hemisphere ipsilateral to the ICA occlusion were significantly lower in patients than in controls (Table 3). In 5 patients ^{1}H-MRS could not be obtained, for technical reasons. In 12 of the 34 patients with ^{1}H-MRS data, lactate was present in the hemisphere ipsilateral to the symptomatic ICA occlusion. Figure 1 provides an example of a spectrum with lactate, and one without lactate.

As a group, patients with lactate had a significantly higher cognitive impairment score, indicating more severe cognitive impairment, than those without lactate (95% confidence interval for mean difference, 1.3 to 8.4) (Figure 2). Also, more patients with lactate had a MRI-detected ischemic lesion in the ipsilateral hemisphere (75% of patients with lactate versus 41% of patients without lactate) (Chi-square, p=0.057). To determine whether it was the presence of lactate or the presence of cerebral ischemic lesions that accounted for the worse cognitive performances, we entered both variables in a linear regression analysis. The presence of lactate was related to cognitive impairment (b=4.7,

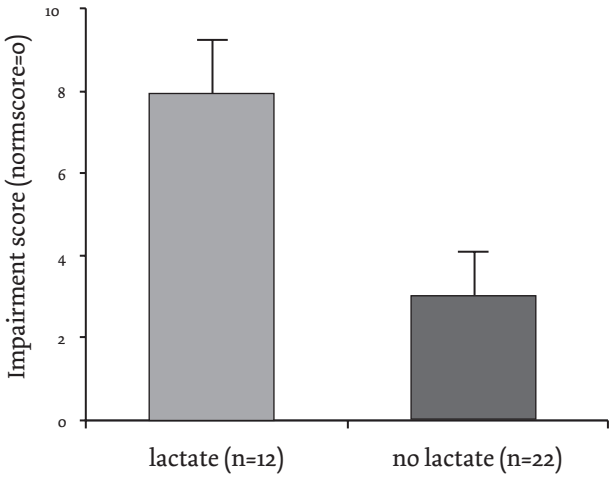

Figure 2. *Mean cognitive impairment score (standard error) in patients with and those without lactate (p=0.008).*

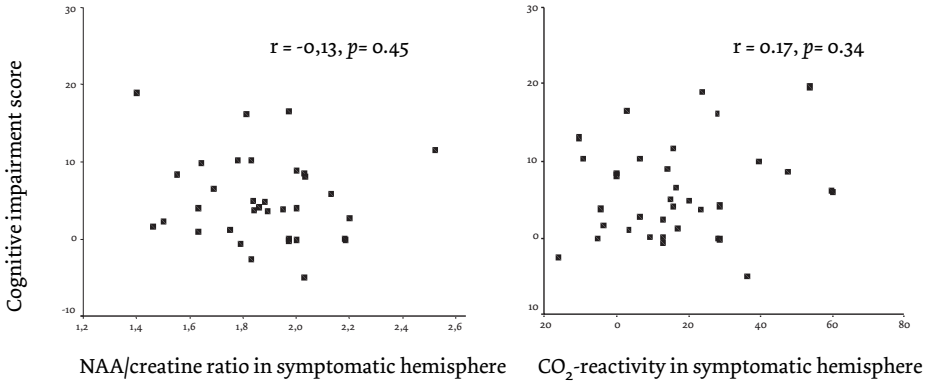

Figure 3. *Correlations between cognitive impairment and the NAA/creatine ratio or CO2-reactivity in the symptomatic hemishere were absent.*
r = Pearson's correlation coefficient

standard error=2.0, p=0.023), whereas the presence of ischemic lesions was not (b=1.7, standard error=1.9, p=0.382).

The cognitive impairment score did not correlate with the ipsilateral CO_2-reactivity, nor with the ipsilateral NAA/creatine ratio (Figure 3). Patients with lactate had a lower mean CO_2-reactivity than those without (7.2 ± 14.4 versus 19.5 ± 16.6, p=0.046).

As white matter lesions have been related to cognitive impairment, and in particular to a decreased psychomotor speed,[27,83] we checked whether the twelve patients with lactate in the centrum semi-ovale had specific impairments of psychomotor speed, compared to the patients without lactate. This was not the case. Of all cognitive tasks, the Modified card sorting task proved to be most useful in discriminating patients with from those without lactate (Discrimination analysis, p<0.001). Psychomotor speed forms no component of this task.

DISCUSSION

In patients with ICA occlusion and ipsilateral TIAs, the presence of lactate in non-infarcted regions of the ipsilateral centrum semi-ovale was associated with more severe cognitive impairment. No correlations were found between cognitive functioning and CO_2-reactivity or the NAA/creatine ratio.
The origin of lactate in non-infarcted brain areas of patients with carotid artery occlusion has not been elucidated yet.[66] It has been suggested that anaerobic glycolysis caused by chronic hypoperfusion produces lactate in these patients. An alternative explanation is that micro-embolic infarcts invisible on MRI led to the metabolic changes.[120] In the current study, patients with lactate had worse CO_2-reactivity than those without lactate, suggesting that hemodynamic compromise was more prominent in patients with lactate. Perhaps, the finding of more severe cognitive impairment in patients with lactate reflects the impact of hemodynamic impairment on cognitive functioning. However, CO_2-reactivity did not correlate with cognitive impairment. Thus, we could not demonstrate a direct relation between hemodynamic compromise and cognitive impairment. In the literature, no data is available on the relationship between cerebral hemodynamics and cognitive impairment in patients with symptomatic carotid occlusion, but correla-

tions have been reported in groups of patients with related diseases. In stroke patients, cognitive impairment correlated better with volume of hypoperfused tissue as measured by MR perfusion imaging than with volume of infarction as measured by diffusion-weighted imaging, both within 24 hours of stroke onset or progression and after reperfusion therapy.[52] In patients with cerebral microangiopathy, cognitive impairment correlated with impaired regional cerebral perfusion (measured by single-photon emission CT) and glucose metabolism (measured by positron emission tomography (PET)), even in the absence of brain atrophy.[104]

No correlations were found between cognitive impairment and number or severity of lacunar infarcts and deep white matter lesions. In patients with subcortical lacunar infarction, the degree of glucose hypometabolism (as measured by PET and corrected for atrophic changes in the brain) correlated with the degree of cognitive impairment, whereas the number of subcortical strokes related only weakly to both of these factors.[69] Thus, impaired metabolic measures, but also regional hypoperfusion have been reported to be a stronger correlate of cognitive impairment than MRI-detected morphological alterations in patients with vascular diseases.

An explanation for the discrepancy in findings between the current study and other studies might be that our measure of hemodynamic compromise was not sensitive enough. In contrast with the studies mentioned before, we did not examine regional CBF, but rather measured TCD CO_2-reactivity in the middle cerebral artery, which may be too crude. Another explanation might be that in all patients, the hemodynamic state of the brain was already impaired to such an extent that further discrimination among patients was not possible. Cognitive impairment and CO_2-reactivity might have been related if we would have examined patients with less impaired cerebral hemodynamics. Finally, in patients with lactate in non-infarcted regions, the damage to the brain may be larger than in patients without lactate and more extensive than can be detected by MRI. This may result in more severe cognitive impairment as a direct result of the ischemic episodes and not necessarily related to a supposedly chronic state of impaired blood flow towards the brain.

We conclude that in patients with ICA occlusion who have suffered from a TIA, ^{1}H-MRS-detected lactate in non-infarcted regions is a better indicator of cognitive impairment than MRI-detected lesions. Cognitive impairment was not associated with decreased CO_2-reactivity.

5 Cognitive functioning and quality of life in patients with symptomatic carotid artery occlusion: a one year follow-up study

F.C. Bakker,
C.J.M. Klijn,
J. van der Grond,
L.J. Kappelle,
A. Jennekens-Schinkel

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INTRODUCTION

Impairment of cognitive functioning has repeatedly been reported in patients with obstructive carotid artery disease (CAD).[9,11] Little is known, however, about the natural history of cognitive deficits in this patient group, as almost all follow-up studies were performed to evaluate the impact of carotid endarterectomy or extracranial-intracranial (EC-IC) bypass surgery on cognition.[9] Patients with cognitive impairment caused by cerebrovascular diseases have an increased risk of progressing to dementia.[36,129] In addition to risk factors such as leuko-araiosis and cerebral atrophy, cerebral hypoperfusion has been suggested to be associated with cognitive decline and vascular dementia.[36,78] Cerebral metabolic changes found on ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) in patients with obstructive CAD have been suggested to indicate compromised cerebral blood flow.[120] In a previous study,[10] we found that ^{1}H-MRS detected lactate in non-infarcted white matter correlated with cognitive impairment in patients suffering from TIAs associated with carotid artery occlusion.

Stroke is well-known to affect health-related quality of life (QoL),[13,116] but few studies have examined long-term QoL in patients with minor ischemic stroke or a transient ischemic attack (TIA). For adequate counselling and care, it is important to know whether transient or relatively moderate disability affects QoL too, and whether cognitive impairment contributes to a low self-perceived QoL.

In the current follow-up study, we examined the courses of cognitive functioning and health-related QoL over the period of one year, in patients with TIAs or an at most moderately disabling stroke. Furthermore, we assessed whether the metabolic state of the brain, as measured by ^{1}H-MRS, predicted the course of cognition in our patients. We selected patients with symptomatic carotid artery occlusion (and not stenosis), as this group may be expected to suffer the most from chronic cerebral hypoperfusion and its consequences.

SUBJECTS AND METHODS

Patients

Between September 1995 and July 1998 113 consecutive patients with symptoms of retinal or cerebral TIA or moderately disabling cerebral ischemic stroke (modified Rankin[12] grade three or better), were recruited from patients referred to the departments of Neurology or Vascular Surgery of the University Medical Center Utrecht, The Netherlands. Symptoms had occurred within six months prior to inclusion in the study, and were attributable to an angiographically proven extracranial occlusion of the internal carotid artery (ICA). Excluded were patients who underwent high-flow EC-IC bypass surgery (n=16), contralateral carotid endarterectomy (n=23) or contralateral angioplasty (n=1) during follow-up. Thus, 73 patients were included in the study (male, 59; female, 14). The excluded patients did not differ from those who were included with respect to their performance on neuropsychological testing and QoL scores at first investigation.
Patients were interviewed and investigated for the presence of vascular risk factors. The degree of stenosis in the contralateral ICA was measured on intra-arterial digital subtraction angiography according to the NASCET criteria.[40] In all patients, antithrombotic medication was prescribed (low dose aspirin in the majority), and vascular risk factors were rigorously treated.
Patients underwent neuropsychological assessment and completed a questionnaire on health-related quality of life (QoL) at the time of inclusion in the study and approximately 6 and 12 months thereafter. Magnetic resonance imaging (MRI) was performed to assess the presence of ischemic lesions in the brain and ^{1}H-MRS was used to study cerebral metabolism. The median time interval between the patients' last ischemic event and the first neuropsychological assessment was 87 days (range: 2 days to 7 months). In each patient, MRI and ^{1}H-MRS and evaluation of QoL were performed within a few days of the neuropsychological assessment.

Controls

Spouses, and occasionally siblings of the patients included in this study and of the operated patients formed a healthy control group. Persons with neurological or psychiatric diseases were excluded. The control group consisted of 73 subjects, 18 males and 55 females. Male patients and male controls were similar in mean age (60 and 57 years

respectively, p=0.17) and median educational level (p=0.40; percentage primary to lower secondary education, 83 and 72 respectively). Likewise, female patients and female controls were similar in mean age (59 and 58 years respectively, p=0.72) and median educational level (p=0.21; percentage primary to lower secondary education, 79 and 73 respectively).

Neuropsychological assessment

The tests, ordered according to the measurement pretensions, and the parameters used for data analysis are listed below. Patients were screened for the presence of language impairment, unilateral spatial agnosia or apraxia. Signs of these disorders in executing the tests, in making conversation, or in moving around were recorded and, if present, further explored by means of a picture-naming and a writing task in case of language impairment, and a drawing task in case of unilateral agnosia.[113]

General Intelligence

Nonverbal intelligence was assessed with the Standard Progressive Matrices (SPM).[94] We used a time limit of twenty minutes, and scored the number of correct answers (maximum=60). In addition, we performed the Vocabulary subtest of the Wechsler Adult Intelligence Scale-Revised[128] (WAIS-R) (maximum=70).

Learning and Memory

Of the Wechsler Memory Scale Form 1 (WMS),[127] we used the raw score (maximum=97). The Verbal Learning and Memory Test (VLMT) [82] is the recently developed Dutch version of the California Verbal Learning Test.[32] The reproductions of a list of sixteen orally presented nouns were summated over five trials (maximum=80). Of the Visual Retention Test part C, administration A (VRT),[109] we scored the number of errors.

Executive function

Of the Trail Making Test (TMT),[96] we used the number of errors (parts A and B) and the increase in execution time from part A to part B. Of the Modified Card Sorting Test (MCST),[86] we scored the number of errors. In the Word production according to lexical rules (UNKA-test),[57] a production time of 60 seconds per phoneme was used and the total number of correct words was counted.

Reaction speed

In the two "go-no go" conditions of the Vienna reaction apparatus,[106] combinations of target stimuli ("light-light" and "light-tone") were presented among irrelevant stimuli that had to be ignored. The median reaction time (msec) was calculated and used as

parameter.

Mood

The VROPSOM[4] is the Dutch version of the Depression Adjective Check List,[72] which screens for the presence of depressive affect. The score was the sum of dysphoric items ticked and euphoric items not ticked.

We obtained an overall measure of cognitive impairment ("cognitive impairment score"), by converting raw scores on all cognitive tasks except Vocabulary to standardized z-scores (mean of normative data minus patient's score, divided by the standard deviation of normative data), summing these z-scores and dividing them by the number of tasks, i.e. eight. A higher impairment score indicates worse cognitive functioning. The performances of the male and female control groups were used as normative data in obtaining the cognitive impairment scores of, respectively, the male and female patients. To correct for any learning effect over time, norm scores were computed separately for each follow-up assessment. Cognitive impairment was considered to be present in the individual patient if his or her performance was ≥ 2 standard deviations (SD) worse than the norm score, in two or more tasks. Likewise, deterioration or improvement of cognitive functioning was defined as, respectively, an increase or decrease of ≥ 2 SD above or below the mean change in controls, in two or more tasks.

Health-related quality of life

Health-related QoL was assessed by means of the MOS Short-Form Health Survey (SF-36).[126] The SF-36 is a self-report questionnaire. It is composed of 36 items, organized into 8 multi-item scales assessing: physical functioning, role limitations due to physical health problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems, and mental health.
The scale scores were converted to standardized z-scores by comparing them with Dutch reference data,[1] corrected for age and sex (patient's score minus mean of normative data, divided by the standard deviation of normative data). A higher z-score indicates a better health-related QoL.

MRI and ^{1}H-MRS

All patients underwent MRI (1.5-Tesla whole body system, ACS/NT-15 model, Philips Medical Systems, Best, The Netherlands, sagittal T1-weighted spin-echo sequence and

T2-weighted spin echo). Infarcts were scored according to type (territorial, border zone, large subcortical, or lacunar). White matter lesions were graded according to the method of Van Swieten et al.[123]

^{1}H-MRS was performed with a single voxel technique (TR, 2000 ms; TE, 136 ms; 2000-Hz spectral width; 2048 time domain data points; 64 signals acquired). In each subject a volume of interest (VOI) (typically 70x35x15) was selected in the centrum semi-ovale of the hemisphere ipsilateral to the ICA occlusion, thus containing primarily white matter. Areas of grey or white matter hyperintensities were excluded from the VOI with a margin of 2 cm, thus reducing the VOI in size. The anterior-posterior and left-right dimensions of the VOIs were chosen such that regions containing subcutaneous lipid were excluded. Since it was not possible to calculate absolute concentrations, data were expressed as the ratio of peak intensities of *N*-acetyl aspartate (NAA) and creatine, and as presence or absence of lactate. In eight patients,^{1}H-MRS could not be obtained, because of claustrophobia or for technical reasons.

Data analysis

Patients with TIAs only were compared with those with a stroke on various risk factors (Chi-square and Fisher's exact test), on the modified Rankin grade (Chi-square), on the findings on angiography (side of the symptomatic ICA occlusion and degree of contralateral carotid obstruction, Chi-square), MRI (Fisher's exact test), and ^{1}H-MRS (Chi-square and Mann-Whitney U), and on the scores for cognitive impairment and health-related QoL ((multivariate) ANOVA).

