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CAROTID STENOSIS, ENDARTERECTOMY, AND THE BRAIN

Brain microcirculation, diffusion, and cognitive function
before and after carotid endarterectomy
in patients with a high-grade carotid stenosis

Lauri Soinne

ACADEMIC DISSERTATION

To be publicly discussed
with the permission of the Medical Faculty of the University of Helsinki
in Auditorium 4, Meilahti Hospital,
on the 20th of November, 2009, at 12 noon.

Helsinki, 2009

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Helsinki University Print 2009

ISBN 978-952-92-6277-9 ((paperback)
ISBN 978-952-10-5805-9 (pdf)
http://ethesis.helsinki.fi

To Kirsi Marjaana

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals (I-IV).

I Soinne L, Helenius J, Saimanen E, Salonen O, Lindsberg PJ, Kaste M, Tatlisumak T. Brain diffusion changes in carotid occlusive disease treated with endarterectomy. *Neurology* 2003;61:1061-1065.

II Soinne L, Helenius J, Tatlisumak T, Saimanen E, Salonen O, Lindsberg PJ, Kaste M. Cerebral hemodynamics in asymptomatic and symptomatic patients with high-grade carotid stenosis undergoing carotid endarterectomy. *Stroke* 2003;34:1655-1661.

III Soinne L, Helenius J, Tikkala I, Saimanen E, Salonen O, Hietanen M, Lindsberg PJ, Kaste M. Tatlisumak T. The effect of severe carotid occlusive disease and its surgical treatment on cognitive functions of the brain. *Brain Cogn* 2009;69:353-9.

IV Soinne L, Saimanen E, Malmberg-Céder K, Kovanen P, Lindsberg PJ, Kaste M, Lassila R. Association of fibrinolytic system and hemorheology with symptoms in patients with carotid occlusive disease. *Cerebrovasc Dis* 2005;20:172-9.

The thesis also contains some unpublished data.

ABBREVIATIONS

ACA	anterior cerebral artery
ACoA	anterior communicating artery
ADC	apparent diffusion coefficient
ADC_{av}	average apparent diffusion coefficient
ANOVA	analysis of variance
ASA	acetosalicylic acid
AVLT-D	Auditory Verbal Learning Test, delayed recall
AVLT-SUM	Auditory Verbal Learning Test, sum score of attempts
BA	basilar artery
BHI	breath-holding index
BNT	Boston Naming Test
CBF	cerebral blood flow
CBV	cerebral blood volume
CB-VISP	Corsi Blocks visual span
CCA	common carotid artery
CEA	carotid endarterectomy
CI	confidence interval
CS	carotid stenosis
CT	computed tomography
DSC MRI	dynamic susceptibility contrast magnetic resonance imaging
DWI	diffusion-weighted magnetic resonance imaging
ECA	external carotid artery
Gd-DTPA	gadolinium diethylenetriaminepenta-acetic acid
GE	gradient-echo
GM	grey matter
Hct	hematocrit
HITS	high-intensity transient signal
HR	hazard ratio
ICA	internal carotid artery
LA	leukoaraiosis
LCT	Letter Cancellation Test
LDL-C	low density lipoprotein cholesterol
MCA	middle cerebral artery
MES	microembolic signal
MRI	magnetic resonance imaging
MTT	mean transit time, the CBV:CBF ratio
PCA	posterior cerebral artery
PCoA	posterior communicating artery
PET	positron emission tomography
PP-SUM	Purdue Pegboard, sum score
PVH	periventricular hyperintensity
PWI	perfusion-weighted imaging
ROI	region of interest
rtPA	recombinant tissue plasminogen activator
RVLT-D	Rey Visual Learning Test, delayed recall

RVLT-SUM	Rey Visual Learning Test, sum score of attempts
SD	standard deviation
STROOP-INT	Stroop Interference, difference of colour/word timing
T	Tesla
TCD	transcranial Doppler
TIA	transient ischaemic attack
TMA	Trail Making Test A
TMB	Trail Making Test B
US	ultrasound
VA	vertebral artery
WF-C	Word Fluency, category
WF-L	Word Fluency, letter
WM	white matter
WMH	white matter hyperintensity
WR-SIMIL	WAIS-R Similarities
W-VESP	WAIS Verbal Digit Span

ABSTRACT

Aims: Carotid atherosclerotic disease is a major cause of stroke, but it may remain clinically asymptomatic. The factors that turn the asymptomatic plaque into a symptomatic one are not fully understood, neither are the subtle effects that a high-grade carotid stenosis may have on the brain. The purpose of this study was to evaluate brain microcirculation, diffusion, and cognitive performance in patients with a high-grade stenosis in carotid artery, clinically either symptomatic or asymptomatic, undergoing carotid endarterectomy (CEA). We wanted to find out whether the stenoses are associated with diffusion or perfusion abnormalities of the brain (I, II) or variation in the cognitive functioning of the patients (III), and to what extent the potential findings are affected by surgery. We further aimed to compare the findings of the clinically symptomatic and asymptomatic subjects (I-IV). Microcirculation was studied both from the viewpoint of perfusion imaging (II) and the procoagulant and anticoagulant activities in the blood (IV). Coagulation and fibrinolytic parameters were compared with the rate microembolic signals (MES) and the macroscopic appearance of stenosing plaques in surgery (IV).

Methods: We recruited 92 consecutive consenting patients fulfilling strict inclusion criteria who were referred to CEA to Helsinki University Central Hospital, ending up with 98 endarterectomies, 54 on symptomatic and 44 on asymptomatic carotids. We used the total study population in study IV, collecting blood samples prior to operation for determination of fibrinogen, thrombin-antithrombin complex, prothrombin fragments PF 1 and 2, tPA antigen and activity, plasminogen activator inhibitor 1 (PAI-1) antigen and activity, D-dimer, and hematocrit. The patients underwent transcranial Doppler (TCD) monitoring of MES counts and vasoreactivity testing with determination of breath-holding index (BHI) before and after surgery (II, IV). During the standard CEA, the macroscopic characteristics of the exposed plaque were recorded. A subpopulation of 46 subjects underwent magnetic resonance imaging with diffusion-weighted and perfusion-weighted sequences with dynamic susceptibility-weighted bolus tracking approach on the day before CEA, as well as 3 and 100 days afterwards (I-III). Of the MR-imaged patients, 44 underwent a comprehensive domainwise neuropsychological assessment according to the same schedule (III). The severity of white matter lesions was graded from conventional images. The imaging and neuropsychological parameters were compared using data on matched, strictly healthy control populations (I, III).

Results: At baseline, regardless of symptoms, the average apparent diffusion coefficients were higher in the ipsilateral white matter (WM), and they were higher than in control subjects. After CEA, the interhemispheric difference was abolished, but the levels remained higher than in controls (I).

Patients with symptomatic stenoses had longer mean transit times and lower cerebral blood flow at baseline than asymptomatic patients, and the difference was more pronounced in WM. Perfusion deficits were associated with symptomatic status, and they were corrected by CEA. In TCD, preoperative pulsatility was lower in symptomatic patients, and only their vasoreactivity improved after surgery (II).

The baseline cognitive performance of the patients was poorer than that of healthy controls in all domains. It was inversely correlated to the severity of leukoaraiosis. Despite transient cognitive worsening after surgery, mostly in attentional tasks, the cognitive performance of the patients improved similarly than in control persons over the months of study. However, patients with deepest hypoperfusion displayed a greater cognitive improvement, most clearly in the domain of executive functions.

Patients with symptomatic plaques had higher hematocrit and a trend for higher tPA antigen and MES rate. Hematocrit, tPA antigen, PAI-1 antigen and activity correlated with the degree of stenosis. In multivariate analysis, tPA antigen and high hematocrit were risk factors for symptomatic stenosis.

Conclusions: Carotid stenosis has an effect on diffusion in the ipsilateral WM, and the effect is partially reversible by CEA. The finding may be associated with the development of leukoaraiosis (I). Asymptomatic and symptomatic subpopulations differ from each other in terms of microcirculation and in their vascular physiological response to removal of stenosis (II). Although CEA may be associated with a transient cognitive decline, a true improvement of cognitive performance by CEA is possible in patients with the most pronounced perfusion deficits (III). Mediators of fibrinolysis and unfavourable hemorheology may contribute to the development of a symptomatic disease in patients with a high-grade stenosis (IV).

1. INTRODUCTION

Carotid arteries are the major suppliers of the human cerebral circulation. They are also predilection sites for atherosclerotic change, a long-standing inflammatory process of the arteries which is the most formidable threat to well-being in aging individuals in the Western world [1, 2]. One of the central manifestations of atherosclerosis is stroke, resulting in the greatest loss of quality-adjusted life years of all diseases [3]. In Finland, approximately 14 000 cases of stroke occur every year [4]. Carotid occlusive disease accounts approximately for 15-20 % of all strokes [5]. A high-grade carotid stenosis (CS), being one of the major causes of stroke, is an important target for preventive treatment.