To examine whether cognitive impairment was restricted to specific domains of functioning, we condensed the cognitive data so that only major components were left, and compared patient groups on these components with multivariate analysis of variance (MANOVA). Components were established (extracted) by means of principal component analysis[111] with varimax rotation, using the raw scores of the control persons at the three neuropsychological assessments. Only components with eigenvalues greater than 1 were retained. Variables with absolute weights above 0.4 were considered to contribute substantially to a component.

By means of Spearman's and Pearson's correlation analysis and linear regression analysis, we examined whether patient characteristics as listed in Table 1 were associated with cognitive impairment, and whether disability according to the modified Rankin scale, severity of cognitive impairment and depressive affect predicted health-related QoL.

Changes over time in cognitive functioning, depressive affect, and health-related QoL were analysed with (uni- and multivariate) repeated measures. Correlations between courses of cognition, depressive affect and QoL were examined with Pearson's correlation analysis and linear regression analysis.

RESULTS

Baseline assessments

Twenty-six patients had had only TIAs within six months before inclusion, and 47 patients had had a non-disabling ischemic stroke. Nearly half of the patients with TIAs had a history of minor ischemic stroke that occurred more than 6 months before inclusion in the study (Table 1). The median time interval between this previous ischemic stroke and inclusion in the current study was 5 years (range, 7 months to 17 years). Eight of the TIA patients (31%) had no ischemic lesions (infarction or white matter lesions) on MRI. The proportions of patients with hyperlipidemia and with a history of ischemic heart disease were higher in patients with TIAs, than in those with a stroke. Metabolism in the centrum semi-ovale was more disturbed in patients with a stroke than in those with TIAs. Compared to previously published control values,[10] the NAA/creatine ratio was decreased, both in patients with TIAs (Mann-Whitney U test, p=0.015) and in those with a stroke (p<0.001).

As a group, patients with a stroke had a higher cognitive impairment score, indicating more severe cognitive impairment, than patients with a TIA (mean cognitive impairment score of patients with stroke, 1.3 [SD 1.0]; of patients with TIAs, 0.8 [SD 0.9]; p=0.018). In both patient groups, the mean cognitive impairment score significantly deviated from zero (p<0.001). Thirty-three patients with a stroke (70%) and ten patients with a TIA (39%) were cognitively impaired (p=0.008). Signs of language impairment were present in fifteen patients with a stroke (32%), and in one patient with a TIA (4%). One patient showed signs of unilateral spatial agnosia; no patient showed signs of apraxia. Cognitive impairment was more severe in stroke patients with language impairment, than in patients with a TIA or patients with a stroke and without language impairment (Table 2). Severity of cognitive impairment did not differ between patients with a TIA and patients with a stroke but without language impairment.

Table 1 Baseline characteristics of patients with ICA occlusion and an ipsilateral TIA or stroke

	TIAs only (n=26)	Stroke (n=47)	*p*-value
Vascular risk factors, n (%)			
hypertension	13 (50)	21 (45)	0.663
diabetes mellitus	3 (12)	8 (17)	0.736
hyperlipidemia	24 (92)	19 (40)	<0.001
history of minor ischemic stroke*	11 (42)	3 (6)	<0.001
history of ischemic heart disease	11 (42)	5 (11)	0.002
history of peripheral vascular disease	8 (31)	12 (26)	0.631
current cigarette smoking	16 (62)	35 (75)	0.249
Internal carotid arteries, n (%)			
side of symptomatic occlusion (left/right)	13/13 (50/50)	25/22 (53/47)	0.794
contralateral stenosis 70%-99%, occlusion	1 (4), 6 (23)	6 (13), 16 (34)	0.206
Presence of ischemic lesions	18 (69)	47 (100)	<0.001
cerebral infarction, n (%)**	15 (58)	47 (100)	<0.001
territorial	7	24	
lacunar	7	13	
large subcortical	0	6	
border zone	5	18	
white matter lesions[a], n (%)	4 (15)	4 (9)	0.444
*^{1}H-MRS****			
lactate, n (%)	6 (27)	20 (47)	0.134
NAA/creatine ratio, median (range)	1.87 (1.4-2.5)	1.67 (1.1-2.5)	0.046
Modified Rankin score			
0, 1, 2, 3, n (%)	13 (50), 7 (27), 5 (19), 1 (4)	4 (9), 9 (19), 28 (60), 6 (13)	<0.001

* Present, if patients had had a stroke more than 6 months before inclusion in the current study.
** Four patients with a TIA and fourteen patients with a stroke had two types of cerebral infarction.
*** Values for the hemisphere ipsilateral to the symptomatic occlusion. In 8 patients ^{1}H-MRS could not be obtained.

Principal component analyses yielded three, normally distributed components of cognition. After reviewing the measurement pretensions of the tests that contributed saliently to each component (Table 3), the components could be adequately characterized by the

Table 2 Cognitive performances at baseline, in patients with ICA occlusion and an ipsilateral TIA, an ipsilateral stroke and no language impairment, and an ipsilateral stroke and language impairment. Deviations from norm data are expressed in mean standard scores.

	TIAs only (n=26) mean (sd)	Stroke, no language impairment (n=32) mean (sd)	Stroke, language impairment (n=15) mean (sd)
*Cognitive tests**			
SPM	1.5 (1.3)	1.9 (1.1)	1.4 (1.1)
WMS	0.3 (1.3)	0.8 (1.2)	2.7 (1.7)**
VLMT	0.5 (0.9)	0.6 (1.1)	1.7 (1.1)**
VRT	0.9 (1.2)	1.4 (1.4)	1.3 (1.5)
TMT	1.4 (2.3)	1.9 (2.4)	4.2 (3.4)**
MCST	0.4 (1.0)	0.5 (1.2)	0.5 (1.1)
UNKA	0.5 (0.9)	0.5 (0.9)	2.1 (0.6)**
RT light-light	0.9 (1.4)	1.1 (1.4)	1.4 (1.6)
Impairment score	0.8 (0.9)	1.1 (0.9)	1.9 (1.0)**

* The tests and their parameters are described in the Subjects and Methods section.
** Stroke patients with language impairment versus other patients: $p \leq 0.001$

labels Problem solving and Memory (component 1), Language and Verbal learning (component 2), and Reaction speed (component 3). As a group, patients showed impairment on each component of cognition. Stroke patients with signs of language impairment showed, as expected, more severe impairment on Language and Verbal learning, than stroke patients without language impairment and TIA patients (respectively, 2.9 (SD 0.9) versus 1.1 (SD 0.8), $p<0.001$).

In addition to duration of symptom(s) on inclusion (TIA versus stroke), the side of the symptomatic ICA occlusion (left versus right), the degree of contralateral ICA stenosis, and the presence of lactate predicted the cognitive impairment score at baseline. Patients with left-sided ICA occlusion had a higher impairment score than patients with right-sided ICA occlusion (patients with left-sided ICA occlusion, 1.4 (SD 1.0); patients with right-sided ICA occlusion, 0.9 (SD 0.8); $p=0.016$). This proved to be related to the presence of language impairment, which mainly (14 out of 16) occurred in patients with left-sided

Table 3 Significant weights in the three components yielded by the PCA Varimax solution for cognitive variables, eigenvalues and the percentage of variance explained by each component.

	Problem solving & Memory	Language & Verbal learning	Reaction speed
Cognitive tests			
SPM	-0.879		
WMS	-0.487	0.683	
VLMT		0.849	
VRT	0.691		
MCST	0.742		
TMT	0.608		
UNKA		0.761	
RT light-light			0.903
RT light-tone			0.840
Eigenvalues	2.52	1.92	1.64
Explained variance (%)	28.03	21.31	18.21

* The tests and their parameters are described in the Subjects and Methods section.

occlusion. When both side of ICA occlusion and presence of language impairment were entered into the statistical model, only the impact of language impairment remained. Patients with more severe contralateral ICA stenosis had worse cognitive performances than those with less severe stenosis (partial correlation coefficient, controlling for duration of symptoms on inclusion and presence of language impairment, 0.30; p=0.01). Patients with lactate on ^{1}H-MRS tended to have worse cognitive performances than those without lactate (patients with lactate, 1.4 (SD 0.8); patients without lactate, 1.0 (SD 1.0); p=0.067). The impact of lactate was significant in the subgroup of patients with TIAs (partial correlation coefficient, controlling for degree of contralateral carotid stenosis, 0.51; p=0.018). None of the other patient characteristics listed in Table 1, including the presence of ischemic lesions on MRI, predicted cognitive impairment at baseline for TIA or stroke patients. Correcting for the time interval between the last ischemic event and the neuropsychological assessment did not change the results on correlates of cognitive

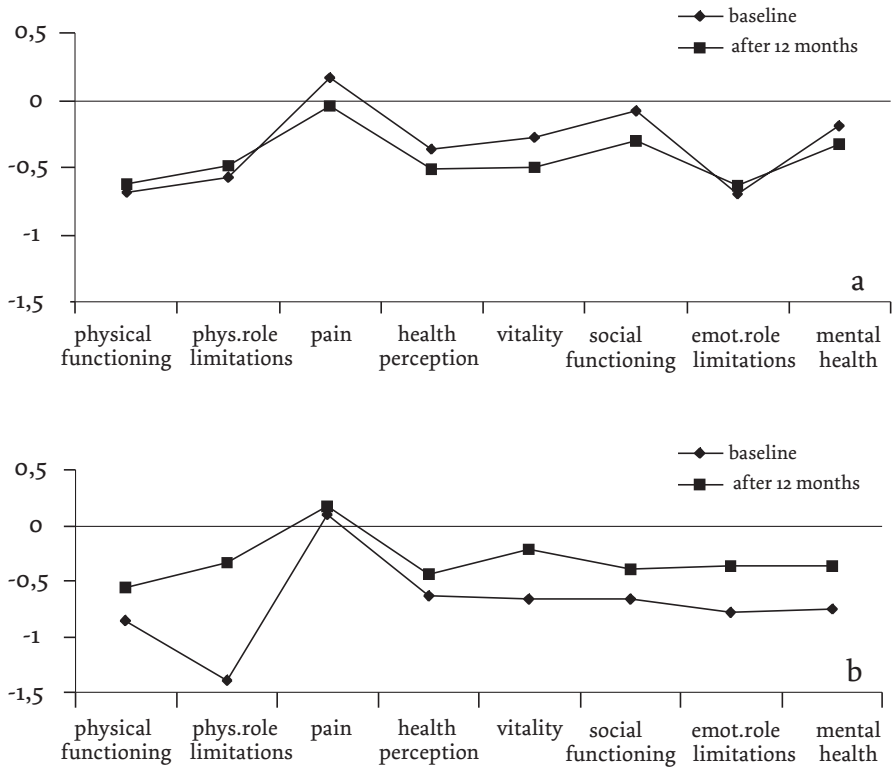

Figure 1. *SF-36 profiles for patients with ICA occlusion and an ipsilateral TIA (a) or stroke (b), at baseline and after 12 months. Deviations from norm data are expressed in mean standard scores.*

impairment.

The mean score on the VROPSOM for depressive affect at baseline did not differ between patients and controls (patients, 11.1 (SD 6.6); controls, 10.8 (SD 5.1); Students' t-test, p=0.76). Eleven patients (15%) and five control persons (7%) had scores in the clinical range of depressive affect (p=0.11). When correcting for the impact of depressive affect, the finding of worse cognitive performances in patients compared to controls still held true.

Patients with a stroke and patients with TIAs only, reported on average a diminished health-related QoL (Figures 1a and 1b). Mean deviation from the norm scores was less than one standard deviation, with the exception of "physical role limitations" for stroke

patients, which deviated almost 1.5 SD from the norm.

Disability according to the modified Rankin scale, and cognitive impairment were associated with impaired QoL on the SF-36 subscales "physical functioning" (r=-0.32, p=0.005, for Rankin grade; r=-0.24, p=0.045 for cognitive impairment) and "social functioning" (r=-0.25, p=0.033, for Rankin grade; r=-0.28, p=0.018, for cognitive impairment). Depressive affect was associated with impaired QoL on all of the subscales of the SF-36 (range of r, -0.33 to -0.60; range of p, <0.001 to 0.005). When simultaneously analyzing the impact of disability, cognitive impairment and depressive affect on QoL, only the impact of depressive affect (on all subscales) and disability (on "physical functioning") remained. The median percentage of explained variance of the prediction equations for the eight subscales was 17.5 (range, 12% to 33%). In the subgroup of patients without depressed mood, QoL was affected on the subscales "physical functioning" (p<0.001), "physical role limitations" (p<0.001), "general health perception" (p=0.003), and "emotional role limitations" (p<0.001). The time interval between the last ischemic event and the assessment of QoL had no impact on the findings at baseline.

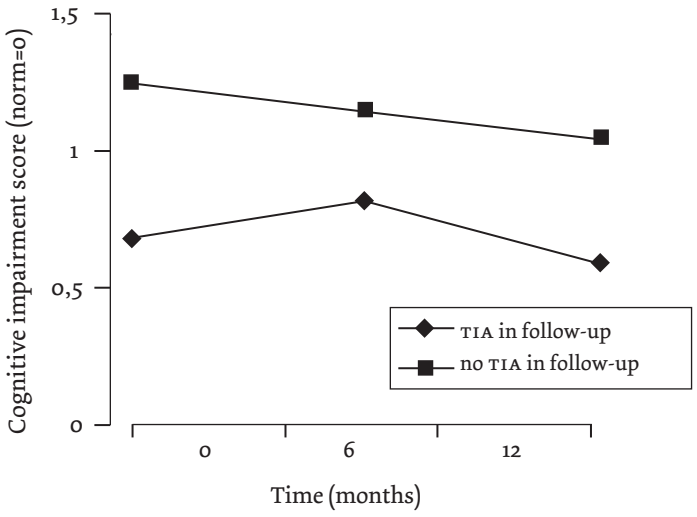

Figure 2. *Course of cognitive impairment over time, for patients with (n=10) and those without (n=56) a TIA during the follow-up period. Deviations from norm data are expressed in mean standard scores.*

Follow-up assessments

Four patients were lost to follow-up due to death after myocardial infarction (n=3) or recurrent ischemic stroke (n=1), and three patients refused neuropsychological assessment at 12 months' follow-up. Thus, sixty-six patients (90%) had completed all three neuropsychological assessments. Eighteen of the seventy-three controls (25%) refused participation at 6 months' follow-up (n=3), 12 months' follow-up (n=9), or both follow-up assessments (n=6). For both patients and controls, no significant differences emerged between those who completed all three neuropsychological assessments and those who were lost to follow-up in sex, mean age, median educational level or mean cognitive impairment score at baseline. Ten of the sixty-six patients had one or more TIAs during the one-year follow-up period. In eight patients, the TIAs occurred within the 6 months' follow-up period, in two patients between 6 and 12 months' follow-up.

Of the total patient group (both patients with a stroke and those with TIAs only at inclusion in the study), only patients without a TIA during the follow-up period improved in cognitive functioning (repeated measures, p=0.001). In patients with a TIA during the follow-up period, there seemed to be a deterioration after the TIA, followed by an improvement of cognitive functioning, although none of these changes were statistically significant (Figure 2).

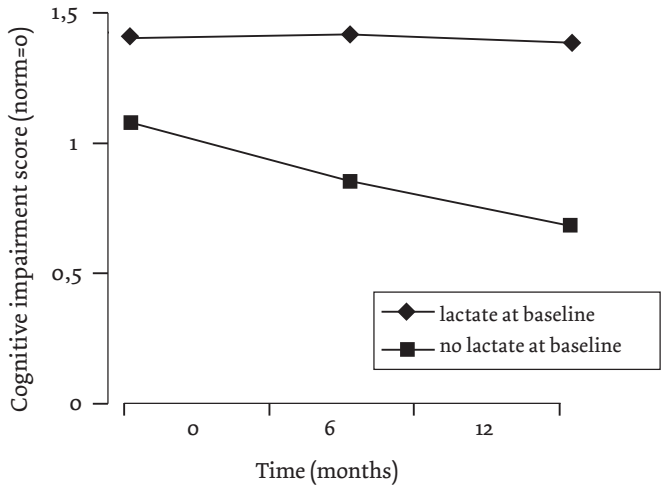

Figure 3. *Course of cognitive impairment over time, for patients without a (recurrent) TIA during the follow-up period, and with (n=22) or without (n=29) lactate at baseline. Deviations from norm data are expressed in mean standard scores.*

Furthermore, cognitive functioning only improved in patients without lactate on ^{1}H-MRS at baseline, whereas it remained at the same (impaired) level in patients with lactate at baseline (repeated measures, interaction effect time-by-group, p=0.002) (Figure 3). Adding the baseline cognitive impairment score as a covariate to the regression model did not change the results.