Stenosing atherosclerotic lesion of the carotid artery may cause stroke by giving rise to embolization of thrombi or plaque debris in the brain or by impairing brain perfusion [6, 7]. The development of CS or occlusion may also occur silently without recognized neurological symptoms. Surgical treatment of a high-grade stenosis by carotid endarterectomy (CEA) is an evidence-based form of treatment, and it improves the long-term outcome and survival of patients with a symptomatic carotid stenosis, but in asymptomatic carotid stenoses the benefit is considerably smaller [8, 9]. Intensive research has suggested many potential biological markers and pathological changes that may render a plaque more vulnerable, but still the process of transformation into an unstable plaque is incompletely understood [10-12].

The role of impaired microcirculation in producing cerebral symptoms is less clear. Unfavourable anatomy or physiology in form of a less well-developed collateralization or cerebrovascular reactivity may give rise to symptoms in a susceptible individual, and the rheological properties of blood could also have an effect, as well as the balance between procoagulant and anticoagulant factors in the blood. It has been suggested that a tight CS might contribute to the development of degenerative changes in the white matter, often referred to as leukoaraiosis (LA) or white matter lesions (WML), consisting of patchy or diffuse areas of hypodensity in the cerebral white matter (WM) on computed tomography or white-matter hyperintensities (WMH) on magnetic resonance imaging (MRI) [13, 14]. The association between CS and LA has not been conclusively shown, although hypoperfusion is considered to play a key role in the pathogenesis of LA [13, 14].

Does CEA have other effects on the brain tissue apart from the prophylaxis of cerebrovascular events? Since the advent of this treatment, the possibility of improving cognitive functioning by restoring blood flow has been discussed. Despite a number of studies, there is no

conclusive evidence that any improvement would occur [15]. To the contrary, surgery may expectedly be a risk factor causing at least a transient decline of cognitive functions even in absence of clinical stroke [16-18]. Many of the studies are descriptive, and repeated assessment of cognition is challenging in patients with multiple concomitant diseases and other confounding elements.

The present-day MRI methodology provides new tools for brain imaging. With diffusion-weighting (DWI) it is possible to reveal hyperacute ischemic change and have an in-vivo measure of biological diffusion shedding new light e.g. to the pathophysiology of WM [19-21]. Perfusion-weighted imaging (PWI) gives a rapid assessment of cerebral microcirculation: dynamic susceptibility-contrast MRI (DSC MRI) is a widely-used method utilizing a simultaneous collection of the MR signal during the passage of a paramagnetic contrast agent bolus through the brain [22, 23]. By acquisition of data it is possible to determine perfusion using mean transit time of the bolus (MTT) , cerebral blood volume (CBV), and cerebral blood flow (CBF) [24-27].

Elucidation of the microcirculation and diffusion by the new MRI techniques could provide new insight into the effect of a high-grade stenosing lesion of carotid artery and its surgical removal on the subserved brain vasculature, in addition to the traditional methods of neuropsychological assessment and the transcranial Doppler ultrasonology. Combining an assay of the central elements of coagulation, fibrinolysis, and hemorheology would integrate the approach with the key determinants of microcirculation on the blood level.

2. REVIEW OF THE LITERATURE

2.1 Anatomy and physiology of carotid arteries and the cerebral circulation

The brain is one of the most metabolically active organs, reflected by a high rate of oxygen consumption [28]. As the brain is unable to store energy, the neurons are most dependent on adequate continuous delivery of oxygen, and blood supply to the brain is highly prioritized in the circulatory system. Although the brain represents only approximately 2 % of the body mass its share of the resting cardiac output is one-fifth [29]. In cases of circulatory compromise this share may considerably increase at the cost of other end-organs. Intracranially, the blood flow is protected by vascular anatomy providing collateral circulation, and by autoregulation of cerebral blood flow (CBF).

2.1.1 Cerebral arterial circulation

The brain receives its blood supply principally through four arteries: two internal carotid arteries (ICA) and two vertebral arteries (VA) [Figure 1]. Convexity of the aortic arch gives rise to the brachiocephalic trunk (innominate artery) giving origin to the right common carotid artery (CCA) and the right subclavian artery. The left common carotid and the left subclavian arteries originate directly from the aortic arch. At the level of the upper border of the thyroid cartilage, the CCAs bifurcate into external and internal carotid arteries (ECA, ICA), the former supplying the jaw, face, neck, and meninges, and the latter passes up the neck without branching, enters the skull through the carotid canal of the petrous bone and supplies the anterior circulation of the brain as well as the eye. Within the cranium, ICA forms a sigmoid carotid siphon which emits the ophthalmic artery before piercing through dura and passes medially to the anterior clinoid process, ascending to the bifurcation where it gives rise to the anterior and middle cerebral arteries (ACA, MCA) right after the origin of the posterior communicating artery. MCA supplies the convexity of the hemisphere and ACA approximately the anterior and upper half of the medial aspect of the hemisphere. The ACAs are interconnected by anterior communicating artery (ACoA) in front of the optic chiasm.

Vertebral arteries arise from the proximal subclavian artery, ascending through the foramina of the transverse processes of the cervical vertebrae. They pass posteriorly around the articular processes of the atlas, entering the skull through the foramen magnum. The two vertebral arteries join each other at the pontomedullary junction, forming the basilar artery (BA) in the midline. BA ascends ventrally up to the ponto-mesencephalic junction, dividing

into the posterior cerebral arteries (PCA). BA gives rise to anterior inferior cerebellar and superior cerebellar arteries along with numerous paramedian, short and long circumferential penetrators. PCAs encircle the midbrain at the tentorial level, and they supply the occipital lobe and the inferior part of the temporal lobe. Small perforating arteries arising from PCA supply also the midbrain, the thalamus, hypothalamus and geniculate bodies. The posterior communicating arteries (PCoA) anastomose with the PCAs after their origin. There are many anatomical variations to the basic arterial tree structure.

Carotid arteries and their branches (the anterior circulation) provide approximately three fourths of the total inflow to the brain in humans, the rest entering the skull through the vertebrobasilar system (the posterior circulation) to the posterior parts of the brain. The systems anastomose at the base of the brain to form the circle of Willis, where PCoAs interconnect MCA and PCA, and so the most cranial part of ICA is connected with the proximal PCA. The carotid flow normally subserves predominantly the ipsilateral cerebral circulation with little cross-over flow to the contralateral side [29].

Collateralization

When ICA fails to produce the ordinary supply to the cerebral vasculature, mainly five sources of alternative flow may be recruited. They are commonly divided into primary and secondary collaterals. The primary collaterals are arterial segments of the circle of Willis, providing existing anastomoses for immediate diversion of blood to areas with shortage of flow. The most important primary collateral route in ICA stenosis or occlusion is the opposite ICA providing the flow via the circle of Willis through ACA. Reversal of flow in the ophthalmic artery is a sign of a secondary collateralization and exchange of blood from ECA to ICA, and another secondary source is leptomeningeal anastomoses on the brain surface. Adequate collateralization may prevent haemodynamic insufficiency and protect from strokes [30-34]; on the other hand, presence of leptomeningeal collaterals has been associated with a greater stroke risk in a few studies [35, 36]. Even in cases of well-developed collateral supply there are regions of the brain that are especially vulnerable to perfusion deficit: borderzone areas between basal cerebral arterial territories including the internal borderzone in the centrum semiovale and corona radiata, as well as the areas subserved by perforating end-arteries supplying the WM and subcortical GM nuclei. There is considerable individual variation in the boundary zones [37].

Secondary collaterals may represent anatomically existent routes, but enhanced capacity of these pathways may require time to develop. The opening and recruitment of collaterals may

be mediated by haemodynamic, metabolic, and neural mechanisms, and angiogenesis may stimulate their growth. There are also precapillary anastomoses between arterioles, but their clinical significance in case of an impending infarction is inconsiderable [29].

The determination of collateral recruitment is not customary in the conventional radiological work-up, and the evaluations have appeared inconsistent even in the digital subtraction angiography (DSA) that provides best information invasively. The modern methods of imaging corroborate the importance of the variable collateral anatomies for CBF [31, 38]. However, the contribution of an individual pathway is not easily assessed or quantified in the clinical practice. Obviously, a more refined diagnostic methodology and approach to study collateralization is needed.

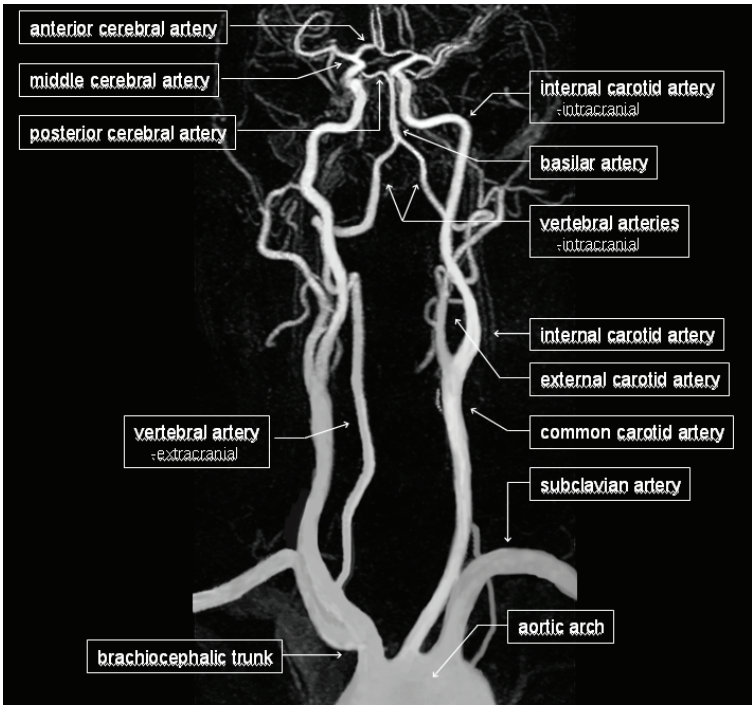


Figure 1. Blood supply to the brain.