None of the other patient characteristics (Table 1), nor the duration of the symptoms on inclusion (stroke or TIAs only), correlated with changes in cognitive functioning at follow-up. Also, patients with subcortical lesions (white matter lesions or subcortical infarcts, n=34) did not differ from those without subcortical lesions with regard to changes in cognition over time (repeated measures, interaction effect time-by-group, p=0.69). On an individual level, seven patients (11%; 5 with cognitive impairment at baseline) showed marked improvement of cognitive functioning at 12 months' follow-up, and two (3%; both with cognitive impairment at baseline) had deteriorated.
Mean depressive affect at 12 months' follow-up was reduced both in patients and controls (repeated measures, p<0.001), as well as the number of persons with scores in the clinical range of depressive affect (4 patients and 2 controls remained). Course of affect over time in patients did not correlate with course of cognition (r=0.15, p=0.25).
Health-related QoL still was affected at 12 months' follow-up, although there was a large improvement on the aspect of "physical role limitations" for stroke patients (Figures 1a and 1b). Changes in QoL over time correlated with changes in depressive affect on the aspect of "social functioning" (r= -0.26, p=0.049): less depressive affect at 12 months' follow-up was associated with better, self-perceived social functioning. No correlations appeared between course of cognition and changes in QoL.

DISCUSSION

Approximately 70% of patients with a non-disabling ischemic stroke and 40% of patients with a TIA, both associated with an ICA occlusion, were cognitively impaired at baseline. Cognitive functioning did not further deteriorate during the follow-up period of one year. Instead, cognition improved in patients who did not have recurrent symptoms at follow-up and in whom ^{1}H-MRS did not show lactate in the centrum semi-ovale of the

hemisphere ipsilateral to the symptomatic ICA occlusion. Self-perceived QoL remained affected at 12 months' follow-up, although not to a large extent. Cognitive functioning had no impact on QoL.

In this study, we investigated cognitive impairment[21,89] rather than vascular dementia as defined by DSM-IV,[3] to detect subtle but potentially clinically meaningful impairment. The clinical relevance of cognitive impairment without dementia is emphasized by the findings of more functional impairment and a higher risk on dependent living, independent of the effects of physical impairment, in subjects with than in those without cognitive impairment.[115] Furthermore, patients with cognitive impairment have a higher risk of progressing to dementia[15,36,129] and of institutionalization and mortality.[98]

We found that in patients with lactate in non-infarcted white matter of the hemisphere ipsilateral to the ICA occlusion, improvement of cognitive functioning did not occur. In addition, the recurrence of TIAs seemed to hamper cognitive improvement. Both the presence of lactate in non-infarcted brain regions ipsilateral to an ICA occlusion and the recurrence of ischemic episodes have been suggested to be related to chronic cerebral hypoperfusion.[65,119,120] Furthermore, the decreased NAA/creatine ratio in non-infarcted white matter may indicate that neurons and axons suffer from ischemia, probably due to a compromised cerebral blood flow.[66] Cerebral hypoperfusion has been suggested to have an adverse impact on cognition, and to be a risk factor for vascular dementia.[10,36,78] The cognitive improvement in patients without lactate and no recurrent symptoms might reflect recovery of cerebral perfusion, due to gradually improved collateral circulation, whereas the absence of improvement in patients with lactate might reflect persisting hemodynamic impairment. Nearly half of our patients had MRI-detected subcortical white matter lesions or lacunar infarcts, which have been reported to cause or contribute to cognitive impairment and vascular dementia.[27,29,34,35,69,78,92] However, the proportion of patients with subcortical lesions was the same for the group of patients with lactate and the group of patients without lactate, and the presence of subcortical lesions did not predict the course of cognitive functioning. An alternative explanation for our findings is that the presence of lactate reflects macrophage activity due to neuronal loss,[71] and that this neuronal loss prevents cognitive improvement to occur. Although the volume of interest for the ^{1}H-MR spectroscopy was chosen such that MRI-detected regions with hyperintensities were excluded, cerebral damage subsequent to infarction may be more widespread than can be seen on MRI.[33,105] The finding that reduced cerebral perfusion pressure without frank infarction does not result in lactate or in NAA reduction, at least

not in patients with carotid artery stenosis,[74] is supportive for this alternative hypothesis. Thus, it cannot be excluded that the absence of cognitive improvement in some of our patients should be considered as to be the result of ischemic brain damage due to micro-emboli or small-vessel disease, instead of persisting low perfusion pressure due to a compromised blood flow to the brain.

Only few studies have been performed on the course of cognitive functioning in non-demented patients with obstructive CAD, who did not undergo revascularization surgery during the follow-up period. In one study on patients with CAD, TIAs and mild cognitive impairment, no changes in cognitive functioning were found at 8 months' follow-up assessment in 13 patients who did not undergo surgery.[28] Another study found cognitive improvement at 8 and 24 months' follow-up assessments in 17 patients with symptomatic CAD who did not undergo surgery.[91] In both studies, the number of patients was small, no separate analyses were done for patients with ICA occlusion, and no correlates of the course of cognition were examined.

Depression and aphasia are common consequences of stroke. As both are reported to decrease cognitive functioning,[5,23,53,58] we examined the impact of both factors on cognition in our patient group. Depressed mood was present in only a minority of the patients and controls. When correcting for the impact of depressive affect on cognitive performances, the finding of cognitive impairment in patients still held true. Therefore, depressed mood did not confound our results. Around one-third of the stroke patients showed signs of language impairment. Patients with language impairment performed worse than those without language impairment on tests that strongly depend on linguistic skills, including two memory tasks. In contrast to other studies,[53,58] our patients with language impairment did not perform worse on tests of non-verbal problem solving. This is likely to be related to the fact that the language impairment in these patients was relatively mild. The finding of more severe cognitive impairment in patients with stroke than in those with TIAs only, was mainly due to the higher frequency of language impairment in the stroke group. When patients with language impairment were excluded, severity of cognitive impairment was similar in patients with stroke and those with TIAs only.

Health-related QoL was impaired both in patients with stroke and in patients with TIAs only. Depressive mood was associated with impaired QoL on all subscales of the SF-36. Disability according to the modified Rankin scale correlated only with self-perceived physical functioning, whereas cognitive impairment had no impact on self-perceived

Qol. Studies on the correlates of QoL in patients with stroke have shown that depression, functional ability and social activities or social support are the main determinants of QoL.[13,75] It has been argued that self-perceived QoL cannot be adequately assessed in depressed patients, as depressive persons give their own situation in all areas of life a worse rating than non-depressive persons.[41] Although patients with depressed mood consistently rated their QoL worse than patients without depressed mood, the latter group still had impaired QoL on four subscales. Our finding that the Rankin score correlated with only one scale of QoL, may be explained by the fact that none of our patients had major stroke, and all of them were at most moderately disabled. The absence of any impact of cognitive functioning on QoL is in accordance with the findings of other studies in patients with ischemic stroke of mild to moderate nature and without aphasia.[59,68] We conclude that cognitive functioning in patients with symptomatic ICA occlusion improves within 1.5 years after the ischemic event, but only when ^{1}H-MRS did not show lactate in the white matter of the hemisphere ipsilateral to the occlusion and patients had no recurrent symptoms. A longer follow-up period is needed to ascertain whether cognitively impaired patients with lactate in non-infarcted white matter have a higher risk of developing vascular dementia.

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6

Cognitive impairment in patients with symptomatic carotid artery occlusion persists after endarterectomy of contralateral carotid artery stenosis

F.C. Bakker,
C.J.M. Klijn,
A. Jennekens-Schinkel,
J. van der Grond,
A.C. van Huffelen,
B.C. Eikelboom,
L.J. Kappelle

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INTRODUCTION

A substantial portion of patients with symptomatic occlusion of the internal carotid artery (ICA) has impaired cognitive functioning, even if focal neurological deficits had disappeared within 24 hours.[11] This cognitive impairment usually is mild and not restricted to specific cortical functions.[11] It has been hypothesized that chronic hypoperfusion of the brain contributes to cognitive impairment in these patients.[39,65] Based on this hypothesis surgical interventions that improve the blood flow towards the brain may halt cognitive decline, or may even improve cognitive functioning. Controlled studies in this field are lacking, but several case reports and small series have suggested that extracranial-intracranial (EC-IC) bypass surgery improves cognition in patients with symptomatic carotid artery occlusion (CAO).[38,46,114,117,133] Other studies, however, could not confirm these findings.[7,16,37,112,135]

No data at all are available on the effect of endarterectomy of a severe contralateral ICA stenosis on cognition in patients with symptomatic ICA occlusion. In such patients endarterectomy has been shown to not only improve the blood flow towards the hemisphere on the operated side, but also on the side of the ICA occlusion.[77,102,130] Examining the effect of revascularization surgery on cognitive functioning is more attractive in these patients than in patients who underwent EC-IC bypass surgery because craniotomy, that itself may affect cognitive functioning, is not performed.

The purpose of this study was to assess whether cognitive functioning in patients with symptomatic CAO and asymptomatic 70 to 99% stenosis of the contralateral ICA, can improve by endarterectomy of the contralateral ICA. In addition we studied whether any of the observed changes in cognitive functioning after endarterectomy were associated with changes in the hemodynamic or metabolic state of the brain, assessed by measurements of transcranial Doppler (TCD) CO_2-reactivity, quantitative flow in the MCA, and the NAA/creatine ratio and the presence of lactate on ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS).

SUBJECTS AND METHODS

Patients

Between September 1995 and July 1998 113 patients with symptoms of retinal or cerebral TIA or at most moderately disabling cerebral ischemic stroke attributable to an angiographically proven extracranial occlusion of the ICA were recruited from consecutive patients referred to the Department of Neurology or Vascular Surgery.
Patients who had a 70 to 99% stenosis of the contralateral ICA were offered carotid endarterectomy (CEA). Thirteen patients who underwent CEA were included in this study. Nine operated patients were excluded because they could not be neuropsychologically tested because of lack of time before surgery took place (2 patients), because they refused to undergo neuropsychological investigation at follow-up (2 patients), because they had a restenosis after CEA for which they had to be re-operated (2 patients), because EC-IC bypass surgery was also performed (1 patient), because the operation took place one year after the occurrence of the last symptoms, because of chronic ocular ischemia (1 patient), or because a recurrent stroke occurred during follow-up (1 patient).
CEA was performed under general anaesthesia and monitored by EEG and transcranial Doppler ultrasonography. During the operation intraluminal shunting was used when the EEG deteriorated after cross-clamping of the carotid artery. In all operated patients patency of the operated ICA was confirmed with duplex ultrasonography 3 months after the operation.

Controls

As a control group we assessed 15 patients with a stenosis of the carotid artery contralateral to the ICA occlusion of 50 to 99% who were not treated with CEA, either because it was technically not feasible (1 patient), because they refused the operation (3 patients), or because the operation was not advised (10 patients). We excluded three control patients because follow-up examinations were not available due to recurrent stroke (2 patients) or cardiac death (1 patient).

Neuropsychological assessment

The tests, ordered according to the measurement pretensions, and the parameters used for the data analysis are listed below.

General Intelligence

Nonverbal intelligence was assessed with the Standard Progressive Matrices (SPM).[94] We used a time limit of twenty minutes, and scored the number of correct answers (maximum=60).

Learning and Memory

Of the Wechsler Memory Scale Form 1 (WMS),[127] we used the raw score (maximum=97). The Verbal Learning and Memory Test (VLMT)[82] is the recently developed Dutch version of the California Verbal Learning Test.[32] The reproductions of a list of sixteen orally presented nouns were summated over five trials (maximum=80). Of the Visual Retention Test part C, administration A (VRT),[109] we scored the number of errors.

Executive function

Of the Trail Making Test (TMT),[96] we used the number of errors (parts A and B) and the increase in execution time from part A to part B. Of the Modified Card Sorting Test (MCST),[86] we scored the number of errors.

In Word production according to lexical rules (UNKA-test),[57] a production time of 60 seconds per phoneme was used and the total number of correct words was counted.

Reaction speed

In one of the "go-no go" conditions of the Vienna reaction apparatus,[106] combinations of stimuli ("light-light") were presented among irrelevant signals that had to be ignored. The median reaction time (msec) was calculated and used as parameter.

Mood

The VROPSOM[4] is the Dutch version of the Depression Adjective Check Lists,[72] which screen for the presence of depressive affect. The score was the sum of dysphoric items ticked and euphoric items not ticked. If a patient scored ≥ 18 the patient's affect was considered depressed.

We obtained an overall measure of cognitive impairment, by converting raw scores on all cognitive tasks to standardized z-scores (mean of normative data minus patient's score, divided by the standard deviation of normative data), and summing these z-scores. A higher impairment score indicates worse cognitive functioning.

The performances of male (n=15) and female (n=40) control persons were used as normative data for, respectively, the male and female patients. Control persons were recruited from the spouses, and occasionally siblings, of the 113 patients. Persons with neurological or psychiatric diseases were excluded, just as those who did not resemble patients in age or educational level. Male patients and male controls were similar in mean age (64 and 60 years respectively, p=0.16) and median educational level (p=0.84; percentage primary to lower secondary education, 58 and 67 respectively). Likewise, female patients and female controls were similar in mean age (57 and 55 years respectively, p=0.57) and median educational level (p=0.60; percentage primary to lower secondary education, 89 and 95 respectively). To correct for any learning effect over time, the normscores were computed separately for each follow-up assessment.
In addition we defined whether or not cognitive impairment was present in the individual patient. If a patient scored ≥2 standard deviations (SD) worse than the normscores in two or more tasks as described above, we considered this patient cognitively impaired.

MR studies: Presence of infarcts, quantitative MCA flow and metabolic measures
MR studies were performed on a 1.5-Tesla whole body system (ACS/NT-15 model; Philips Medical Systems, Best, The Netherlands). Details on the applied MR protocol have been described previously.[120]
MR imaging (MRI) consisted of a sagittal T1-weighted spin-echo sequence and a transaxial T2-weighted spin echo sequence.
MRA quantitative flow measurements were performed in the left and right MCA. To visualize the circle of Willis, a 3D time of flight was performed. On the basis of the reconstruction of the circle of Willis in three dimensions, two 2D PC single slices were positioned perpendicular to the left and right MCA. All flow values were obtained by integrating across manually drawn regions of interest, which enclosed the vessel lumen as closely as possible.
^{1}H-MRS was performed with a single voxel technique. In each subject a volume of interest (VOI, typically 70 x 35 x 15 mm) was selected in the centrum semi-ovale of each hemisphere, which contained primarily white matter. Care was taken to avoid areas of infarction and regions containing subcutaneous lipid. Since it was not possible to calculate absolute concentrations, data are expressed as ratios of peak intensities of N-acetylaspartate (NAA) and creatine (Cr), and as absence or presence of lactate.

TCD CO_2- reactivity

The TCD sonography was performed with a Multi-Dop X device (DWL, Sipplingen, Germany). CO_2-reactivity was measured simultaneously in both the MCAs, with a 2-MHz Doppler probe with the subject in the supine position. The TCD probe was fitted in a light metal frame, which was firmly fixed to the head with two ear pieces and an adjustable nose saddle. After a 2-minute baseline period, subjects inhaled a gas mixture of 5% CO_2 and 95% O_2 (carbogene) for the next two minutes. The carbogene was inhaled through a mouthpiece connected to a respiratory balloon, and the use of a nose clip ensured proper inhalation. The CO_2 content of the breathing gas was monitored continuously with an infrared gas analyser. A spectral TCD recording of 5 seconds was made after 1 minute during the baseline period and after 1.5 minutes of carbogene inhalation. CO_2-reactivity was expressed as the relative change in blood flow velocity (BFV) after 1.5 minutes of carbogene inhalation, according to the equation $[(BFV_{CO2}\text{-}BFV_{baseline}) / BFV_{baseline}] \times 100\%$. The mean of the maximal BFV values during the spectral TCD recordings was used in this calculation.

Statistical Analysis

Patient characteristics, degree of contralateral ICA stenosis, side of CEA and shunt use, MR lesions, timing of the neuropsychological assessment in relation to symptoms and operation, and scores for cognitive impairment and depressive affect were compared between operated and non-operated patients by Student's *t* test, Mann-Whitney U test, c^2 test, or Fisher's Exact test, whichever was appropriate.

Subsequently the difference between operated and non-operated patients in time courses of depressive affect and both the sumscore for cognitive impairment and the z-score for each cognitive task were analysed by (uni- and multivariate) repeated measures.

Likewise the difference in time courses of transcranial Doppler CO_2-reactivity, of quantitative flow in the MCA, and of the NAA/Cr ratio were compared. Difference in CO_2-reactivity at baseline between operated and non-operated patients was analyzed by linear regression analysis both crude and adjusted for the time interval between patients' last symptoms and the investigation. The presence of lactate on ^{1}H-MRS was compared between operated and non-operated patients at the three time points by c^2 test or by Fisher's Exact test, whichever was appropriate.

Finally, correlations between time course of cognitive functioning and time courses of TCD CO_2-reactivity, of quantitative flow in the MCA, and of the NAA/Cr ratio were exam-

ined with Pearson's correlation analysis, in the total patient group (operated and non-operated patients).
P-values of <0.05 were considered significant.

RESULTS

Patient characteristics and the proportions of patients with MR lesions did not differ between patients with symptomatic ICA occlusion who underwent endarterectomy for contralateral asymptomatic carotid stenosis and control patients (Table 1). Operated patients had on average a higher degree of contralateral ICA stenosis (mean difference, 11; 95% CI, 3 to 20; *p*-value, 0.01). In operated patients the median time intervals between their last symptoms and the neuropsychological assessments were shorter than in control patients (*p*-values, first time interval, <0.01; second time interval, 0.04; third time interval, 0.09).

At baseline, operated and control patients had on average similar cognitive impairment scores, and similar scores for depressive affect (Table 2). On individual analysis, 6 operated patients (46%) and 8 control patients (53%) were found to be cognitively impaired. The mean score for depressive affect did not differ between cognitively impaired and unimpaired patients (mean difference, 0.74; 95% CI, -3.3 to 4.8; *p*-value, 0.71).

The time course of cognitive functioning for patients who did and those who did not undergo CEA is shown in Figure 1. Overall, cognitive performances did not improve over time (*p*-value, 0.13), and we found no differences in the time course between operated and non-operated patients (effect time-by-group, *p*-value, 0.94). Correction for the differences in degree of contralateral ICA stenosis and the time interval between patient's last symptoms and the first neuropsychological assessment did not change the results (data not shown). Analysis of the time course of performances on individual tests revealed significant improvements on three of the eight cognitive tasks (SPM, VLMT, Reaction speed) but again, there were no differences in the extent of improvement between patients who underwent CEA and those who didn't (data not shown).

As compared to baseline scores, mean depressive affect at 12 months' follow-up was

Table 1 Patient characteristics, degree of contralateral ICA stenosis, side of CEA and shunt use, MR lesions, and timing of the neuropsychological assessment in patients with symptomatic ICA occlusion who did and those who did not undergo endarterectomy for contralateral asymptomatic carotid artery stenosis (CEA).

	CEA n=13	no CEA n=15
Patient characteristics		
male / female, n	9 / 4	10 / 5
age, mean ± SD, years	63 ± 7	61 ± 13
retinal ischemia /hemispheric ischemia, n	3 / 10	2 / 13
rankin grade: 0 / 1 / 2 / 3, n	2 / 5 / 4 / 2	3 / 4 / 5 / 3
Degree of contralateral stenosis, mean ± SD	80 ± 10	68 ± 12
Side of CEA, left / right, n	6 / 7	–
Shunt used, n (%)	8 (62%)	–
MR lesions, n (%)	9 (69%)[†]	13 (87%)[‡]
borderzone infarcts, n	4	6
territorial infarcts, n	3	6
large subcortical, n	0	3
lacunar infarcts, n	3	2
white matter lesions, n	2	1
Time between last ischemic event and neuropsychological investigation, median (range), days		
first (preoperative) assessment	46 (1-194)	135 (22-200)
second (postoperative) assessment	277 (195-412)	329 (240-428)
third (postoperative) assessment	453 (391-594)	496 (413-606)
Time between neuropsychological investigation and CEA, median (range), days		
first (preoperative) assessment and CEA	41 (1-97)	–
second (postoperative) assessment and CEA	183 (111-203)	–
third (postoperative) assessment and CEA	363 (314-442)	–

[†] In 3 patients 2 types of ischemic lesions were present, in 1 patient 3 types.
[‡] In 2 patients 2 types of ischemic lesions were present, in 1 patient 3 types.

Table 2 Neuropsychological assessment scores and depressive affect in patients with symptomatic ICA occlusion who did and those who did not undergo endarterectomy for contralateral asymptomatic carotid artery stenosis (CEA).

	CEA n=13	no CEA n=15	
Cognitive impairment			
score, mean ± SD	8.2 ± 8.1	11.5 ± 8.3	Mean difference -3.3 (-9.7 to 3.1)
present, n (%)	6 (46)	8 (53)	*p*-value 0.71
Depressive affect			
score, mean ± SD	11 ± 4	13 ± 6	Mean difference -2 (-6 to 2)
present, n (%)	1 (8%)	4 (29%)	*p*-value 0.33

reduced in both operated and non-operated patients (*p*-value, 0.01). At 12 months' follow-up, none of the operated patients and only one of the non-operated patients had a depression score in the clinical range of depressive affect. Course of affect over time did not

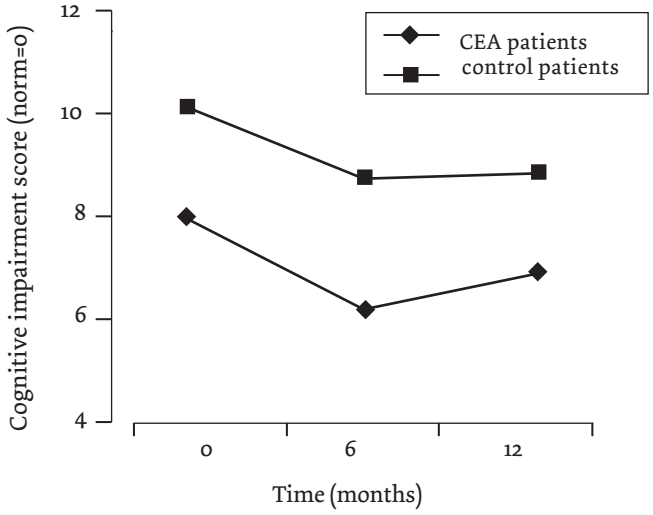


Figure 1. *Course of cognitive impairment over time, for patients who did (n=13) and those who did not (n=15) undergo endarterectomy for asymptomatic contralateral carotid artery stenosis (CEA).*

correlate with course of cognition (Pearson correlation, -0.17; *p*-value, 0.41).
Figure 2 shows the time course of CO_2-reactivity, of MCA flow, and of NAA/Cr in the hemisphere on the side of the ICA occlusion and on the side of the ICA stenosis in patients who did and in those who did not undergo CEA. At baseline CO_2-reactivity in the hemisphere ipsilateral to the side of the ICA occlusion was lower in the group of operated patients (mean ± SD, 6 ± 18) than in non-operated patiens (mean ± SD, 23 ± 20; mean difference, 17; 95% CI, 2 to 32; *p*-value, 0.03). After correction for the time interval between patients' last symptoms and assessment of CO_2-reactivity, this difference was no longer significant (adjusted mean difference, 14; 95% CI -3 to 31; *p*-value, 0.10). After the CEA,

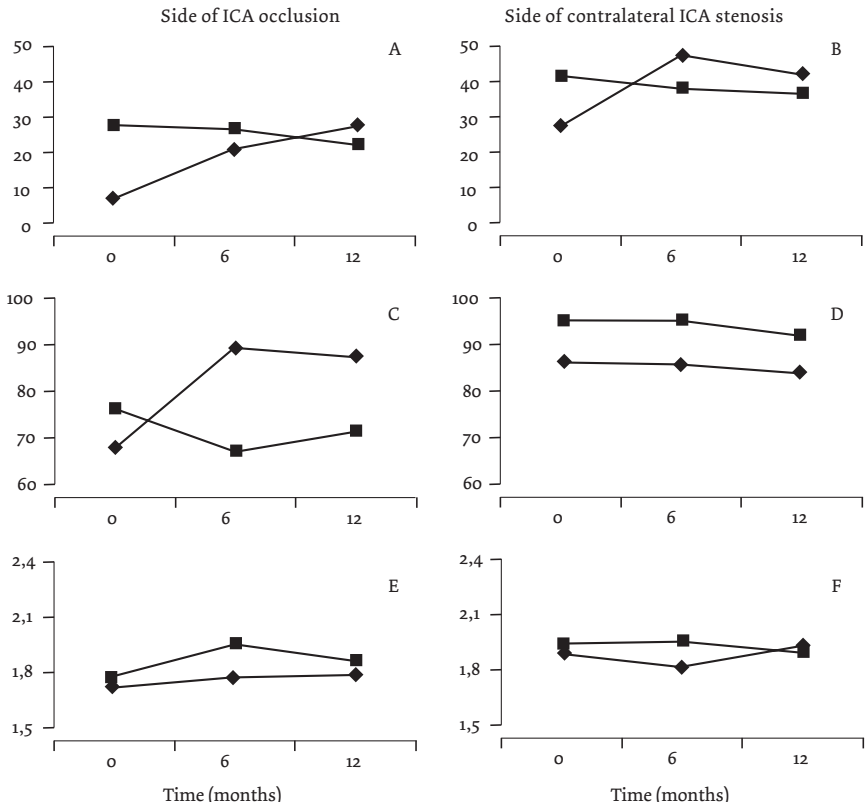


Figure 2. *Time course of CO_2-reactivity (panel a and b), MCA flow (panel c and d), and NAA/Cr (panel e and f) in the hemisphere on the side of the ICA occlusion and on the side of the contralateral ICA stenosis in patients who did (n=13, ▫) or did not (n=15, ▫) undergo endarterectomy for contralateral asymptomatic carotid artery stenosis.*

CO_2-reactivity in the hemisphere ipsilateral to the side of the ICA occlusion improved, whereas no changes over time were found for non-operated patients (effect time-by-group, *p*-value, 0.01). The time course of CO_2-reactivity in the hemisphere on the side of the ICA stenosis tended to differ between operated and non-operated patients (effect time-by-group, *p*-value, 0.07), but overall, CO2-reactivity did not change over time (*p*-value, 0.30).

In patients who underwent CEA of their asymptomatic ICA stenosis, flow in the MCA on the side of the ICA occlusion improved, whereas such improvement was not observed in non-operated patients (effect time-by-group, *p*-value, <0.01). The flow in the MCA on the operated side showed no changes over time (*p*-value, 0.86) and no difference in time course was found for operated and non-operated patients (effect time-by-group, *p*-value, 0.99).
In both hemispheres NAA/Cr ratio's did not change significantly over time (*p*-value, ipsilateral to occlusion, 0.20; ipsilateral to stenosis, 0.81) and their time course was not different for operated and non-operated patients (*p*-value, ipsilateral to occlusion, 0.58; ipsilateral to stenosis, 0.42). In both operated and non-operated patients the number of patients with lactate diminished over time (Table 3). No significant differences between operated and non-operated patients in the presence of lactate were found at any of the three time points (Table 3).

Examining the total patient group (operated and non-operated patients), cognitive

Table 3 Presence of lactate in the hemisphere at the side of the ICA occlusion in patients who did and those who did not undergo endarterectomy for contralateral asymptomatic carotid artery stenosis (CEA), at baseline and after six and twelve months.

	CEA n=13	no CEA n=13*	*p*-value
Presence of lactate			
assessment 1, n	6	7	1.00
assessment 2, n	4	8	0.24
assessment 3, n	1*	3	0.60

* In two patients the presence of lactate could not be assessed.

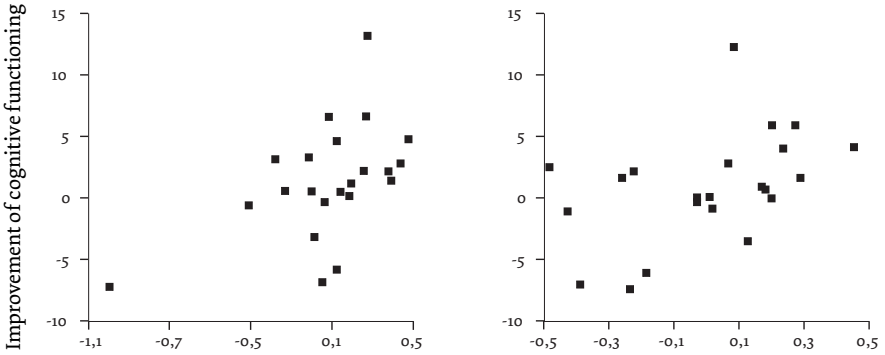


Figure 3. *Correlations between cognitive improvement during the 12 months' follow-up period and increase of the NAA/Cr ratio in the hemisphere on the side of the ICA occlusion (panel a; Pearson correlation, 0.51; p-value, 0.02) and on the side of the contralateral ICA stenosis (panel b; Pearson correlation 0.46; p-value, 0.03).*

improvement was associated with an increased NAA/Cr ratio in both hemispheres (Figure 3), whereas no correlations appeared between cognitive improvement and improvement of CO_2-reactivity (*p*-value, ipsilateral to occlusion, 0.60; ipsilateral to stenosis, 0.24) or flow in the MCA (*p*-value, ipsilateral to occlusion, 0.98; ipsilateral to stenosis, 0.92).

DISCUSSION

This study shows that cognitive functioning in patients with symptomatic carotid artery occlusion does not improve by endarterectomy of contralateral carotid artery stenosis despite amelioration of CO_2-reactivity and the amount of MCA flow on the side of the ICA occlusion.