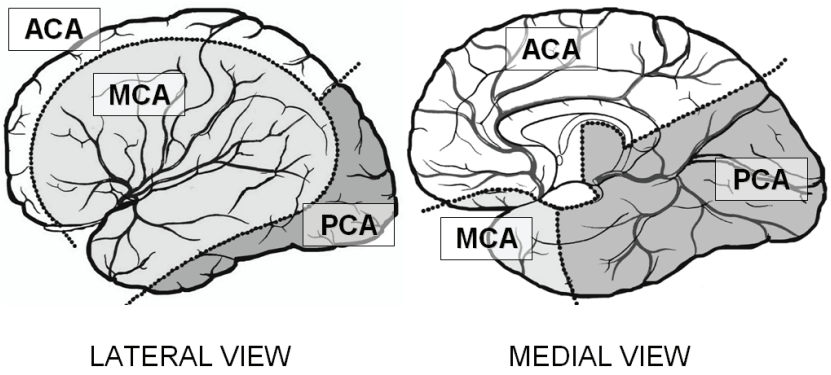


Figure 2. The supply territories of the main cerebral arteries, middle cerebral (MCA), anterior cerebral (ACA), and posterior cerebral (PCA) arterial territory.

2.1.2 Cerebral perfusion and its physiology

Cerebral perfusion denotes microcirculation of the brain, which essentially refers to the blood flow through the cerebral vascular bed with its capillary networks, and the exchange of gases and nutrients therein. Most of the blood in the brain is located in the capillaries, and this volume forms approximately 4 % of the GM and 1-2 % of the WM volume. The net blood pressure causing the flow through the capillary network is called cerebral perfusion pressure (CPP), and it represents the pressure gradient across the cerebral vascular bed. Consequently, for an estimate of mean CPP, intracranial pressure is subtracted from the mean arterial pressure [39]. CPP needs to be maintained within adequate limits to avoid hypoperfusion leading to ischaemia, as well as hyperperfusion implying inadequately high perfusion pressure and blood flow, which can be detrimental to the brain tissue and lead to hyperemia, vasogenic oedema, and secondary elevation of the intracranial pressure [39].

The efficiency of microcirculation is dependent on arterial blood pressure, blood velocity, the structure and characteristics of the capillary network and its permeability, and the diffusion rates of gases and solutes. Usually, the perfusion is symmetrical in the hemispheres, and the perfusion rates are higher in the GM than in the WM. In resting humans, the average blood flow in GM is estimated to be 69 ml/100 g/min, and in WM 28 ml/100 g/min. Brain perfusion may be characterized with parameters such as mean transit time (MTT) in seconds,

cerebral blood volume (CBV) in mL/100 g, and cerebral blood flow (CBF) in mL/100 g/min, and their relationship may be given as

$$MTT = CBV / CBF \quad [25, 26, 39-41]$$

CBF is influenced by many factors including carbon dioxide, oxygen, blood pressure, and metabolic demand. Its coupling to brain metabolism is tight, and the local blood flow varies markedly in proportion to brain activity as proposed originally by Roy and Sherrington in 1890 [42], to ensure adequate oxygen delivery. How much the oxidative metabolism increases with brain activation and what mechanisms mediate the haemodynamic response are still debated issues, although it is evident that glial cells and calcium also play a role in the signaling process of neurons [43, 44]. An important regulator of basal CBF is nitric oxide synthesized by endothelial cells, catalyzed by one of the isoforms of nitric oxide synthetase (eNOS) [45-47].

Cerebrovascular reactivity

Cerebrovascular autoregulation refers to the fast-acting metabolic, myogenic, and neurogenic mechanisms that maintain cerebral blood flow constant over a wide range of perfusion pressure, shielding the brain against hypoxia at low perfusion pressure and against brain oedema at high perfusion pressure [48-50].

This constancy is mainly brought on by vasodilatation or vasoconstriction on the precapillary level depending on whether perfusion pressure needs to be increased or decreased. Although changes in blood pressure are transmitted to the cerebral circulation, normally functioning autoregulation tends to return the original level within seconds [49]. The overall mechanism of autoregulation is not fully understood. The myogenic hypothesis indicating a direct response of smooth muscle in resistance arterioles to alterations in perfusion pressure could explain the short reaction time. Endothelial factors, primarily nitric oxide, have been attributed a tentative mediating role in autoregulatory response; however, despite a small pilot study finding impaired dynamic autoregulation after nitric oxide synthetase inhibition in humans, the experimental results are mixed [51].

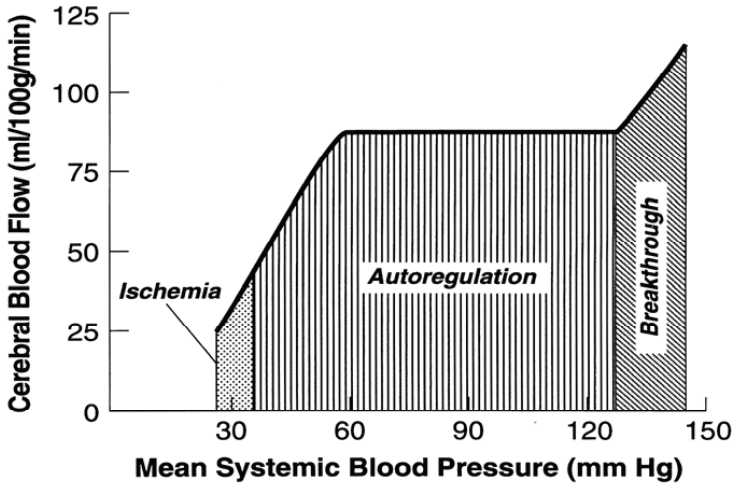


Figure 3. Blood pressure – cerebral blood flow curve showing the autoregulatory plateau
(reproduced with permission from Hademenos GJ, Massoud TF. *The Physics of Cerebrovascular Diseases*. New York: Springer-Verlag; 1998)

The efficiency of autoregulation as a physiological mechanism is restricted by internal thresholds; in the normal brain, CBF is maintained constant at arterial pressures approximately over the range from 50-65 to 125-170 mmHg according to various estimates [29, 49, 52]. Yet, the upper and lower ends of the autoregulatory plateau are not constant. Many external factors have a strong bearing on the autoregulatory function: autoregulation is strongly influenced by arterial carbon dioxide and oxygen levels, e.g. attenuated by hypercapnia and enhanced by hypocapnia, largely mediated by pH changes, and sympathetic activation shifts the autoregulatory curve rightwards preventing exercise from leading into cerebral hyperperfusion [49, 53]. Sex steroid hormones have been shown to change vascular reactivity, estrogen tending to enhance vasodilation and testosterone vasoconstriction [54-57]. Age and gender are determinants of cerebral vasoreactivity as well [58-60]. Long-standing changes may be induced by chronic states, such as chronic hypertension causing a rightward shift in the autoregulatory curve [61].

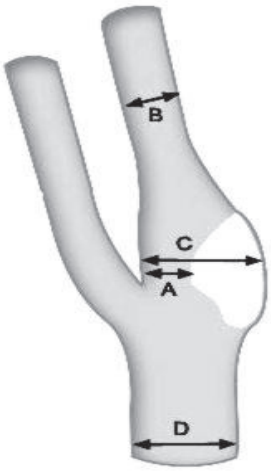
Vasomotor reactivity implies the compensatory potential of the blood-flow regulating vessels, primarily arterioles and precapillary sphincters with diameters not more than 50 μm by change of their diameter. This potential can be specifically tested by observing the response in

CBF or blood flow velocity to an evoked haemodynamic change, e.g. in arterial blood pressure or posture, or to a change in the carbon dioxide content of blood, which may be induced with CO_2 inhalation, breath holding, hyperventilation, or administration of acetazolamide, carbonic anhydrase, which has a potent vasodilating effect on the cerebral resistance vasculature [48, 62, 63]. Also changes in oxygen content trigger autoregulatory responses. Vasoactive infusions have also been used, such as L-arginine. Continuous assessment methods utilizing spontaneous variations in CPP without specific clinical intervention have also been described [64, 65]. According to the testing methodology we can talk either about static or dynamic autoregulation: the former refers to an overall comparison of steady-state measurements whereas the latter takes into account the latency of the response [66, 67].

Autoregulation is impaired by several diseases such as ischemic stroke, traumatic brain injury, and subarachnoid haemorrhage [68-71]. Autoregulatory reactions may gradually decline in increasing degrees of ischaemia, and clinically lower vasomotor reactivity has been detected ipsilaterally in symptomatic carotid stenosis [72, 73]. Impaired vasomotor reactivity has been associated not only with poorer collateralization but also with a greater stroke risk in ICA stenosis or occlusion and the perioperative need for shunting during CEA [34, 74-78]. Conversely, the significance of autoregulation as a protective mechanism is evident in traumatic brain injury, in which preserved autoregulation is associated with good outcome [64, 65, 68].

2.2 Imaging methods of carotid disease and cerebral blood flow

Cerebral angiography became the study of choice for brain vasculature and disorders after its invention 1927, and it gave the user a dynamic qualitative image of the cerebral circulation as filling-up and then wash-out of vessels with contrast. Later on, the revolutions of computed tomography (CT) and magnetic resonance imaging (MRI) for structural imaging restricted the use of cerebral angiography to vessel imaging. At present, digital subtraction angiography (DSA) is still considered the gold standard for the imaging of a carotid stenosis as well as cerebral vasculature. However, in consequence of the fast technical development CT angiography and MR angiography together with ultrasound, even in vessel imaging DSA has to a great extent been replaced by less invasive or non-invasive methods in the clinical practice, and the safer newer methods have also paved the way for quantitative assessment of CBF.



A = narrowest point of ICA stenosis
B = normal-width artery distal to ICA stenosis
C = estimated original width at the narrowest point of stenosis
D = normal CCA proximal to the bulb

- NASCET method of measurement: stenosis = (B-A)/B ∗ 100 %.
- ECST method: stenosis = (C-A)/C ∗ 100 %.
- Common carotid method: stenosis = (D-A)/D ∗ 100 %

Figure 4. Calculation of stenosis degree.

2.2.1 Measurement of carotid stenosis

Subjective visual assessment of the stenosing lesion is not sufficient for guiding treatment decisions but a method of measurement is necessary [79]. A variety of methods have been used to this end, which together with the generally poor study designs has largely undermined the possibility of meta-analytical approach [80]. Of three most commonly used methods, the NASCET (The North American Symptomatic Carotid Endarterectomy Trial) measurement has become the standard in practice [81, 82]. The NASCET method compares the minimal residual lumen at the point of stenosis to a normal ICA width, with parallelly aligned walls, measured beyond the bulb area (Figure 4) [81]. The ECST (European Carotid Surgery Trial) measurement compares the minimal residual lumen at the point of stenosis to the estimated 'normal' diameter of the carotid bulb [83]. The common carotid index method comparing the minimal residual lumen to the diameter of normal CCA may be the most reproducible but despite an earlier recommendation it is not commonly used [84]. The ECST method involves a hypothetical measurement that may induce subjective variation, and it leads to higher percentages of stenosis compared to NASCET method, which could produce an underestimation of percentage and cannot be applied in cases of near-occlusion. In principle, the three measurements are mathematically convertible [84]. The percentages of stenosis in the following are given according to NASCET method if not otherwise indicated.

2.2.2 Imaging cerebral blood flow

The first successful quantitative measurements of the CBF with inhaled nitrous oxide as the tracer were published in 1945 [85]. At present, there are several techniques for imaging and quantitative measurement of CBF and metabolism in addition to structural imaging. Part of them utilize different kinds of diffusible inert tracers, nonradioactive such as ^{131}Xenon in xenon-enhanced CT, or radioactive such as technetium-99m-hexamethyl-propylamine-oxime (^{99}Tc-HM-PaO) in single-photon emission computed tomography (SPECT) or various positron-emitting radioisotopes, e.g. 18-fluorodeoxyglucose (^{18}FDG) or 15-oxygen (^{15}O) in positron emission tomography (PET). These methods are based on quantification of the accumulated diffusible indicator in the brain tissue, and consequently they give an image of the true perfusion of the tissue. The advantages of xenon-enhanced CT are acquisition of both structural images and quantitative CBF estimates, whereas the disadvantages are the sedative and CBF-increasing effect of the tracer as well as often movement artifacts and low signal-to-noise ratio [86]. PET is a versatile tool yielding several physiological parameters in addition to flow, such as oxygen metabolism, but it is better suited to research purposes as its use is restricted by availability, technical demands, expenses, and the limited spatial resolution. Implementation of single-photon emission computed tomography is simpler and the expenses are more reasonable but its resolution is lower and quantitation problematic, and the longer half-lives of the radiotracers make repeated measurements difficult.

The tracers may also be intravascular, measuring the flow inside the vascular compartment, as in perfusion CT and dynamic susceptibility-contrast perfusion MRI (DSC MRI). The high-speed helical CT scanners and image reconstruction software have enabled the development of perfusion CT methodology, where the acquisition of data is possible during the passage of an iodinated contrast agent, and the perfusion can be calculated on a pixel-by-pixel basis from the arterial enhancement (arterial input function). The advantages of the method are acquisition of both structural images, angiography, and maps of mean transit time (MTT) and cerebral blood volume (CBV) and CBF, on a widely available equipment. The disadvantages are the burden of radiation and contrast agent exposure, which limit repeated imaging. Up to now, the coverage of the brain has also been limited, but this setback is greatly overcome by the modern multi-detector row scanners. At present, perfusion CT has already become a validated and fast technique that can be used to guide acute stroke therapy and predict outcome. In a similar manner, DSC MRI utilizes a nondiffusible intravascular tracer whose effect on magnetic susceptibility during its passage is evaluated by a fast series of MR scanning (the MRI methodology is discussed in more detail in the section *2.2.4*)

2.2.3 Ultrasonology

Medical ultrasound (US) utilizes emission of high-frequency inaudible sound pulses (usually of the range 2-20 MHz) and gathering of the reflected sound from the body. The pulses are repeated in a rapid succession in slightly different directions, and the position of the structure producing the reflection can be calculated from the time interval between transmission of the pulse and reception of the reflection. It is an ideal method for soft tissue imaging, limited by its inability to penetrate air or gas. Speed of ultrasound varies in different tissues depending on their density and elasticity; for instance, bone distorts and rapidly attenuates the propagation of the sound wave.

An observer of a moving source of sound waves will measure higher or lower frequency than that actually emitted by the source depending on whether the source is moving towards or away from the observer. This phenomenon is known as the Doppler effect, named after the Austrian physicist Christian Doppler who first described it. The Doppler shift, frequency difference between the emitted and reflected sound signal, can be utilized in medical ultrasonology of moving targets by transmitting a sound signal and observing the change of frequency. The frequency difference can be given as

$$f_d = f_t - f_r = 2 f_t v \cos \theta / c$$

where v is the velocity of the target, c the speed of sound in tissue, θ the angle between the US beam and the moving target, and f_t the transmitted and f_r the received frequency.

In vasculature, the reflection is predominantly from moving erythrocytes in the sample volume, and thus the Doppler shift signal contains a spectrum of frequencies. The ultrasound system may utilize continuous wave emission with a separate transducer for reception of the returning ultrasound, or pulsed wave emission which can provide also a depth estimation of the source of the reflected beam with a single transducer both emitting and receiving the sound [87]. With application of different ultrasonological techniques it is possible to visualize the vessel morphology (B-mode imaging), combine the spectral analysis or colour-coded blood flow with morphology in a real-time viewing (Duplex sonography or colour-coded Doppler flow imaging). Power Doppler imaging produces colour coding of the flow based on the amplitude of the signal. With modern techniques, it has been possible to improve the detection of surface morphology with construction of three-dimensional ultrasound or enhance the signal-to-noise ratio with contrast agent and harmonic imaging [88].

Noninvasive imaging is the mainstay of screening methodology in vascular disease. Since the introduction of the Doppler principle into the medical field over three decades ago, US methods have become the first line of imaging. In investigation of carotid disease, US is the most commonly performed imaging method [89]. In principle, US examinations are easily applied, but they require training and expertise, and as such they are highly operator-dependent. They can be used repeatedly, and the cost is very reasonable in comparison to other techniques. Transcranial Doppler approach was introduced into clinical practice in 1981 [90].

Ultrasonological determination of stenosis degree is the screening method for detection of carotid stenosis. In its early forms, the atherosclerotic process may be reflected by the measured thickness of the wall structure (intima-media thickness, IMT), which has been used as a surrogate in many follow-up trials and is associated with clinical atherosclerosis, e.g. coronary events [91]. In intermediate and high-grade stenosis of advanced atherosclerotic process, it is possible to observe the echogenicity of the plaque. Fibrous tissue and calcifications produce more shadowing, and lipid-laden plaques are associated with more echolucency, as well as intraplaque haemorrhage or thrombosis. Heterogeneous plaques and echolucency as a sign of greater lipid content or intraplaque haemorrhage have been associated with a greater stroke risk [92]; however, the viewing angles are limited, and the assessment of plaque morphology or surface structure is not considered very reliable [93, 94]. So far, studies on the predictive value of intraplaque composition have not yielded uniform results that would guide treatment decisions. Finally, at the later stages of atherosclerotic process, detection of the stenosis and quantification of its degree is the most clinically important parameter. Consequently, different diagnostic criteria have been proposed for a high-grade (70-99 %) stenosis. Peak systolic velocity (PSV) > 230 cm/sec, end-diastolic velocity (EDV) > 100 cm/sec, and ICA PSV/CCA PSV ratio > 4.0 have been found to provide optimized accuracy, and these cut-off points form the basis of a consensus statement for the US velocity criteria in CS [89]. However, these criteria do not apply to near-occlusions, and US cannot reliably differentiate occlusion from a near-total carotid occlusion [88, 89].