A substantial number of patients with symptomatic ICA occlusion show impaired cognitive function on formal neuropsychological testing.[10] It has been hypothesized that improvement of the flow status of the brain after CEA of a contralateral asymptomatic ICA stenosis could improve cognition in these patients.[65] In this study we could not confirm this hypothesis. Several factors may have influenced our negative findings. Firstly,

the neuropsychological tests that we used may not have been sensitive enough to detect small changes in cognitive functioning after CEA. However, we found significant improvements in cognitive performances on three tasks. Separate analyses of the performances on these tasks also did not reveal any differences in the extent of improvement between operated and control patients. Another explanation may be that the increase of MCA flow and CO_2-reactivity, although statistically significantly different between operated and control patients, in absolute terms was too small to cause a substantial improvement in the functional state of brain tissue. Our finding that metabolism, as measured by the NAA/Cr ratio and the presence of lactate in non-infarcted white matter, improved to the same extent in operated and control patients might support this hypothesis. Furthermore, the improvement in CO_2-reactivity observed in patients who underwent CEA is not necessarily caused by the operation. There was less room for improvement in the control patients, as the CO_2-reactivity was on average higher in these patients than in operated patients. In addition CO_2-reactivity has been shown to improve spontaneously over time.[130] A third explanation may be that the main cause of cognitive impairment in patients with symptomatic carotid artery occlusion is brain damage due to emboli or micro-angiopathy, and not chronic cerebral hypoperfusion. Our finding that metabolism improved irrespective of whether CEA is performed, might indicate that the initial metabolic changes were induced by ischemic lesions.[102] Likewise, cognitive improvement associated with improvement of the NAA/Cr ratio, might reflect recovery from ischemic brain damage, instead of recovery due to increased blood flow to the brain.[36,78,120]

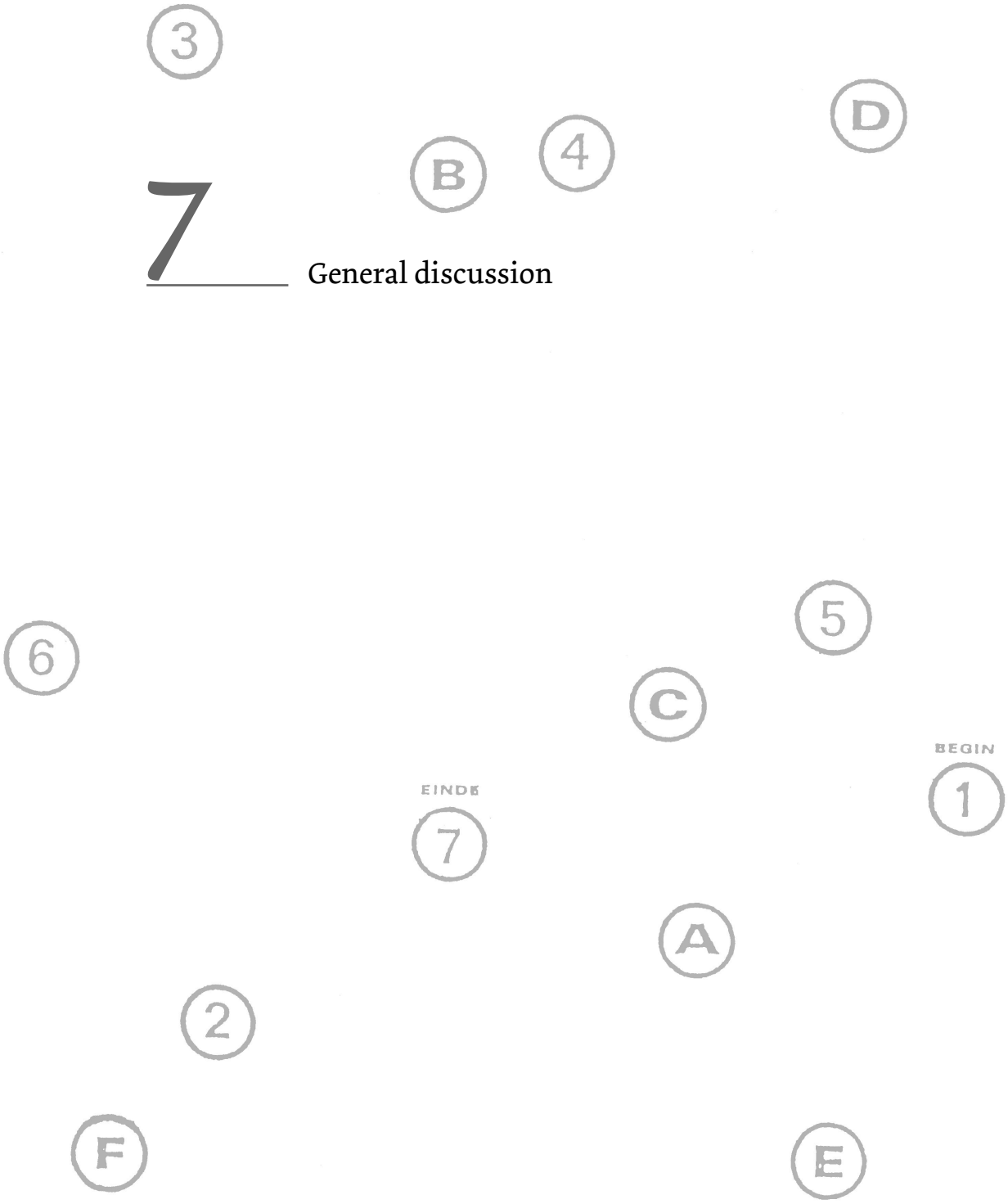
Studies in patients with symptomatic or asymptomatic ICA stenosis, or studies that included patients with carotid artery disease not further specified, have shown contradicting results for the effect of CEA on cognitive functioning, varying from deterioration to improvement of cognition after CEA.[42,50,55,73] No data is available on the effect of CEA in patient groups with severe bilateral carotid artery disease, similar to the patients in the current study. Also, none of the studies have examined the relation between changes in cognitive functioning and changes in CO_2-reactivity or metabolism after CEA.[73] In 31 patients who suffered from TIAs, cognitive improvement after CEA was not associated with improved regional cerebral blood flow as measured by ^{133}Xenon SPECT. Contrary to the findings on cognition, only 2 of the patients had improved regional cerebral blood flow.[48]

A limitation of our study is that the decision to perform CEA was not determined by ran-

domisation, which may have caused a selection bias. Another limitation is that the duration of follow-up was relatively short. Since cognitive deterioration may be a gradual process, the current study cannot exclude more long-term differences in cognitive functioning between operated and non-operated patients. Furthermore, the number of patients studied was relatively small. However, this is a consequence of our decision to assess a homogeneous group of patients characterized by a compromised cerebral blood flow.

We conclude that in patients with symptomatic ICA occlusion and asymptomatic contralateral ICA stenosis, endarterectomy of the contralateral ICA stenosis results in improvement of the hemodynamic state of the brain. This improvement is not accompanied by better recovery of cognition within one year, as operated and non-operated patients showed similar improvement in cognitive functioning over time.

7 General discussion



Frequency of cognitive impairment

The findings of the clinical studies as described in this thesis support the impressions from the literature review (chapter 2) that a substantial portion of patients with symptomatic carotid artery disease (CAD) is cognitively impaired in the subacute phase after the occurrence of ischemic symptoms, even if the focal neurological deficits resolved within 24 hours. Thus, recovery of focal neurological deficits does not guarantee undisturbed cognitive functioning in patients with CAD.

The literature yielded no data on the prevalence of cognitive impairment in patients with symptomatic CAD. Using a criterion that enabled us to trace subtle cognitive impairment, we found cognitive impairment in approximately 50% of the patients with a TIA and 70% of the patients with a minor ischemic stroke. Although we classified the patients as "impaired" or "not impaired" in a principled way, these proportions are merely an approximation of the true frequencies of occurrence, as we could not compare patients' performances with test data on their premorbid level of functioning.

Nature of cognitive impairment

Cognitive behaviour, as assessed by psychological tests, is multi-determined. A disorder in one area of cognition can manifest itself on a wide range of psychological tests, thereby invalidating the measurement pretension of those tests.[24,30] This is corroborated by our finding that the presence of language impairment hampers the performances on a variety of tests, including tests of memory and learning (chapter 5). Realising this, we made an attempt to characterise the nature of cognitive impairment in our patient group empirically. Having ordered the assessment procedures according to the measurement pretensions into domains of cognition (chapters 3-6), and having inspected the pattern of deficits within and between the domains without finding evidence of particular vulnerable domains (chapters 3, 5), we went on to verify the tenability of this domain-bound ordering from the viewpoint of the test data, by using Principal Component Analysis (chapter 5). Three robust components emerged and, again, the findings in the patients indicated that the vulnerability of cognition was not related to specific cognitive functions.

The absence of a consistent pattern of deficits across the domains or components in the patient group may be explained by the heterogeneity in location of the ischemic lesions (if present), but also by the diffuse nature of the impact of an impaired blood flow to the brain.

Degree and course of cognitive impairment

The degree and nature of cognitive impairment in the patient group did not justify a diagnosis of vascular dementia.[35,51,97] However, patients with cognitive impairment caused by cerebrovascular diseases have an increased risk of progressing to dementia.[36,129] Identifying prognostic indicators of dementia in patients with CAD is relevant in view of early treatment options. The literature contains no data on the natural history of cognitive impairment in patients with symptomatic ICA occlusion (chapter 2). Based on our clinical studies, progress to dementia is not to be expected in the short term, i.e. 1.5 years after the occurrence of the ischemic event (chapter 5). In fact, in the absence of ischemic symptoms during the follow-up period, cognitive functioning improved in a substantial portion of patients who did not undergo surgery, although it did not return to normal levels. A longer follow-up period is needed to determine whether patients with symptomatic ICA occlusion may progress to dementia, and to identify prognostic indicators for dementia.

Pathophysiological basis of cognitive impairment

An obvious cause of cognitive impairment in patients with symptomatic CAD is brain damage due to the ischemic event(s). In addition, chronic cerebral hypoperfusion has been suggested to cause or contribute to cognitive impairment in these patients.[39,65] Our finding of impaired cognition in patients with symptoms of retinal but no cerebral ischemia, and in patients without ischemic lesions visible on MRI may support this hypothesis (chapter 3). To gain more insight into the pathophysiological processes underlying the cognitive impairment, we examined whether cerebral hemodynamic and metabolic measurements correlated with cognitive functioning. Impaired vasomotor reactivity as measured by Doppler CO_2-reactivity in the middle cerebral artery (MCA) did not correlate with cognitive functioning (chapter 4). Also, improvement of MCA volume flow and CO_2-reactivity did not result in recovery of cognitive functioning (chapter 6). We proposed several explanations for the absence of a relation between (changes in) MCA flow and CO_2-reactivity and (changes in) cognitive functioning (chapters 4, 6). In contrast to the negative findings on the hemodynamic measurements, the presence of lactate in non-infarcted white matter ipsilateral to the ICA occlusion was associated with cognitive impairment, and seemed to be a prognostic indicator for cognitive improvement failing to occur at follow-up (chapters 4, 5). Also, increases of the NAA/creatine

ratio's in white matter of both hemispheres were associated with improvement of cognitive functioning at follow-up (chapter 6). The origin of metabolic changes in non-infarcted brain regions has not been elucidated yet, but in patients with severe obstructive CAD, it has been suggested to indicate a compromised cerebral blood flow (CBF).[120] A common origin, i.e., regional hypoperfusion due to the ICA occlusion and insufficient collateral circulation, may thus account for the association between cognitive impairment and metabolic changes. The lack of evidence for a relation between cognitive functioning and hemodynamic measurements in our patients may refute this hypothesis, but may also indicate that our measures of hemodynamic compromise were not sensitive enough. Regional measures of CBF might be more appropriate to examine the relation between cognition and cerebral hypoperfusion (chapter 4).

Health-related quality of life

Health-related quality of life (QoL) is a multidimensional concept, that includes the subjective rating of physical, mental, and social aspects of functioning.[19] Using a health status measure that incorporates these aspects, both patients with a TIA and those with a minor ischemic stroke reported subnormal levels of health-related QoL (chapter 5). Depressive mood, as measured by a checklist, proved to be a strong correlate of low QoL, whereas physical disability had limited and cognitive impairment had no impact on QoL (chapter 5). These findings are in accordance with findings in patients with stroke, showing that depression and social support are among the main determinants of health-related QoL.[13,75] This may limit the usefulness of self-perceived QoL as an outcome measure for surgical interventions.[18,26,125]

Limitations of the study

The main purpose of our study was to acquire knowledge on cognitive functioning in a well-defined segment of the patient population with obstructive CAD, for the benefit of adequate counselling and care. In the course of the study, the question of causality of cognitive impairment was raised. Although the exploration of correlates of cognitive impairment in our patient group yielded interesting results, the interpretation of the data is limited due to characteristics of the patient group. For example, a large proportion of the patients had suffered from cerebral symptoms, as was evident from MR

imaging. In view of the possible impact of cerebral ischemic lesions on cognition, patients with hemodynamically significant but asymptomatic carotid obstruction may have been a more appropriate group to examine the impact of chronic cerebral hypoperfusion on cognition.

Recommendations for future research

To determine the course of cognitive functioning in patients with symptomatic ICA occlusion, a follow-up period of one year is short. It would be most interesting to investigate whether cognitive functioning continues to improve in the absence of recurrent symptoms, whether the presence of lactate on ^{1}H-MRS proves to be a prognostic indicator for cognitive functioning at long-term follow-up, and whether revascularization surgery has long-term effects on cognition.

To examine the impact of chronic cerebral hypoperfusion on cognition, we would recommend the use of techniques that measure perfusion at tissue rather than artery level. Arterial spin-labelled blood flow MRI might be an attractive imaging technique.[2]

References

1. Aaronson NK, Muller M, Cohen PDA, Essink-Bot M-L, Fekkes M, Sanderman R, Sprangers MAG, Te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 health survey in community and chronic disease populations. J Clin Epidemiol 1998; 51(11): 1055-1068.
2. Alsop DC, Detre JA, Grossman M. Assessment of cerebral blood flow in Alzheimer's disease by spin-labeled magnetic resonance imaging. Ann Neurol 2000; 47: 93-100.
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (4th ed.). Washington, D.C., American Psychiatric Association. 1994.
4. Arrindell WA, van Rooijen LB. De VROPSOM: de meting van depressief affect met de Nederlandse bewerking van de Depression Adjective Check Lists (DACL). Gedragstherapie 1999; 32(4): 297-304.
5. Austin MP, Mitchell P, Goodwin GM. Cognitive deficits in depression. Possible implications for functional neuropathology. Br J Psychiatry 2001; 178: 200-206.
6. Baird AD, Adams KM, Shatz MW, Brown GG, Diaz F, Ausman JI. Can neuropsychological tests detect the sites of cerebrovascular stenoses and occlusions? Neurosurgery 1984; 14(4): 416-423.
7. Baird AD, Ausman JI, Diaz FG, Dujovny M, Adams KM, Shatz MW. Neurobehavioral and life-quality changes after cerebral revascularization. J Consult Clin Psychol 1988; 56(1): 148-151.
8. Baird AD, Boulos R, Mehta B, Adams KM, Shatz MW, Ausman JI, Diaz FG, Dujovny M. Cerebral angiography and neuropsychological measurement: the twain may meet. Surg Neurol 1985; 23: 641-650.
9. Bakker FC, Klijn CJM, Jennekens-Schinkel A, Kappelle LJ. Cognitive disorders in patients with occlusive disease of the carotid artery: a systematic review of the literature. J Neurol 2000; 247: 669-676.
10. Bakker FC, Klijn CJM, Jennekens-Schinkel A, van der Tweel I, van der Grond J, van Huffelen AC, Tulleken CAF, Kappelle LJ. Cognitive impairment is related to cerebral lactate in patients with carotid artery occlusion and ipsilateral transient ischemic attacks. Stroke 2003, in press.
11. Bakker FC, Klijn CJM, Jennekens-Schinkel A, van der Tweel I, Tulleken CAF, Kappelle LJ. Cognitive impairment in patients with carotid artery occlusion and ipsilateral transient ischemic attacks. Submitted for publication.
12. Bamford JM, Sandercock PAG, Warlow CP, Slattery J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1989; 20: 828.
13. Bays CL. Quality of life of stroke survivors: a research synthesis. J Neurosci Nurs 2001; 33(6): 310-316.
14. Benke T, Neussl D, Aichner F. Neuropsychological deficits in asymptomatic carotid artery stenosis. Acta Neurol Scand 1991; 83: 378-381.
15. Bennet DA, Wilson RS, Schneider JA, Evans DA, Beckett LA, Aggarwal NT, Barnes LL, Fox JH, Bach J. Natural history of mild cognitive impairment in older persons. Neurology 2002; 59: 198-205.
16. Binder LM, Tanabe CT, Waller FT, Wooster NE. Behavioral effects of superficial temporal artery to middle cerebral artery bypass surgery: preliminary report. Neurology 1982; 32: 422-424.
17. Boeke S. The effect of carotid endarterectomy on mental functioning. Clin Neurol Neurosurg 1981; 83(4): 209-217.
18. Bossema E, Dreessen N, Brand N, Moll F, Ackerstaff R, van Doornen L. Kwaliteit van leven voor en na carotis endarteriëctomie. Gedrag en gezondheid 2002; 30(4): 262-271.
19. Bosworth HB, Siegler IC, Olsen MK, Brummett BH, Barefoot JC, Williams RB, Clapp-Channing NE, Mark DB. Social support and quality of life in patients with corony artery disease. Qual Life Res 2000; 9: 829-839.
20. Bouma A, Mulder J, Lindeboom J. Neuropsychologische diagnostiek; handboek. Lisse, Swets and Zeitlinger. 1996.
21. Bowler JV, Steenhuis R, Hachinski V. Conceptual background to vascular cognitive impairment. Alzheimer dis assoc dis 1999; 13(Suppl 3): S30-S37.
22. Breteler MBB. Vascular risk factors for Alzheimer's disease: an epidemiologic perspective. Neurobiol Aging 2000; 21: 153-160.