Transcranial Doppler ultrasound

Transcranial Doppler ultrasound (TCD) measures local blood flow velocity and direction in the proximal intracranial arteries through skull bone or its natural openings [90]. It is mainly used in the assessment and management of cerebrovascular disease, such as acute infarction, emergence of vasospasm after subarachnoid haemorrhage or elevations of intracranial

pressure. It is a suitable method for continuous monitoring, and it can be used to demonstrate right-to-left cardiac shunts, to quantify the rate of microembolization to the brain, to support the diagnosis of cerebral circulatory arrest, or to study vasomotor reactivity [95]. Recent studies indicate that TCD may enhance the lysis of acute cerebrovascular thrombi, because the recanalization rate in TCD-monitored rtPA-thrombolyses has been higher; however, proper application may be crucial as the insonation may not be harmless [96-98].

The major advantages are low cost of use, noninvasiveness, repeatability, option of continuous monitoring, and that it provides the simplest bedside method for non-invasive crude estimation of CBF. In addition to being operator-dependent, the main disadvantage is limitation to imaging of certain segments of the main intracranial arteries, and a minority of subjects do not have any applicable US window at all temporally [95]. A more accurate depiction of vascular anatomy and smaller arterial branches and venous structure is possible with transcranial colour-coded sonography methodology.

Pulsatility index

Gosling index of pulsatility (PI) is a measure for the shape of the spectral waveform, calculated by

PI = (Peak systolic velocity – end-diastolic velocity)/mean flow velocity [99]

PI is a relatively constant TCD parameter, normally within the range of 0.5-1.4 [100]. Higher values are associated with decreased compliance of the vasculature or increased intracranial pressure, lower values with low-resistance states such as poststenotic flow or arteriovenous malformation [100]. Although PI is often considered a measure of downstream vascular resistance, it is dependent on the driving force as well as downstream impedances, so it is an inaccurate reflection of the vascular resistance [101].

Detection of emboli

Particulate and gaseous material in the blood flow differ from erythrocytes by acoustic impedance properties; the reflection and the scattering of the Doppler US beam enhances the intensity of the received signal which is called ‘a high-intensity transient’ signal (HIT), or generally microembolic signal (MES) in TCD. These have been detected in various manifestations of vascular and cardiac disease, such as carotid stenosis, aortic arch atheroma,

atrial fibrillation, or myocardial infarction, or general cerebrovascular disease. Especially, HITS may be encountered in connection with cardiovascular procedures and surgery, including coronary bypass, catheterization and cardioversion, as well as carotid endarterectomy or angioplasty. Therefore, continuous monitoring of MES can be used in surveillance under operation. The problems of MES detection are not only the variability of occurrence but also of the methodology and detection thresholds, determination of the type of the signal detected, and the differentiation from artifacts, and these reduce the interobserver agreement and overall comparability of studies. New automated methods of discrimination are being developed.

In carotid occlusive disease, ulceration of the plaque with platelet aggregates and fibrin clots may give rise to MES, and asymptomatic occurrence of MES has indicated an increased risk of cerebral ischemic events [102]. It is suggested that MES detection could also be used in evaluation of response to antithrombotic therapy [103-105]. During CEA, TCD monitoring may provide data on the MES occurrence in different phases of the procedure as well as yield real-time haemodynamic information. MES maxima usually occur during the dissection phase, shunting, release of clamping, closure of wound, and during the first hours after the procedure. Their number has correlated to the ensuing MRI lesions, and the development of postoperative cerebral ischaemia [106, 107]. The haemodynamic monitoring may reveal decreases in flow velocities that indicate corrective measures to be taken, e.g. shunt placement, or appropriate medication and fluid administration. In one study, MES during dissection and closure, > 90% decrease in MCA velocity and > 100% increase in PI at clamp release were associated with intraoperative stroke [108]. Correspondingly, a notable (> 100%) rise in flow velocity after clamp release may predict increased risk for postoperative hyperperfusion syndrome [109, 110].

Cerebrovascular vasomotor reactivity

Since the vasodilating effect of carbon dioxide (CO_2) is primarily based on vasoreactivity of arterioles and precapillary sphincters, the blood velocity in the basal arteries is roughly proportional to CBF. As the effect on the basal cerebral arteries is small, TCD is a suitable and widely adopted method for evaluation of reactivity of the brain vasculature [63, 111, 112]. Thus, on manipulation of pCO_2 concentration, the change in flow velocity in basal arteries reflects the change of diameter in vasomotor arterioles. A simple screening test for co-operative subjects is breath-holding, where the patient is instructed to hold the breath for at

least 30 seconds. By following the flow velocity during testing it is possible to derive a breath-holding index (BHI) [113, 114]

$$BHI = [(V_{bh} - V_r)/ V_r * 100] / s$$

where V_{bh} denotes mean MCA velocity at the end of breathing holding period, V_r the resting MCA mean velocity, and s the seconds of time of breath holding.

Another way to induce a vasodilatory stimulus is to administer acetazolamide, a carbonic anhydrase inhibitor, which causes an increase in cellular and extracellular CO_2, leading to a rise in blood flow velocity [62]. The same effect is produced by increasing pCO_2 concentration in inhaled air [63].

2.2.4 Magnetic resonance imaging

Magnetic resonance imaging (MRI) is still a relatively recent invention although it is a highly developed and extremely versatile imaging modality. MRI is based on relaxation behavior of hydrogen atoms or protons when they are placed in a strong external magnetic field and transiently perturbed with radiowaves. When hydrogen atoms with their dipolar magnetic fields are in an external magnetic field, the spinning nuclei become aligned with the external field, either parallel or antiparallel to it. The parallel alignment is slightly more common, leading to a net effect of a weak longitudinal magnetization. Although the alignment is not perfect, i.e. the precession movement of protons involves a vector in the plane perpendicular to the external field, there is no net transverse magnetization. Radiofrequency pulses used to perturb the protons produce transverse magnetization, and the MRI systems may be regarded as designed to measure this effect.

Diffusion-weighted imaging

By diffusion-weighting (DW), it is possible to track the molecular motion of water (the Brownian movement of protons), i.e. diffusion, by labeling the molecules with very fast-changing magnetic gradients. The application of a spin echo T2 sequence with two opposed equal gradient pulses to create DW was first described by Stejskal and Tanner (1965), but not until decades later was the MR equipment advanced enough for clinical application of DWI [20].

The signal intensity (SI) of a DW image may be expressed as

$$SI = SI_0 * \exp(-b * ADC)$$

where SI_0 is the baseline signal intensity (T2-weighted image, b = 0) and

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)$$

where b denotes the diffusion sensitivity factor implying the degree of diffusion-weighting, γ the gyromagnetic ratio, G the magnitude of gradient pulses, δ the gradient duration, and Δ the time between the two gradient pulses. ADC denotes apparent diffusion coefficient, and it gives a measure for diffusion in living tissue.

Diffusion is anisotropic in biological tissues because of natural boundaries to diffusion of water [115, 116]. Thus, measurement of diffusion is direction-dependent and, in principle, needs to be done in several directions [116]. A basic approach would be to reconstruct images in which the white matter anisotropy is averaged, which would render them to subjective evaluation and visualization of areas with diffusion abnormality. Another more quantitative approach would be to construct image maps of ADC, cancelling the T2 weighting of basic echo planar sequence, which would allow a reproducible assessment of abnormal signal as well as the signal of normal-appearing tissue. Acquisition of images in at least three orthogonal directions will ensure a rotationally invariant estimate of isotropic diffusion [117]. In the course of postprocessing the images, their natural logarithms may be averaged to form the rotationally invariant resultant image. By applying linear least-squares regression, this image and the natural logarithm of the T2-weighted image used as a reference can be fitted to the b values, and the negative slope of the ensuing line will represent the average ADC value (ADC_{av}). More advanced postprocessing requires the possibility of using the strong sensitizing gradients with at least six different spatial orientations. This approach forms the basis for the diffusion tensor imaging, which allows estimation of white matter anisotropy (fractional anisotropy) and mean diffusivity of the tissue, and thus integrity of the tissue microstructure [117-120].

Diffusion and ischaemia

When blood supply to the tissue is diminished and the flow decreases below a critical level, which may be below 20 ml/100 g/min, ensuing energy metabolism failure (electrical failure)

disrupts electrolyte and water homeostasis (membrane failure) triggering a process that leads to cytotoxic oedema [121-124]. The ADC of brain water is seen to decline already within minutes after onset of ischaemia [125, 126]. Experimentally, the mean diffusivity of brain water declines abruptly within the first 15 minutes of stroke, and diminishes for hours to a plateau level that may be 60 % of normal [127]. Subsequently, the acute drop in diffusivity and the ADC values is modified by ensuing vasogenic oedema and increased tissue water, peaking at 1-2 days and declining within 4-8 days [128, 129]. In parallel, the process of deteriorating cellular integrity contributes to the diffusion change. As a result, diffusivity levels are 'pseudonormalized' within several days after stroke onset, and they continue to rise for days and weeks [130-135]. Nevertheless, it is notable that the early ADC decrease may also be reversible; still, the reversal may not exclude selective neuronal loss in the rescued area [136-139]. At the chronic stage, the consistently high diffusivity reflects the few barriers to water movement in the lesions after necrotic cell death [130, 135, 140]. Especially at the hyperacute stage of ischaemia, DWI methodology has become an essential and unique tool of modern imaging. By now, its applications are considerably larger and continuously expanding.