23. Channon S, Green PSS. Executive function in depression: the role of performance strategies in aiding depressed and non-depressed participants. J Neurol Neurosurg Psychiatry 1999; 66: 162-171.
24. Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology 1992; 42: 473-480.
25. Cimino CR. Principles of neuropsychological interpretation. In: Vanderploeg RD (ed.). Clinician's guide to neuropsychological assessment. Hove, New Yersey: Lawrence Erlbaum Associates. 1994; 69-112.
26. Dardik A, Minor J, Watson C, Hands LJ. Improved quality of life among patients with symptomatic carotid artery disease undergoing carotid endarterectomy. J Vasc Surg 2001; 33: 329-333.
27. De Groot JC, De Leeuw F-E, Oudkerk M, van Gijn J, Hofman A, Jolles J, Breteler MMB. Cerebral white matter lesions and cognitive function: the Rotterdam scan study. Ann Neurol 2000; 47: 145-151.
28. De Leo D, Serraiotto L, Pellegrini C, Magni G, Franceschi l, Deriu GP. Outcome from carotid endarterectomy. Neuropsychological performances, depressive symptoms and quality of life: 8-months follow-up. Int J Psychiatr Med 1987; 17: 317-325.
29. DeCarli C, Grady CL, Clark CM, Katz DA, Brady DR, Murphy DGM, Haxby JV, Salerno JA, Gillette JA, Gonzalez-Aviles A, Rapoport SI. Comparison of positron emission tomography, cognition, and brain volume in Alzheimer's disease with and without severe abnormalities of white matter. J Neurol Neurosurg Psychiatry 1996; 60: 158-167.
30. Deelman B, Eling P. Klinische neuropsychologie. In: Deelman B, Eling P, De Haan E, Jennekens-Schinkel A, van Zomeren E (eds.). Klinische neuropsychologie. Amsterdam, Boom. 1997; 15-38.
31. Delaney RC, Wallace JD, Egelko S. Transient cerebral ischemic attacks and neuropsychological deficit. J Clin Neuropsychol 1980; 2(2): 107-114.
32. Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test; research edition. New York, The Psychological Corporation. 1987.
33. Demougeot C, Walker P, Beley A, Marie C, Rouaud O, Giroud M, Brunotte F. Spectroscopic data following stroke reveal tissue abnormality beyond the region of T2-weighted hyperintensity. J Neurol Sci 2002; 199(1-2): 73-78.
34. Desmond DW. Cognition and white matter lesions. Cerebrovasc Dis 2002; 13(suppl 2): 53-57.
35. Desmond DW, Erkinjuntti T, Sano M, Cummings JL, Bowler JV, Pasquier F, Moroney JT, Ferris SH, Stern Y, Sachdev PS, Hachinski VC. The cognitive syndrome of vascular dementia: implications for clinical trials. Alzheimer dis assoc dis 1999; 13(Suppl 3): S21-S29.
36. Desmond DW, Moroney JT, Sano M, Stern Y. Incidence of dementia after ischemic stroke. Stroke 2002; 33(9): 2254.
37. Drinkwater JE, Thompson SK, Lumley JSP. Cerebral function before and after extra-intracranial carotid bypass (short report). J Neurol Neurosurg Psychiatry 1984; 47: 1041-1043.
38. Ferguson CG, Peerless SJ. Extracranial-intracranial bypass in the treatment of dementia and multiple extracranial arterial occlusion. Stroke 1976; 7: 13.
39. Fisher CM. Senile dementia - a new explanation for its causation. Can Med Assoc J 1951; 65: 1-7.
40. Fox AJ. How to measure carotid stenosis. Radiology 1993; 186: 316-318.
41. Fruhwald S, Loffler H, Eher R, Saletu B, Baumhackl U. Relationship between depression, anxiety and quality of life: a study of stroke patients compared to chronic low back pain and myocardial ischemia patients. Psychopathology 2001; 34: 50-56.

42. Greber C, Ruchat P, Karapanayiotides T, Kemeny V, Piechowski-Jozwiak B, Despland PA, Bogousslavsky J, Devuyst G. Carotid endarterectomy is associated with sustained improvement of cognitive functions in symptomatic and asymptomatic patients. Stroke 2003; 34: 321.
43. Gregg EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL, Venkat Narayan KM, Cummings SR. Is diabetes associated with cognitive impairment and cognitive decline among older women? Arch Intern Med 2000; 160: 174-180.
44. Grubb RLJr, Derdeyn CP, Fritsch SM, Carpenter DA, Yundt KD, Videen TO, Spitznagel EL, Powers WJ. Importance of hemodynamic factors in the prognosis of symptomatic carotid artery occlusion. JAMA 1998; 280: 1055-1060.
45. Hamster W, Diener HC. Neuropsychological changes associated with stenoses or occlusions of the carotid arteries: a comparative psychometric study. Eur Arch Psych Neurol Sci 1984; 234: 69-73.
46. Hart RP, Rosner MJ, Muizelaar JP. Recovery from aphasia following extracranial-intracranial bypass surgery: case report. J Clin Exp Neuropsychol 1985; 7(3): 224-230.
47. Hemmingsen R, Mejsholm B, Boysen G, Engell HC. Intellectual function in patients with transient ischaemic attacks (TIA) or minor stroke: long-term improvement after carotid endarterectomy. Acta Neurol Scand 1982; 66: 145-159.
48. Hemmingsen R, Mesjholm B, Vorstrup S, Lester J, Engell HC, Boysen G. Carotid surgery, cognitive function, and cerebral blood flow in patients with transient ischemic attacks. Ann Neurol 1986; 20: 13-19.
49. Henon H, Durieu I, Guerouaou D, Lebert F, Pasquier F, Leys D. Poststroke dementia: incidence and relationship to prestroke cognitive decline. Neurology 2001; 57: 1216-1222.
50. Heyer EJ, Sharma R, Rampersad A, Winfree CJ, Mack WJ, Solomon RA, Todd GJ, McCormick PC, McMurtry JG, Quest DO, Stern Y, Lazar RM, Conolly ES. A controlled prospective study of neuropsychological dysfunction following carotid endarterectomy. Arch Neurol 2002; 59: 217-222.
51. Hijdra A, Koudstaal PJ, Roos RAC (eds.). Neurologie. Utrecht, Bunge. 1994.
52. Hillis AE, Barker PB, Beauchamp NJ, Gordon B, Wityk RJ. MR perfusion imaging reveals regions of hypoperfusion associated with aphasia and neglect. Neurology 2000; 55: 782-788.
53. Hochstenbach J, Mulder T, Limbeek van J, Donders R, Schoonderwaldt H. Cognitive decline following stroke: a comprehensive study of cognitive decline after stroke. J Clin Exp Neuropsychol 1998; 20(4): 503-517.
54. Iddon JL, Sahakian BJ, Kirkpatrick PJ. Uncomplicated carotid endarterectomy is not associated with neuropsychological impairment. Pharmacol Biochem Behav 1997; 56(4): 781-787.
55. Irvine CD, Gardner FV, Davies AH, Lamont PM. Cognitive testing in patients undergoing carotid endarterectomy. Eur J Vasc Endovasc Surg 1998; 15: 195-204.
56. Ivnik RJ, Smith GE, Tangalos EG, Petersen RC, Kokmen E, Kurland LT. Wechsler memory scale: IQ-dependent norms for persons ages 65 to 97 years. Psychol assessment 1991; 3(2): 156-161.
57. Jennekens-Schinkel A, Lanser JBK, van der Velde EA, Sanders EACM. Performances of multiple sclerosis patients in tasks requiring language and visuoconstruction. Assessment of outpatients in quiescent disease stages. J Neurol Sci 1990; 95: 89-103.
58. Kauhanen M-L, Korpelainen JT, Hiltunen P, Maata R, Mononen H, Brusin E, Sotaniemi KA, Myllyla VV. Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. Cerebrovasc Dis 2000; 10: 455-461.
59. Kauhanen M-L, Korpelainen JT, Hiltunen P, Nieminen P, Sotaniemi KA, Myllyla VV. Domains and determinants of quality of life after stroke caused by brain infarction. Arch Phys Med Rehabil 2000; 81: 1541-1546.
60. Kelly MP, Garron DC, Javid H. Carotid artery disease, carotid endarterectomy, and behavior. Arch Neurol 1980; 37: 743-748.

61. Kelly MP, Kaszniak AW, Garron DC. Neurobehavioral impairment patterns in carotid disease and Alzheimer disease. Int J Clin Neuropsychol 1986; 8(4): 163-169.
62. Kilander L, Nyman H, Boberg M, Hansson L, Lithell H. Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. Hypertension 1998; 31: 780-786.
63. King DA, Caine ED. Cognitive impairment and major depression: beyond the pseudodementia syndrome. In: Grant I, Adams KM (eds). Neuropsychological assessment of neuropsychiatric disorders. Oxford, Oxford University Press. 1996; 200-217.
64. Klijn CJM, Kappelle LJ, Algra A, van Gijn J. Outcome in patients with symptomatic occlusion of the internal carotid artery or intracranial arterial lesions: a meta-analysis of the role of baseline characteristics and type of antithrombotic treatment. Cerebrovasc Dis 2001; 12(3): 228-234.
65. Klijn CJM, Kappelle LJ, Tulleken CAF, van Gijn J. Symptomatic carotid artery occlusion; a reappraisal of hemodynamic factors. Stroke 1997; 28: 2084-2093.
66. Klijn CJM, Kappelle LJ, van der Grond J, Algra A, Tulleken CAF, van Gijn J. Magnetic resonance techniques for the identification of patients with symptomatic carotid artery occlusion at high risk of cerebral ischemic events. Stroke 2000; 31: 3001-3007.
67. Klijn CJM, Kappelle LJ, van der Zwan A, van Gijn J, Tulleken CAF. Excimer laser-assisted high-flow extracranial/intracranial bypass in patients with symptomatic carotid artery occlusion at high risk of recurrent cerebral ischemia: safety and long-term outcome. Stroke 2002; 33: 2451-2458.
68. Kwa VIH, Limburg M, de Haan RJ. The role of cognitive impairment in the quality of life after ischaemic stroke. J Neurol 1996; 243: 599-604.
69. Kwan LT, Reed BR, Eberling JL, Schuff N, Tanabe J, Norman D, Weiner MW, Jagust WJ. Effects of subcortical cerebral infarction on cortical glucose metabolism and cognitive function. Arch Neurol 1999; 56: 809-814.
70. Lezak MD. Neuropsychological assessment (3rd ed.). New York, Oxford University Press. 1995.
71. Lopez-Villegas D, Lenkinski RE, Wehrli SL, Ho W-Z, Douglas SD. Lactate production by human monocytes/macrophages determined by proton MR spectroscopy. Magn Reson Med 1995; 34: 32-38.
72. Lubin B. Adjective checklists for measurement of depression. Arch Gen Psychiatry 1965; 12: 57-62.
73. Luhn S, Crawley F, Harrison MJG, Brown MM, Newman SP. Impact of carotid endarterectomy upon cognitive functioning; a systematic review of the literature. Cerebrovasc Dis 1999; 9: 74-81.
74. Lythgoe D, Simmons A, Pereira A, Cullinane M, Williams S, Markus HS. Magnetic resonance markers of ischaemia: their correlation with vasodilatory reserve in patients with carotid artery stenosis and occlusion. J Neurol Neurosurg Psychiatry 2001; 71: 58-62.
75. Mackenzie AE, Chang AM. Predictors of quality of life following stroke. Disabil Rehabil 2002; 24(5): 259-265.
76. Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. Brain 2001; 124: 457-467.
77. Markus HS, Harrison MJH, Adiseshiah M. Carotid endarterectomy improves haemodynamics on the contralateral side: Implications for operating contralateral to an occluded artery. Br J Surg 1993; 80: 170-172.
78. Meyer JS, Rauch G, Rauch RA, Haque A. Risk factors for cerebral hypoperfusion, mild cognitive impairment, and dementia. Neurobiol Aging 2000; 21: 161-169.
79. Meyer JS, Rauch GM, Crawford K, Rauch RA, Konno S, Akiyama H, Terayama Y, Haque A. Risk factors accelerating cerebral degenerative changes, cognitive decline and dementia. Int J Geriatr Psychiatr 1999; 14: 1050-1061.
80. Meyer JS, Rogers RL, Judd BW, Mortel KF, Sims P. Cognition and cerebral blood flow fluctuate together in multi-infarct dementia. Stroke 1988; 19: 163-169.

81. Mielke R, Herholz K, Grond M, Kessler J, Heiss W. Severity of vascular dementia is related to volume of metabolically impaired tissue. Arch Neurol 1992; 49: 909-913.
82. Mulder JL, Dekker R, Dekker PH. Verbale leer en geheugen test; handleiding. Lisse, Swets & Zeitlinger. 1996.
83. Mungas D, Jagust WJ, Reed BR, Kramer JH, Weiner MW, Schuff N, Norman D, Mack WJ, Willis L, Chui HC. MRI predictors of cognition in subcortical ischemic vascular disease and Alzheimer's disease. Neurology 2001; 57(12): 2229-2235.
84. Murkin JM, Newman SP, Stump DA, Blumenthal JA. Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. Ann Thorac Surg 1995; 59: 1289-1295.
85. Naugle RI, Bridgers SL, Delaney RC. Neuropsychological signs of asymptomatic carotid stenosis (brief report). Arch Clin Neuropsychol 1986; 1: 25-30.
86. Nelson HE. A modified card sorting test sensitive to frontal lobe defects. Cortex 1976; 12: 313-324.
87. Nielsen H, Hojer-Pedersen E, Gulliksen G, Haase J, Enevoldsen E. A neuropsychological study of 12 patients with transient ischemic attacks before and after EC/IC bypass surgery. Acta Neurol Scand 1985; 71: 317-320.
88. Nielsen H, Hojer-Pedersen E, Gulliksen G, Haase J, Enevoldsen E. Reversible ischemic neurological deficit and minor strokes before and after EC/IC bypass surgery: a neuropsychological study. Acta Neurol Scand 1986; 73: 615-618.
89. O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, Bowler JV, Ballard C, DeCarli C, Gorelick PB, Rockwood K, Burns A, Gauthier S, DeKosky ST. Vascular cognitive impairment. Lancet Neurology 2003; 2: 89-98.
90. Parker JC, Granberg BW, Nichols WK, Jones JG, Hewett JE. Mental status outcomes following carotid endarterectomy: a six-month analysis. J Clin Neuropsychol 1983; 5(4): 345-353.
91. Parker JC, Smarr KL, Granberg BW, Nichols WK, Hewett JE. Neuropsychological parameters of carotid endarterectomy: a two-year prospective analysis. J Consult Clin Psychol 1986; 54(5): 676-681.
92. Pohjasvaara T, Erkinjuntti T, Vataja R, Kaste M. Dementia three months after stroke: baseline frequency and effect of different definitions of dementia in the Helsinki stroke aging memory study (SAM) cohort. Stroke 1997; 28: 785-792.
93. Pohjasvaara T, Leskela M, Vataja R, Kalska H, Ylikoski R, Hietanen M, Leppavuori A, Kaste M, Erkinjuntti T. Post-stroke depression, executive dysfunction and functional outcome. Eur J Neurol 2002; 9: 269-275.
94. Raven JC, Court JH, Raven J. Standard progressive matrices; manual. Oxford, Oxford University Press. 1992.
95. Reitan RM, Wolfson D. Influence of age and education on neuropsychological test results. Clin Neuropsychol 1995; 9(2): 151-158.
96. Reitan RM, Wolfson D. Theoretical, methodological and validational bases of the Halstead-Reitan neuropsychological test battery. In: Grant I, Adams KM (eds.). Neuropsychological assessment of neuropsychiatric disorders. Oxford, Oxford University Press. 1996; 3-42.
97. Rockwood K, Bowler JV, Erkinjuntti T, Hachinski V, Wallin A. Subtypes of vascular dementia. Alzheimer dis assoc dis 1999; 13(Suppl 3): S59-S65.
98. Rockwood K, Wentzel C, Hachinski V, Hogan DB, MacKnight C, McDowell I. Prevalence and outcomes of vascular cognitive impairment. Neurology 2000; 54: 447-451.
99. Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogonzo JM, Brun A, Hofman A, Moody DM, O'Brien MD, Yamaguchi T, Grafman J, Drayer BP, Bennet DA, Fisher M, Ogata J, Kokmen E, Bermejo F, Wolf PA, Gorelick PB, Bick KL, Pajeau AK, Bell MA, DeCarli C, Culebras A, Korczyn AD, Bogousslavsky J, Hartmann A, Scheinberg P. Vascular dementia: diagnostic criteria for research studies. Neurology 1993; 43: 250-260.