Apparent diffusion coefficient (ADC)

Apart from ischaemia, the ADC of tissue water may change in many acute and chronic states. Acutely, the process of cortical spreading depression first characterized by Leão in 1944 involves a propagating wave of cortical depolarization, which is associated with displacement of water molecules and transiently lowered water diffusion [141, 142]. In the same way, ADC changes characterize peri-infarct depolarizations, which accompany ischemic lesions and seem to worsen ischaemia, either by number of depolarization waves or their duration [143-145]. ADC levels have been shown to decrease also in hypoglycemia [146, 147]. Epileptic activity may give rise to cellular oedema and postictally vasogenic, and DWI changes seem closely associated to ictal phenomena [148-150]. In brain trauma, it is possible to visualize diffuse parenchymal changes not apparent in conventional sequences with DWI, and it may be helpful in prediction of outcome in diffuse axonal injury [151-155]. In abscesses, ADC values are strongly decreased, which may be due to restricted water mobility with high viscosity and cellularity within the lesion [156, 157]. The most common demyelinating disorder, multiple sclerosis (MS) causes a variety of DWI changes: acute demyelinating lesions with infiltrated inflammatory cells, vasogenic oedema and demyelination with preserved axons usually increases ADC levels but also decreased levels may be encountered, hypothetically explained with intramyelinic oedema [158]. In herpes simplex encephalitis the ADC levels may be decreased, or rarely increased in cases of vasogenic oedema. In neoplasia, ADC levels may be

useful in differentiating some tumours, e.g. low-grade gliomas are associated with higher levels than high-grade gliomas or lymphomas [159]. DWI can be informative in acute leukoencephalopathies such as posterior reversible leukoencephalopathy, hypertensive encephalopathy, and eclampsia, as well as toxic encephalopathies associated with the use of cyclosporin, tacrolimus, interferon alpha, or immunoglobulin therapy [160-164]. The clinical value in this setting is centered on the ability of DWI to differentiate between vasogenic and cytotoxic oedema, as the latter may at times represent irreversibly lost ischemic tissue: cytotoxic oedema lowers the ADC values and appears hypointense on ADC maps, whereas vasogenic oedema increases the ADC values, appearing hyperintense on ADC maps [165-167].

Also chronic processes affecting cellular microstructure would be expected to have an effect on ADC values. Longitudinal studies reveal age-related increases in intracranial cerebrospinal fluid-filled spaces, mainly at the cost of cortical gray matter volume [168-170]. The most common parenchymal change in the white matter (WM) degeneration or leukoaraiosis (see p. 42), is radiologically a patchy or diffuse attenuation of the white matter which makes it look hyperintense on T2-weighted MRI [13]. Leukoaraiosis is associated with elevated ADC values, which correlate with the degree its severity [171, 172]. Furthermore, in cases with more severe leukoaraiosis, also the normal-appearing WM has higher ADC levels [171]. On the other hand, normal healthy aging seems associated with fairly little changes in ADC levels, although some frontally weighted increase in diffusivity and decline in fractional anisotropy with aging has been detected [173-175].

Perfusion-weighted imaging

Perfusion-weighted imaging indicates depicting microcirculation with MR techniques. Perfusion weighting may be based on susceptibility techniques (DSC MRI) or blood oxygenation-level dependent imaging (BOLD). The more invasive DSC MRI with either SE- or GE-based sequences is commonly used clinically [176-179]. Imaging based on BOLD is largely utilized for cortical activation studies and more in research purposes.

Dynamic susceptibility-weighted bolus tracking

DSC MRI is performed by combining the simultaneous use of a paramagnetic contrast agent, such as gadolinium diethylenetriaminepenta-acetic acid (Gd-DTPA), and a rapid collection of the MR signal during the passage of the bolus through the brain [23]. Gd-DTPA induces a pronounced susceptibility effect and spin dephasing, extending approximately to 5 μm from

the capillaries into the brain tissue. The susceptibility difference between the contrast agent and the brain tissue creates local magnetic field gradients, diminishing phase coherence and signal intensity in the tissue surrounding the vessel. Gd-DTPA is cleared from the brain tissue in seconds, leading to recovery of signal intensity [180-182]. During hypoperfusion, the drop in signal intensity is less accentuated and may be negligible in the ischemic brain, which creates a contrast between hypoperfused and normal regions. The temporal and spatial resolution of the technique have been improved by technical advances, improving signal-to-noise ratio and acquisition speed. By now, it is possible to cover a large volume of the brain.

Quantification of the signal change to yield absolute haemodynamic parameters involves extensive postprocessing of raw images, and the values seem dependent on the applied methodology [179, 183-186]. One of the most commonly used has been the deconvolution approach, referring to the determination of MTT and CBF from arterial and concentration curves in the tissue [26, 187]. DSC MRI data analysis for producing quantitative results has inherent limitations and thus far has not fulfilled the criteria of strict quantification [183, 188-191]. Crucially, the quantitative analysis of perfusion data is based solely on the measurement of an arterial input function, which has intrinsic requirements difficult to fulfill with DSC MRI [192]. Furthermore, although the shape of the function can be determined with a fair accuracy, its height remains arbitrary [25]. Moreover, signal change in relation to the concentration of contrast agent is different in brain tissue and larger vessels, and blood hematocrit in microvasculature is estimated to be lower than generally in the systemic circulation, and individual variation therein would be an additional confounding element [25]. The signal is also affected by the orientation of large vessels in the magnetic field. Although the method has provided reproducible results in human studies, the basic assumptions of the approach may be restrictive in study of elderly patient populations with severe cardio- and cerebrovascular disease [25, 26, 193-195].

2.3 Carotid occlusive disease

Narrowing and occlusion of precerebral arteries subserving the brain was independently described by Wepfer and Willis in the 17th century, and the former already appreciated the potential of the finding to cause strokes [196]. In 1856, Rudolf Virchow described a case of carotid occlusion in a patient who had lost vision from one eye [196]. As a result of various reports and findings, it became evident by the early 20th century that carotid disease was one of the central causes of cerebral ischaemia. Development of vascular imaging with arteriography contributed to the understanding of carotid occlusive disease that enabled the observation of stenosing lesions in vivo[197]. Clinically, especially the work of C. Miller Fisher paved the way for understanding of the clinical significance of occlusive lesions as well as of the potential value of restoring the circulation by treatment [198, 199].

2.3.1 Epidemiology and risk factors

The estimated overall prevalence of carotid artery plaques in general population-based studies has varied from one-eighth to over one-fourth, depending especially on age [200-203]. However, the prevalence of stenosis degree considered clinically significant (usually exceeding 50 %) is clearly lower, less than 10 %, as a rule [203-209]. In two large studies, the prevalence rates of clinically significant stenosis in populations above 65 years of age have been 5-7 % in females and 7-9 % in males, and the recent meta-analysis ended up with figures of 12.5 % for men and 6.9 % for women in the age group of 70 years or more [204, 205, 210] . In high-risk subpopulations, such as males in their late seventies, the prevalence may have been as high as 28 % [201]. In the same way, co-existence of peripheral arterial disease or ischemic coronary heart disease increases the prevalence of carotid occlusive disease severalfold [211-215].

Carotid atherosclerosis is associated with several non-modifiable and modifiable risk factors. Of the non-modifiable risks, age and male sex have consistently come out in population-based studies and meta-analysis [94, 200, 202-204, 209, 210]. Of the modifiable risks, arterial hypertension is strongly associated with the development of carotid atherosclerosis, especially systolic hypertension, according to a few population-based studies [209, 210, 216]. Smoking seems to be a considerable independent risk factor for CS, along with being a risk for general vascular disease [217]. Such an overall risk factor is also diabetes mellitus, in particular type 2, which is a notable risk factor for CS [218]. Physical inactivity is also associated with increasing carotid atherosclerosis, although the efficacy of physical exercise as a preventive intervention is not unequivocal. Smoking may effectively counteract the benefit from physical activity and

optimized diet [219]. There is evidence that also renal disease and non-alcoholic liver disease are risk factors for carotid atherosclerosis, as well as obstructive sleep apnoea [220-223]. Homocysteine has been shown to correlate with the severity of carotid atherosclerosis in several large studies [224-226]. However, the intervention studies with homocysteine lowering have failed to show effect in stroke prevention or carotid atherosclerosis [227, 228]. Evolving hypotheses involve lifestyle factors such as shift work, which may be associated with earlier carotid atherosclerosis [229].

2.3.2 Overall stroke risk

Stenosing lesions in the carotid system may account for 15-20 % of all ischemic strokes [5]. However, the causality between the mere existence of a stenosing lesion and a stroke is not easy to establish, which complicates the evaluation of the true incidence and prevalence of symptomatic carotid disease. In a population-based study, the incidence of stroke among white Americans with at least a moderate carotid stenosis was estimated as 27 per 100 000 [230]. A few stroke databases have registered the frequency of moderate or high-grade carotid stenosis in stroke patients. In the Oxfordshire Community Stroke Project, up to 40 % of all anterior circulation strokes had at least a moderate carotid stenosis or occlusion, whereas in the Lausanne Stroke Registry not more than 13 % of stroke patients had at least a moderate-grade stenosis [5, 231]. The pooled analysis of the major randomized CEA trials showed that a stenosis exceeding 70 % was detected in 21 % of patients who experienced TIA or stroke, and a moderate stenosis (50 - 69%) in 25 % of patients [232].