100. Russell E. A multiple scoring method for the assessment of complex memory functions. J Consult Clin Psychol 2000; 43: 800-809.
101. Russell E, Neuringer L, Goldstein G. Assessment of brain damage: a neuropsychological key approach. New York, Wiley Interscience. 1970.
102. Rutgers DR, Klijn CJM, Kappelle LJ, Eikelboom BC, van Huffelen AC, van der Grond J. Sustained bilateral hemodynamic benefit of contralateral carotid endarterectomy in patients with symptomatic internal carotid artery occlusion. Stroke 2001; 32: 728-734.
103. Sabri O, Hellwig D, Schreckenberger M, Schneider R, Kaiser HJ, Wagenknecht G, Setani K, Reinartz P, Zimny M, Mull M, Ringelstein EB, Buell U. One-year follow-up of neuropsychology, MRI, rCBF and glucose metabolism (rMRGlu) in cerebral microangiopathy. Nuklearmedizin 2000; 39: 43-49.
104. Sabri O, Ringelstein EB, Hellwig D, Schneider R, Schreckenberger M, Kaiser HJ, Mull M, Buell U. Neuropsychological impairment correlates with hypoperfusion and hypometabolism but not with severity of white matter lesions on MRI in patients with cerebral microangiopathy. Stroke 1999; 30: 556-566.
105. Saunders DE, Clifton AG, Brown MM. Measurement of infarct size using MRI predicts prognosis in middle cerebral artery infarction. Stroke 1995; 26: 2272-2276.
106. Schuhfried G. Wiener Testsystem. Mödling, Dr. G. Schuhfried Ges. M.b.H. 1994.
107. Seidenberg M, Parker JC, Nichols WK, Davenport J, Hewett JE. Carotid stenosis and atherosclerotic heart disease: interactive effects on cognitive status. Int J Clin Neuropsychol 1985; 7(1): 45-48.
108. Shallice T. From neuropsychology to mental structure. Cambridge, Cambridge University Press. 1988.
109. Sivan AB. Benton Visual Retention Test; manual. New York, The Psychological Corporation. 1992.
110. Sixma H, Ultee W. Een beroepsprestigeschaal voor Nederland in de jaren tachtig. Mens en maatschappij 1983; 58: 360-381.
111. Stevens J. Exploratory and confirmatory factor analysis. Applied multivariate statistics for the social sciences. Mahwah, New Jersey, Lawrence Erlbaum Associates. 1996; 362-428.
112. Stirling Meyer J, Lotfi J, Martinez G, Caroselli JS, Mortel KF, Thornby JI. Effects of medical and surgical treatment on cerebral perfusion and cognition in patients with chronic cerebral ischemia. Surg Neurol 1990; 34: 301-308.
113. Strub RL, Black FW. The mental status examination in neurology (4th ed.). Philadelphia, F.A. Davis Corporation. 2000.
114. Tatemichi TK, Desmond DW, Prohovnik I, Eidelberg D. Dementia associated with bilateral carotid occlusions: neuropsychological and haemodynamic course after extracranial to intracranial bypass surgery. J Neurol Neurosurg Psychiatry 1995; 58: 633-636.
115. Tatemichi TK, Desmond DW, Stern Y, Paik M, Sano M, Bagiella E. Cognitive impairment after stroke: frequency, patterns, and relationship to functional abilities. J Neurol Neurosurg Psychiatry 1994; 57: 202-207.
116. Tengs TO, Yu M, Luistro E. Health-related quality of life after stroke: a comprehensive review. Stroke 2001; 32: 964-972.
117. Tsuda Y, Yamada K, Hayakawa T, Ayada Y, Kawasaki S, Matsuo H. Cortical blood flow and cognition after extracranial-intracranial bypass in a patient with severe carotid occlusive lesions. A three year follow-up study. Acta Neurochir (Wien) 1994; 129: 198-204.
118. Van den Burg W, Saan RJ, van Zomeren AH, Boontje AH, Haaxma R, Wichmann TE. Carotid endarterectomy: does it improve cognitive or motor functioning? Psychol Med 1985; 15: 341-346.
119. Van der Grond J, Eikelboom BC, Mali WPThM. Flow-related anaerobic metabolic changes in patients with severe stenosis of the internal carotid artery. Stroke 1996; 27: 2026-2032.

120. Van der Grond J, van Everdingen KJ, Eikelboom BC, Kenez J, Mali WPTM. Assessment of borderzone ischemia with a combined MR imaging - MR Angiography - MR Spectroscopy protocol. J Magn Reson Imaging 1999; 9: 1-9.
121. Van Everdingen KJ, Klijn CJM, Kappelle LJ, Mali WPTM, for the Dutch EC-IC Bypass Study Group. MRA flow quantification in patients with a symptomatic internal carotid artery occlusion. Stroke 1997; 28: 1595-1600.
122. Van Everdingen KJ, Visser GH, Klijn CJM, Kappelle LJ, Mali WPTM, van der Grond J. Role of collateral flow on cerebral hemodynamics in patients with an unilateral ICA occlusion. Ann Neurol 1988; 44: 167-176.
123. Van Swieten JC, Hijdra A, Koudstaal PJ, van Gijn J. Grading white matter lesions on CT and MRI: a simple scale. J Neurol Neurosurg Psychiatry 1990; 53: 1080-1083.
124. Van Whitlock R, Lubin B, Noble E. Factor structure of the state and trait versions of the depression adjective check lists. J Clin Psychol 1995; 51(5): 614-625.
125. Vriens EM, Post MWM, Jacobs HM, van Huffelen AC, Eikelboom BC. Changes in health-related quality of life after carotid endarterectomy. Eur J Vasc Endovasc Surg 1998; 16: 395-400.
126. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Med Care 1992; 30: 473-483.
127. Wechsler D. Wechsler memory scale; manual. San Antonio, TX, The Psychological Corporation. 1974.
128. Wechsler D. Wechsler Adult Intelligence Scale-Revised; manual. New York, The Psychological Corporation. 1981.
129. Wentzel C, Rockwood K, MacKnight C, Hachinski V, Hogan DB, Feldman H, Ostbye T, Wolfson C, Gauthier S, Verreault R, McDowell I. Progression of impairment in patients with vascular cognitive impairment without dementia. Neurology 2001; 57: 714-716.
130. Widder B, Kleiser B, Krapf H. Course of cerebrovascular reactivity in patients with carotid artery occlusions. Stroke 1994; 25: 1963-1967.
131. World Health Organization. International classification of Functioning, Disability and Health. 2002. Available from URL: http://www3.who.int/icf/icftemplate.cfm.
132. Yamauchi H, Fukuyama H, Nagahama Y, Katsumi Y, Dong Y, Konishi J, Kimura J. Atrophy of the corpus callosum associated with cognitive impairment and widespread cortical hypometabolism in carotid artery occlusive disease. Arch Neurol 1996; 53: 1103-1109.
133. Yanagihara T, Marsh WR, Piepgras DG, Ivnik RJ. Dementia in bilateral carotid occlusive disease. Stroke 1990; 21: I-99.
134. Youngjohn JR, Larrabee GJ, Crook TH. New adult age- and education-correction norms for the Benton visual retention test. Clin Neuropsychol 1993; 7(2): 155-160.
135. Younkin D, Hungerbuhler JP, O'Connor M, Goldberg H, Burke A, Kushner M, Hurtig H, Obrist W, Gordon J, Gur R, Reivich M. Superficial temporal-middle cerebral artery anastomosis: effects on vascular, neurologic, and neuropsychological functions. Neurology 1985; 35: 462-469.
136. Zillmer EA, Waechtler C, Harris B, Khan F. The effects of unilateral and multifocal lesions on the WAIS-R: a factor analytic study of stroke patients. Arch Clin Neuropsychol 1992; 7: 29-40.
137. Zubicaray de G, Ashton R. Nelson's (1976) modified card sorting test: a review. Clin Neuropsychol 1996; 10(3): 245-254.

Summary

Patients with obstructive disease of the carotid artery (CAD) are at increased risk of (recurrent) ischemic events. The cause of ischemic symptoms in these patients may be thrombo-embolism, i.e. occlusion of intracranial arteries by emboli originating from atherosclerotic plaques. In addition, hemodynamic disturbances as a result of chronic cerebral hypoperfusion have been suggested to play a role in patients with severe CAD. Cognitive impairment is a common consequence of cerebral ischemic stroke, its reported prevalence ranging up to 50% three months after the occurrence of the stroke. Little is known, however, about the prevalence and severity of cognitive impairment in patients with only transient or minor disabling symptoms of cerebral ischemia. Cognitive impairment in patients with severe CAD but without ischemic stroke has been suggested to reflect the impact of chronic cerebral hypoperfusion on the functional state of brain tissue. If chronic cerebral hypoperfusion causes or contributes to cognitive impairment in patients with severe CAD, surgical interventions to improve the blood flow to the brain may halt or even reverse cognitive decline in these patients. Findings on the impact of revascularization surgery on cognitive functioning are contradictory, however, varying from deterioration to improvement of cognition after surgery. Before conclusions can be drawn on the effectiveness of revascularization surgery in preventing (further) cognitive decline, knowledge is required on (prognostic indicators for) the course of cognitive functioning in patients with severe CAD who do not undergo revascularization surgery.
The objective of this thesis was to ascertain the prevalence, the nature and severity, the course, and the correlates of cognitive impairment in patients with symptomatic CAD. Besides a systematic review of the literature, a prospective follow-up study of patients with symptomatic carotid artery occlusion was performed. We studied patients with occlusion (and not stenosis) of the carotid artery, as this group may be expected to suffer the most from chronic cerebral hypoperfusion and its consequences.

Between September 1995 and July 1998, 113 patients with a transient ischemic attack (TIA) or a minor ischemic stroke associated with an ipsilateral occlusion of the carotid artery were recruited from consecutive patients referred to the departments of Neurology or Vascular Surgery of the University Medical Center Utrecht, The Netherlands. Patients were interviewed and investigated for the presence of vascular risk factors. A comprehensive neuropsychological examination and assessments of health-related quality of life and depressive mood took place at three points in time: after inclusion in the study,

and 6 and 12 months thereafter. Healthy spouses, and occasionally siblings, of the patients were asked to cooperate with the neuropsychological assessment, thus providing data on normal cognitive functioning and effects of re-testing. To gain more insight into the pathophysiological processes underlying the cognitive impairment, we examined the presence of cerebral ischemic lesions by means of magnetic resonance imaging (MRI); quantitative flow in the middle cerebral artery by means of magnetic resonance angiography (MRA); cerebrovascular reserve capacity, a measure of compromised cerebral blood flow, in the middle cerebral artery by means of transcranial Doppler ultrasound (CO_2-reactivity); and cerebral metabolism (the NAA/creatine ratio and the presence of lactate in non-infarcted regions of the centrum semi-ovale) by means of magnetic resonance spectroscopy (^{1}H-MRS).

Chapter 2 presents a systematic review of the literature between 1980 and 1999 on cognitive impairment in patients with obstructive CAD. The majority of the reviewed studies found that cognitive functioning in groups of patients with obstructive CAD is impaired, even if patients have had only transient symptoms of cerebral ischemia. As none of the papers mentioned the percentage of patients with cognitive impairment, data on the prevalence of cognitive impairment in patients with obstructive CAD is lacking. Most studies were designed to address the outcome after surgery and, hence, included only patients suitable for surgery. As a consequence, transversal and longitudinal data on cognitive functioning in patients with obstructive CAD who do not undergo revascularization surgery is lacking. None of the studies examined the relative impact of ischemic brain lesions and chronic cerebral hypoperfusion on cognitive functioning.

In **chapters 3** and **4**, we describe the results of the transversal study on the prevalence, the nature and severity, and the correlates of cognitive impairment in 39 patients with a TIA associated with an ipsilateral carotid artery occlusion.
Fifty-four percent of the patients was cognitively impaired. The vulnerability of cognition was not related to specific cognitive functions. Cognitive impairment was mild in severity. Impairment occurred also in patients with isolated retinal symptoms and in those without cerebral ischemic lesions on MRI, which argues against an exclusive role for structural brain damage in the pathogenesis of cognitive impairment. We examined whether cognitive impairment was associated with a decreased cerebrovascular reserve capacity, and impaired cerebral metabolism. CO_2-reactivity and the NAA/creatine ratio

did not correlate with cognitive functioning. In contrast, the presence of lactate in non-infarcted white matter ipsilateral to the carotid artery occlusion was associated with cognitive impairment, and proved to be a stronger correlate of cognitive impairment than MRI-detected lesions. The origin of lactate in non-infarcted brain regions has not been elucidated yet, but in patients with carotid artery occlusion, it has been suggested to indicate a compromised CBF. Thus, although we could not demonstrate a direct relation between hemodynamic compromise and cognitive impairment, the results suggest that chronic cerebral hypoperfusion contributes to cognitive impairment.

Chapter 5 presents the results of the longitudinal study on cognitive functioning and quality of life (QoL) in 73 patients with TIA(s) only (n=26) or a minor ischemic stroke (n=47) associated with an ipsilateral carotid artery occlusion, who did not undergo revascularization surgery during the one year follow-up period.
Thirty-three patients with a stroke (70%) and ten patients with TIA(s) only (39%) were cognitively impaired. In general, cognitive functioning did not further deteriorate during the follow-up period of one year. Instead, cognition improved in patients who did not have recurrent symptoms at follow-up and in whom 1H-MRS did not show lactate in non-infarcted white matter of the hemisphere ipsilateral to the symptomatic carotid artery occlusion. In patients with lactate, cognitive functioning remained at the same (impaired) level. The cognitive improvement in patients without lactate and no recurrent symptoms might reflect recovery of cerebral perfusion, due to gradually improved collateral circulation, whereas the absence of improvement in patients with lactate might reflect persisting hemodynamic impairment.
Self-perceived QoL, as measured with the MOS Short-Form Health Survey, was affected both at baseline and at 12 months' follow-up, although not to a large extent. When simultaneously analysing the impact of physical disability, cognitive impairment and depressive affect on QoL, only the impact of depressive affect and, to a smaller extent, physical disability remained. Cognitive impairment had no impact on QoL.

In the study described in **chapter 6**, we examined the effect of a contralateral carotid endarterectomy (CEA) on cognitive functioning. Furthermore, we investigated whether changes in cognitive functioning during the follow-up period were associated with changes in the hemodynamic or metabolic state of the brain. In 13 patients with symptomatic carotid artery occlusion who underwent contralateral CEA and in 15 control

patients with symptomatic carotid artery occlusion who were not operated on, we assessed cognitive functioning, quantitative flow and CO_2-reactivity in the middle cerebral artery (MCA), and the NAA/creatine ratio's and the presence of lactate in the centrum semi-ovale of both hemispheres.
At baseline, six operated patients (46%) and eight control patients (53%) were cognitively impaired. Cognitive functioning improved to the same extent in patients who did and those who did not undergo CEA. CO_2-reactivity and MCA flow on the side of the carotid artery occlusion improved after CEA, but did not improve in control patients. No differences in time courses of the NAA/creatine ratios and the presence of lactate were found between operated and control patients. Examining the total patient group (operated and control patients), cognitive improvement was associated with increased NAA/creatine ratio's, whereas no correlations appeared between cognitive improvement and improvement of CO_2-reactivity or MCA flow.
Thus, contralateral CEA results in improvement of the hemodynamic state of the brain. This improvement is not accompanied by better recovery of cognition within one year, as operated and non-operated patients showed similar improvement in cognitive functioning over time.

In **chapter 7**, the results of the described studies are discussed. It is concluded that in patients with TIA(s) or a minor ischemic stroke associated with an ipsilateral carotid artery occlusion 1) cognitive functioning in the subacute phase after the occurrence of (transient) ischemic symptoms is impaired in a substantial portion of patients; 2) the vulnerability of cognition is not related to specific cognitive functions; 3) cognitive impairment is mild in severity; 4) cognitive functioning may improve in the 1.5 years after the occurrence of the ischemic event, if symptoms do not recur; 5) severity and course of cognitive impairment correlate with measures of metabolism in non-infarcted white matter, but not with quantitative flow and CO_2-reactivity in the MCA; 6) endarterectomy of contralateral carotid artery stenosis results in improvement of MCA flow and CO_2-reactivity, but not in improvement of cognitive functioning within one year; 7) on average, health-related quality of life remains affected 1.5 years after the occurrence of the ischemic event, although not to a large extent.