The overall annual risk of stroke attributed to the presence of a carotid stenosis seems fairly low, of the magnitude of 1.5 % or less [207, 233, 234]. Still, on a population level, it was associated with a threefold stroke risk [235]. Prevalent cardiovascular disease increases the stroke risk at least twofold, raising it to a level around 3 % per year, and the individual risk depends on the presence of additional risk factors such as age, hypertension, peripheral arterial disease, and diabetes mellitus, in addition to coronary heart disease [236-241]. Higher degrees of stenoses are associated with a greater stroke risk, approximately 4-8 % [238, 241, 242]. The association to the stenosis degree is not linear, however, as asymptomatic near-occlusions as well as occlusions that have remained silent are associated with a low stroke risk, probably due to sufficient collateralization [243-245]. Notably, also the stroke etiology is heterogeneous, according to NASCET data suggesting cardioembolic or small-vessel etiology in up to 45% of cerebral ischaemia in subjects with a significant asymptomatic carotid stenosis [243, 246].

Stroke risk in symptomatic carotid disease

The clinical manifestations of a symptomatic state are transient ischemic attacks (TIA) and hemispheric strokes (see *2.3.3*), and their occurrence dramatically increases the risk of vascular events. A high risk of early recurrence after TIA and minor stroke is evidenced by a number of studies, and the risk seems to be highest in large-artery atherosclerosis [247-252]. A very high recurrence risk, weighted towards the very first days, has been described especially in patients with carotid stenosis, with a reported rate of 21 % at two weeks [248, 253]. Although the major endarterectomy trials recruited patients with nondisabling condition and relatively late, as a whole, they still show the benefit of early surgery [232]. This marked difference in stroke risk between recently symptomatic and asymptomatic high-grade stenosis indicates that the underlying processes in the stenosis are not static but the plaque may become unstable or 'active'. The natural course of stroke risk in the medical arms of the major randomized trials has indicated a rapid decline, reaching the level of an asymptomatic stenosis within two years [81, 83]. The risk is lower in women (hazard ratio [HR] 0.79, 95 % confidence interval [CI] 0.64-0.97), and higher in patients older than 65 years (HR 1.70, CI 1.28-1.56), higher in patients with hemispheric TIA or stroke in comparison to those with amaurosis fugax (HR 1.88-2.33, CI 1.38-3.13), and higher in diabetics (HR 1.31, CI 1.05-1.65) and in cases of an irregular or ulcerated plaque (HR 1.35, CI 1.11-1.64) [254].

2.3.3 Pathophysiology

The clinical syndromes caused by ICA disease result from two principal mechanisms that are not mutually exclusive: 1) intracranial arterial thrombosis caused by embolism or extension of thrombus into the cerebral arteries, and, 2) perfusion failure caused by haemodynamic insufficiency [255]. The most common cause of arterial narrowing is atherosclerosis - a chronic, indolent, and essentially inflammatory disease process, which has a predilection for large- and medium-sized arteries and leads to the accumulation of lipids and fibrous tissue material into the vessel wall. A considerably smaller minority of stenosing lesions are caused by arterial dissection, post-radiation damage, large-vessel vasculitides such as Takayasu arteritis, or connective tissue pathology such as fibromuscular dysplasia [256].

Modes of clinical presentation

Transient ischemic attack (TIA) is defined as 'a clinical syndrome characterized by an acute loss of focal cerebral or monocular function with symptoms lasting less than 24 hours and

which are thought to be due to inadequate cerebral or ocular blood supply as a result of low blood flow, thrombosis or embolism associated with disease of the arteries, heart, or blood' [257]. Proposed definition of stroke has been recently revised as 'a clinical syndrome characterized by an acute loss of cerebral function with symptoms lasting more than 24 h or leading to death, and which is thought to be due to either spontaneous haemorrhage into the brain substance (haemorrhagic stroke) or inadequate cerebral blood supply to a part of the brain (ischemic stroke) as a result of low blood flow, thrombosis or embolism associated with diseases of the blood vessels (arteries or veins), heart or blood' [258]. Thus, both manifestations are typified by sudden onset and a focal neurological loss, usually maximal intensity at onset, whereas distinguished by the duration of symptoms.

The differentiating timeline is arbitrary, based on mutual agreement [259]. Actually, TIA and stroke form a continuum, as indicated by an identical etiology and prognosis for vascular events of patients with focal symptoms lasting less or more than 24 hours [260]. Longer duration of symptoms is associated with a greater likelihood of a visible ischemic lesion in imaging as well as a greater risk of recurrence [261-263]. In general, in more than half of TIA cases, signs of ischaemia in relevant locations are displayed by DWI or combination of DWI and PWI [264-267]. As the duration of TIA is generally considerably shorter than 24 hours and new methods of imaging allow visualization of hyperacute ischaemia, new definitions and timelines have been suggested [268, 269]. The recent guideline has adopted a tissue-based definition ('A transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction'), and recommends neuroimaging preferably with MRI [270]. Approximately 23 % of strokes are preceded by TIA, and the subsequent stroke risk may be even higher after TIA than after a hemispheric stroke, and the prognosis may be improved by active and undelayed measures and investigations in specialist stroke services [271].

Transient monocular blindness, amaurosis fugax, which is usually a short-lived phenomenon of monocular visual curtain-like or foggy obscuration of vision lasting seconds to minutes, represents a classical form of carotid TIA [272]. Often the loss of vision starts from the upper part of the visual field, and less frequently appears ascending from below, but it may also be patchy or sectorial [272, 273]. Altitudinal presentation, speed of onset within seconds, abundance of attacks as well as visual loss induced by bright light ('retinal claudication') are often associated with carotid etiology, whereas constricting pattern of the visual loss or the presence of positive light phenomena may increase the possibility of other etiologies [274-276]. Apart from carotid etiology, especially the possibility of giant cell arteritis in the elderly should be considered, as well as ophthalmological causes such as retinal venous occlusion, vitreous

haemorrhage, or optic nerve disease as differential diagnoses [274, 277, 278]. In a population-based series from the U.S.A., amaurosis fugax accounted for 24 % of carotid TIAs [279]. In connection with atheromatous carotid disease, the annual risk of stroke or death after amaurosis fugax is estimated as 3-5 %, which is approximately 50 % lower than the risk after hemispheric symptoms [257, 280].

Hemispheric symptoms in TIA or stroke caused by a CS may stem from large-vessel territories, mainly MCA or sometimes ACA, their branches, or infarctions may occur in the watershed or borderzone territories between ACA and MCA or MCA and PCA, or lenticulostriate artery level between the deep and superficial perforators, the internal borderzone. Watershed infarctions may be more common in association to severe stenoses, but any typical patterns may be difficult to identify because of individual variation [281, 282]. Thus, the hemispheric symptoms of CS are predominantly anterior circulation syndromes. The most common manifestations of hemispheric TIAs involve motor and sensory dysfunction of contralateral limbs, purely motor dysfunction, sensory dysfunction, and isolated dysphasia [272]. Contralateral distal arm and hand are the most consistently affected parts. A specific albeit uncommon manifestation is 'limb-shaking TIA', episodes of irregular flapping, twisting, trembling or wavering movement of contralateral arm or leg, which is usually associated with severe CS and thought to result from haemodynamic insufficiency [283-285]. The stroke syndromes related to a symptomatic CS overlap with those resulting from other embolic sources, and cannot be differentiated on clinical grounds, despite some distinguishing features on group level, such as fractional arm weakness in symptomatic CS (hand and shoulder differently affected) or reduced consciousness in cardioembolism [286]. The clinical manifestations include the whole range of findings in combinations or in isolation, sensomotor hemiparesis, aphasia or dysphasia, apraxia, and neglect. Ocular infarctions may also occur, by way of central retinal artery or branch occlusions and ischaemic optic neuropathy.

Atherosclerotic plaque and its destabilization

The complex pathophysiological process of the stenosing plaque, during which lipid and other blood-borne material accumulates in the vessel wall, involves various pathways of disease operating and interacting at the different stages, often silently over years and decades until its clinical manifestations appear. Inflammation is one of the central factors throughout the process up to the activation stage of the plaque, whereas endothelial dysfunction has an integral role especially at the initiating and earlier stages [287]. Branching sites with turbulent

flow are preferential places for lesion formation, partly mediated by altered mechanical stress [288]. As a rule, the early lesions evolve slowly, and the encroachment of lumen is balanced by adaptive vasodilatation and enlargement of the vessel (remodeling). Although the clinical manifestations are local, the pathological process is systemic, as evidenced by the frequent findings in other vascular beds than the one clinically affected [289]. The course of disease is highly variable, depending on the acquired risks as well as the genetic risk, and according to recent evidence, the course need not be inevitably progressive [290, 291]. A prospective population-based ultrasound has shown that the early-stage steady and slow progression may later on be abrupt and episodic, possibly as a result of disruptive events and healing periods [292].