Samenvatting

Patiënten met een vernauwing of afsluiting van de voorste halsslagader lopen een verhoogd risico op het krijgen van een herseninfarct, ook wel cerebrale ischemische beroerte genoemd. Hierdoor veroorzaakte uitvalsverschijnselen kunnen onder andere bestaan uit problemen met praten, verlammingen of een stoornis in het gevoel van armen of benen. Indien uitvalsverschijnselen binnen 24 uur verdwijnen spreken we van transient ischemic attacks (TIAs), dat wil zeggen voorbijgaande aanvallen van bloedtekort. Een mogelijke oorzaak van cerebrale ischemie is het verstopt raken van bloedvaten in de hersenen door bloedpropjes die loslaten van de verstopping in de halsslagader. Chronisch gestoorde bloeddoorstroming in de hersenen van patiënten bij wie de bloedtoevoer naar de hersenen ernstig tekortschiet wordt genoemd als andere oorzaak.
Infarcering van de hersenen leidt vaak tot stoornissen in het cognitieve functioneren. De prevalentie van cognitieve stoornissen drie maanden na het optreden van het infarct kan oplopen tot 50%. Er is weinig bekend over de prevalentie en de mate van cognitief disfunctioneren bij patiënten met slechts voorbijgaande of niet-invaliderende symptomen van cerebrale ischemie. Cognitieve stoornissen bij patiënten met ernstige vernauwing of afsluiting van de halsslagader maar zonder herseninfarcering, zouden een uiting kunnen zijn van de invloed van een gestoorde bloeddoorstroming op de functionele staat van hersenweefsel. Indien chronische verstoring van de bloeddoorstroming in de hersenen een schadelijke invloed heeft op het cognitieve functioneren, is het op theoretische gronden denkbaar dat operatief ingrijpen ter verbetering van de bloedtoevoer naar de hersenen de cognitieve achteruitgang kan stoppen, of deze zelfs kan terugdraaien. De bevindingen ten aanzien van de invloed van een carotis endarteriëctomie (het schoonmaken van het bloedvat) of bypass operatie (het aanleggen van een omloop) op het cognitieve functioneren lopen echter sterk uiteen, variërend van verslechtering tot verbetering van de cognitie na de operatie. Voordat conclusies getrokken kunnen worden over de effectiviteit van revascularisatie in het voorkómen van (verdere) cognitieve achteruitgang, is er kennis nodig over (prognostische indicatoren van) het beloop in cognitie bij patiënten met verstopping van de halsslagader die géén operatie ondergaan.

Het doel van het onderzoek dat ten grondslag ligt aan dit proefschrift was het achterhalen van de prevalentie, de aard en mate, het beloop, en de correlaten van cognitieve stoornissen bij patiënten met een symptomatische vernauwing of afsluiting van de halsslagader. Hiertoe zijn een literatuurstudie, en een prospectieve follow-up studie van patiënten met een symptomatische afsluiting van de voorste halsslagader uitgevoerd.

We hebben ervoor gekozen patiënten met een afsluiting, en niet vernauwing, van de halsslagader te onderzoeken, aangezien deze groep naar verwachting het sterkst te maken heeft met (gevolgen van) een chronisch gestoorde bloeddoorstroming in de hersenen.
Tussen september 1995 en juli 1998 zijn 113 patiënten met een TIA of een ten hoogste matig ernstig invaliderend herseninfarct en een ipsilaterale afsluiting van de voorste halsslagader gerekruteerd uit opeenvolgende patiënten van (poliklinieken van) de afdelingen Neurologie of Vasculaire Chirurgie van het Universitair Medisch Centrum Utrecht. Op drie momenten in de tijd werden patiënten onderzocht op het cognitieve functioneren, de aan gezondheid gerelateerde kwaliteit van leven en het depressief affect: bij insluiting in de studie, 6 maanden na insluiting en 12 maanden na insluiting. De gezonde partners, en soms de broers of zussen, van de patiënten werden gevraagd medewerking te verlenen aan het neuropsychologische onderzoek, om gegevens over het normale cognitieve functioneren en eventuele test-hertest effecten te verkrijgen.
Om inzicht te krijgen in de pathofysiologische processen die ten grondslag liggen aan de cognitieve stoornissen, onderzochten we de aanwezigheid van herseninfarcten gemeten met beeldvorming van de magnetische resonantie (MRI); kwantitatieve bloeddoorstroming gemeten met MR angiografie (MRA); autoregulatie van de bloeddoorstroming gemeten met transcranieel Doppler onderzoek (CO_2-reactiviteit); en de stofwisseling in niet-geïnfarceerde delen van de hersenen gemeten met ^{1}H-MR spectroscopie (^{1}H-MRS; NAA/creatine ratio en aanwezigheid van lactaat).

Hoofdstuk 2 geeft de bevindingen weer van de literatuurstudie naar het cognitieve functioneren bij patiënten met een vernauwing of afsluiting van de halsslagader. De meerderheid van de studies beschreven in de literatuur concludeert dat het cognitieve functioneren bij deze patiënten is gestoord, ook bij patiënten die enkel TIAs hadden gehad en geen ischemische beroertes. Geen van de studies beschrijft de percentages van patiënten met en zonder cognitieve stoornissen, zodat cijfers over de prevalentie van cognitieve stoornissen bij patiënten met een vernauwing of afsluiting van de halsslagader ontbreken. De meerderheid van de studies was opgezet om de invloed van operatief ingrijpen op het cognitieve functioneren te bepalen, en includeerden zodoende enkel patiënten die een carotis endarteriëctomie of een bypass operatie ondergingen. Het gevolg hiervan is dat transversale en longitudinale gegevens over het cognitieve functioneren bij patiënten met een verstopping van de halsslagader die niet in aanmerking

komen voor zo'n operatie ontbreken in de literatuur. Een andere belangrijke bevinding van de literatuurstudie is dat de afzonderlijke invloed van cerebraal weefselversterf en een chronische gestoorde bloeddoorstroming op het cognitieve functioneren niet tot nauwelijks is onderzocht.

In **hoofdstuk 3** en **4** beschrijven we de resultaten van de transversale studie naar de prevalentie, de aard en mate, en de correlaten van cognitieve stoornissen bij 39 patiënten met een TIA en een ipsilaterale afsluiting van de halsslagader. Bij 54% van de patiënten werden (milde) cognitieve stoornissen geconstateerd. Binnen de groep met stoornissen kwam geen consistent patroon van uitval op de cognitieve taken naar voren. De kwetsbaarheid van cognitie lijkt dan ook niet beperkt te zijn tot specifieke cognitieve functies. Cognitieve stoornissen waren ook aanwezig bij patiënten met enkel retinale symptomen van ischemie en bij patiënten zonder afwijkingen op de MRI, wat erop duidt dat structurele hersenbeschadiging niet de enige oorzakelijke factor is voor cognitieve stoornissen. Wij onderzochten of meetresultaten gerelateerd aan de regulatie van de bloeddoorstroming en de stofwisseling in de hersenen verband hielden met de cognitieve verrichtingen. CO_2-reactiviteit en de NAA/creatine ratio correleerden niet met de cognitie. Daarentegen was de aanwezigheid van lactaat in niet-geïnfarceerde gebieden van de hersenen ipsilateraal aan de afgesloten halsslagader geassocieerd met cognitieve stoornissen. De mate van cognitief disfunctioneren hing sterker samen met de aanwezigheid van lactaat dan met de aanwezigheid van ischemische afwijkingen op de MRI. De herkomst van lactaat in niet-geïnfarceerde delen van de hersenen is nog onbekend, maar bij patiënten met afsluiting van de halsslagader zou het kunnen wijzen op een gestoorde cerebrale bloeddoorstroming. Dus, alhoewel we geen direct verband konden aantonen tussen een gestoorde bloeddoorstroming en stoornissen in de cognitie, de resultaten wijzen erop dat chronisch verminderde bloedtoevoer naar de hersenen bijdraagt aan het ontstaan van cognitieve stoornissen.

Hoofdstuk 5 geeft de bevindingen weer van de longitudinale studie naar het cognitieve functioneren en de kwaliteit van leven bij 73 patiënten met enkel een TIA (n=26) of een ten hoogste matig ernstig invaliderend herseninfarct (n=47) samengaand met een ipsilaterale afsluiting van de halsslagader. Geen van de patiënten onderging een revascularisatie operatie gedurende het jaar dat ze gevolgd werden.

Bij 33 patiënten met een herseninfarct (70%) en 10 patiënten met een TIA (39%) werden cognitieve stoornissen geconstateerd. Over het algemeen ging het cognitieve functioneren niet verder achteruit gedurende de follow-up periode van 1 jaar. De cognitie verbeterde juist, bij die patiënten die geen terugkerende symptomen hadden gedurende de follow-up periode en bij wie er geen lactaat aangetoond werd in niet-geïnfarceerde delen van de hersenen ipsilateraal aan de afgesloten halsslagader. Bij patiënten met lactaat trad er daarentegen geen verbetering (maar ook geen verslechtering) op in het cognitieve functioneren. De cognitieve verbetering bij patiënten zonder lactaat en zonder terugkerende symptomen zou het gevolg kunnen zijn van herstel van de cerebrale bloeddoorstroming door de ontwikkeling van collaterale bloedvoorziening (d.w.z. bloedtoevoer via natuurlijke omwegen), terwijl het uitblijven van cognitieve verbetering bij patiënten met lactaat uiting kan zijn van het voortduren van een gestoorde bloeddoorstroming in de hersenen.
De subjectief ervaren kwaliteit van leven was aangetast, hoewel niet in sterke mate. Met name de mate van depressief affect, en in mindere mate de fysieke beperkingen, bleken een negatief effect op de kwaliteit van leven te hebben. De aanwezigheid van cognitieve stoornissen had daarentegen geen invloed op de subjectief ervaren kwaliteit van leven.

In de studie beschreven in **hoofdstuk 6** bestudeerden wij de invloed van een contralaterale carotis endarteriëctomie op het cognitieve functioneren. Tevens onderzochten we of veranderingen in het cognitieve functioneren gedurende de follow-up periode samenhingen met veranderingen in (regulatie van) de bloeddoorstroming en in de stofwisseling van de hersenen. Bij 13 patiënten met een symptomatische afsluiting van de halsslagader die carotis endarteriëctomie ondergingen en bij 15 controlepatiënten met een symptomatische afsluiting van de halsslagader onderzochten wij het cognitieve functioneren, kwantitatieve bloeddoorstroming en CO_2-reactiviteit in de middelste slagader naar de hersenen, en de NAA/creatine ratio's en de aanwezigheid van lactaat in niet-geïnfarceerde witte stof van de hersenen.
Voorafgaande aan de operatie hadden 6 operatiepatiënten (46%) en 8 controlepatiënten (53%) cognitieve stoornissen. Het cognitieve functioneren verbeterde in dezelfde mate bij patiënten die wel en patiënten die geen operatie ondergingen. CO_2-reactiviteit en bloeddoorstroming in de middelste slagader aan de zijde van de afgesloten halsslagader verbeterden bij de operatiepatiënten, maar niet bij de controlepatiënten. Er kwamen geen verschillen in het tijdsbeloop van de NAA/creatine ratio's en de aanwezigheid van lactaat

naar voren tussen geopereerde en niet-geopereerde patiënten. Bij analyse van de gegevens van de totale patiëntengroep (operatie- en controlepatiënten) bleek cognitieve verbetering samen te hangen met een verhoging van de NAA/creatine ratio's, terwijl er geen verband bestond tussen cognitieve verbetering en verbetering van de CO_2-reactiviteit of de kwantitatieve bloeddoorstroming in de middelste slagader.
Samenvattend resulteert carotis endarteriëctomie in een verbeterde bloeddoorstroming in de hersenen. Deze verbetering gaat echter niet gepaard met cognitieve verbetering binnen het tijdsbestek van 1 jaar, aangezien het beloop in het cognitieve functioneren gelijk was tussen de geopereerde en niet-geopereerde patiënten.

In **hoofdstuk 7** worden de bevindingen van de beschreven studies bediscussieerd. We concluderen dat bij patiënten met enkel een TIA of een ten hoogste matig ernstig invaliderend herseninfarct samengaand met een ipsilaterale afsluiting van de halsslagader 1) het cognitieve functioneren in de subacute fase na het optreden van de (voorbijgaande) ischemische symptomen in gematigde mate gestoord is in een aanzienlijk deel van de patiënten; 2) de kwetsbaarheid van cognitie niet beperkt is tot enkele specifieke cognitieve functies; 3) het cognitieve functioneren kan verbeteren in de anderhalf jaar na het optreden van de ischemische symptomen, mits de symptomen niet terugkeren; 4) de mate en het beloop van cognitief disfunctioneren samenhangen met meetresultaten van de stofwisseling in niet-geïnfarceerde delen van de hersenen, maar niet met kwantitatieve bloeddoorstroming en CO_2-reactiviteit in de middelse slagader naar de hersenen; 5) endarteriëctomie van de contralaterale vernauwing in de halsslagader resulteert in een verbeterde bloeddoorstroming en CO_2-reactiviteit, maar niet in een verbetering van het cognitieve functioneren binnen een tijdsbestek van 1 jaar; 6) gemiddeld genomen de aan gezondheid gerelateerde, subjectief ervaren kwaliteit van leven in gematigde mate aangetast is.

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Curriculum Vitae

Floor Bakker was born on October 5th, 1972 in Nijmegen, The Netherlands. In 1991, after graduating secondary school at the Sint-Joriscollege in Eindhoven, she commenced her university education in Psychology at the University of Utrecht, The Netherlands. She obtained her master's degree in October 1998, after completing a traineeship at the Sector of Neuropsychology, Wilhelmina Children Hospital, Utrecht. From 1997 to 2001 she worked as a researcher at the Department of Neurology, University Medical Center Utrecht, which resulted in this thesis. Since May 2001 she has been working as a researcher at the Rutgers Nisso Group, the Dutch center of expertise on sexuality.

List of publications

Publications based on the studies described in this thesis

Bakker FC, Klijn CJM, Jennekens-Schinkel A, Kappelle LJ. Cognitive disorders in patients with occlusive disease of the carotid artery: a systematic review of the literature. J Neurol 2000; 247: 669-676.

Arrindell WA, Bakker FC, Jennekens-Schinkel A, van Rooijen LB. De VROPSOM: herhaalde metingen van depressief affect. Gedragstherapie 2002; 35 (3): 287-295.

Bakker FC, Klijn CJM, Jennekens-Schinkel A, van der Tweel I, Tulleken CAF, Kappelle LJ. Cognitive impairment in patients with carotid artery occlusion and ipsilateral transient ischemic attacks. Submitted for publication.

Bakker FC, Klijn CJM, Jennekens-Schinkel A, van der Tweel I, van der Grond J, van Huffelen AC, Tulleken CAF, Kappelle LJ. Cognitive impairment is related to cerebral lactate in patients with carotid artery occlusion and ipsilateral transient ischemic attacks. Stroke 2003, in press.

Bakker FC, Klijn CJM, van der Grond J, Kappelle LJ, Jennekens-Schinkel A. Cognitive functioning and quality of life in patients with symptomatic carotid artery occlusion: a one year follow-up study. Submitted for publication.

Bakker FC, Klijn CJM, Jennekens-Schinkel A, van der Grond J, van Huffelen AC, Eikelboom BC, Kappelle LJ. Cognitive impairment in patients with symptomatic carotid artery occlusion persists after endarterectomy of contralateral carotid artery stenosis. Submitted for publication.

Other publications

Bakker FC, Sandfort TGM. Veilig vrijen en condoomgebruik bij jongeren en jong-volwassenen. Stand van zaken september 2001 en ontwikkelingen sinds april 1987. NISSO-rapport, 2001.

Bakker F, Vanwesenbeeck I. Veilig vrijen en condoomgebruik bij jongeren en jong-volwassenen. Stand van zaken september 2002 en ontwikkelingen sinds september 1987. RNG-rapport, 2002.

Van Fulpen M, Bakker F, Breeman L, Poelman J, Schaalma H, Vanwesenbeeck I. Vmbo scholieren, seksualiteit en seksuele vorming. Een effectonderzoek naar de vernieuwde versie van het lespakket "Lang leve de liefde". RNG-rapport, 2002.

Vanwesenbeeck I, Bakker F, Van Fulpen M, Paulussen T, Poelman J, Schaalma H. Seks en seksuele risico's bij Vmbo scholieren anno 2002. Tijdschrift voor Seksuologie 2003; 27(1): 30-39.