Atherosclerosis is essentially a pathology of the intimal layer, leading to accumulation of lipid in the intima, collection of inflammatory cells, and proliferation of smooth muscle cells [288, 293, 294]. The first stages ('fatty streak' with lipid-containing foam cells) may appear already in childhood. The endothelial cells have many physiological functions, forming a selectively permeable barrier layer between the vessel wall and flowing blood with tight intercellular junction complexes, a non-thrombogenic surface producing effectors that regulate inflammatory and immunological stimuli [288]. Endothelial injury, promoted e.g. by lipids, shear stress and flow disturbances, may lead to impaired vasodilatation and increased adherence of leukocytes, impaired fibrinolysis, and finally even to apoptotic denudation and severe loss of protective functions [295]. Smooth muscle cells may be transformed into proliferative forms, and with extracellular matrix elements they may be forming a fibrous cap covering the denuded plaque [296, 297]. Elevated lipid levels, particularly low-density cholesterol (LDL), cause the ingestion of LDL which undergoes oxidation becoming still more atherogenic, further impairing the endothelial function, and triggering proinflammatory reactions [294]. Inflammatory cells, predominantly circulating monocytes, may enter the dysfunctional vessel wall by means of adhesion molecules and become macrophages, and after engulfing the lipid material, foam cells. Apart from macrophages, also T and B lymphocytes as well as mast cells are involved during the atherogenesis. Search for antigens in study of immune activation ongoing in the lesions has raised interest in several pathogens such as Chlamydia pneumoniae, Epstein-Barr and Herpes simplex type-2 viruses, and an association between antibody titers and progression of atherosclerosis has been found [298]. However, there is little prospective evidence that the antibodies predict vascular risk, and the intervention trials with antibiotics have not been successful [299]. It is possible that advanced plaques gather bacterial DNA and no single agent has a causative role although microbes may have etiopathogenetic role in the process [300].

Activation or destabilization of the atherosclerotic plaque, turning it into a symptomatic phase, is difficult to predict. As the plaque grows and stenosis degree increases, thrombus formation is more common, giving more easily rise to distal embolization from the stenosis, and the risk is increased in the presence of ulceration or eccentricity of the plaque [301]. Other mechanisms of symptom generation are local occlusion by a thrombus, which is more infrequent, and occlusion of small vessel origins by the growing plaque [293]. Several minor studies comparing plaque pathology in symptomatic and asymptomatic stenoses have implicated a significant association between symptoms and plaque rupture, thinning of fibrous cap, and infiltration by macrophages and T cells [10]. A large histopathological study confirmed the high degree of inflammatory infiltration and cap rupture in symptomatic plaques as well as the association between the pathology to time course since the last event [302]. The components of the fibrous cap may be depleted by various matrix-degrading metalloproteinases and other proteases expressed by inflammatory cells and smooth muscle cells, predisposing to rupture. The lipid core of the plaque contains high concentrations of tissue factor, which is very thrombogenic in contact with blood and presented especially by apoptotic macrophages [303]. The blood contact is followed by deposition of thrombocytes, and the ensuing thrombosis is dependent on the balance between procoagulant and anticoagulant activity in the blood. Adhesion molecule expression has been suggested to be associated with symptomatic state, either as correlating positively to the endothelial expression or negatively to the expression in intima-media [12, 304]. Apart from the mechanism of cap degradation, the other mechanism of plaque rupture is physical force, predisposing sites with high structural stress to disruption.

Identification of the vulnerable atherosclerotic plaque is challenging. By now, it is accepted that the composition of the lesion may be the major determinant of the clinical manifestation of atherothrombosis rather than the mere grade of stenosis or volume of the plaque. This has sparked an interest in the novel methods of imaging the plaque and created a trend of molecular imaging. Considerable progress is expected in the next few years by a multimodal approach to patients with CS, by combining clinical history and epidemiology, versatile imaging, and biochemical markers for better identification of vulnerable plaques [305].

Coagulation, haemostasis, and haemorheology

Coagulation of blood and haemostasis, arrest of blood flow, are the very essence of atherothrombotic strokes. Clinical thrombosis involves blood flow, platelet-vessel

interactions, and the coagulation system. The phenomenon of blood coagulation is a highly interwoven interaction of platelet activation, fibrin formation for the backbone of the thrombus, and fibrinolysis for its breakdown. The intertwined elements need to be considered together to have an overview of the clotting process (for a simplified outline, see Figure 5) [306, 307]. The intricate balance between procoagulant and anticoagulant or fibrinolytic activity in blood could be crucial in generation of symptoms in cerebrovascular disease, and appropriate haemostatic markers would be of interest in identifying and possibly treating high-risk groups.

Several potential markers measurable *in vivo* are produced during the cascades. One of the key players is thrombin which induces conversion of fibrinogen into fibrin at the end of the cascade, but it has multiple actions as a procoagulant activator of several coagulation factors and platelets as well as an anticoagulation effect through protein C activation, which also enhances fibrinolysis [306, 307]. When thrombin is cleaved from prothrombin, either by intrinsic or extrinsic activation system, prothrombin fragments 1 and 2 (PF 1 and 2) are released into the plasma, reflecting the degree of prothrombin activation and thrombin generation. The predominant thrombin inhibitor is antithrombin III, the most important inhibitor of coagulation proteases, and the forming thrombin-antithrombin complex has also been used as an assessable indicator of thrombin activity [308]. Fibrinolytic activity is dependent on the conversion of plasminogen to plasmin, in which tissue-type plasminogen activator (t-PA), of endothelial origin, appears to have a central role [306, 309, 310]. t-PA activity is regulated by several inhibitors, especially type 1 plasminogen activator inhibitor (PAI-1). Fibrin cleavage by plasmin produces several degradation products, such as fibrinopeptide A and B as well as cross-linked D-dimer, which is considered specific to fibrin polymer [306, 311]. In prospective studies, PF 1 and 2 levels have predicted cerebral and cardiac ischemic events and t-PA antigen levels have predicted stroke, and especially fibrinogen has been shown to be an independent risk factor for stroke and its severity [312-317]. Still, the haemostatic markers have not yet produced useful prognostic variables for routine clinical use, partly for methodological reasons [270, 318].

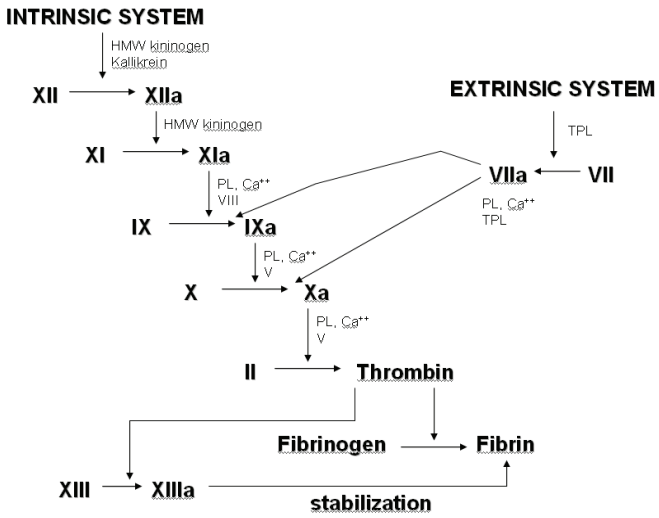


Figure 5. Outline of coagulation cascade (HMW = high molecular weight kininogen; PL = phospholipid; TPL = tissue thromboplastin)
[according to Wessler & Gitel, *N Engl J Med* 1984;311:645-52, with permission].

Flow characteristics of blood, rheology, determine its ability to perfuse the brain; consequently, haemorheology is an important variable also in cerebral ischaemia. Blood is a non-Newtonian fluid, the viscosity of which in normal circumstances mainly depends on red blood cell mass, hematocrit (Hct), and fibrinogen, which constitutes the largest quantity of high-molecular-weight proteins in the plasma [319]. Not only high fibrinogen but also high Hct can be regarded as a risk factor for stroke. In humans, CBF is inversely correlated with blood viscosity, although autoregulation to some extent counteracts the fluctuations and protects the brain [320, 321]. At the acute stage, haemorheological abnormalities are common, and they may partly be due to non-specific acute-phase changes such as fibrinogen increase but in many cases they may just as well be chronic [322-324]. All the same, elevated Hct in acute stroke may be associated with reduced reperfusion and tissue survival rates and increased mortality [325-327]. Despite the potential effect on CBF, acute intervention trials aiming at haemodilution in acute ischemic stroke have not proven to improve survival or outcome [328].

In the context of carotid stenosis, platelets have essential functions not only in primary haemostasis and in acute vascular events but also in endothelial repair and during the formation and growth of atherosclerotic plaques. The mere presence of atherosclerotic plaque may lead to platelet activation [329-331]. The degree of arterial stenosis is an important factor in recruiting platelet deposition, contributing to the instability of the forming platelet-rich thrombus at the stenotic site [332]. Also, the contribution of thrombin generation in an experimental model of shear force-induced thrombosis and its inhibition during high grade stenosis-associated thrombus formation demonstrate that the growth of these thrombi is indeed thrombin-dependent [332, 333]. Clinical observations supporting this view have been reported [334, 335]. Accordingly, a disturbed balance between the finely regulated procoagulant and fibrinolytic activity in blood could contribute in the process when an asymptomatic CS turns into a symptomatic one. The stability of the atherosclerotic plaque could also be regulated by local fibrinolytic activity in the plaque macrophages. As a potent activator of matrix metalloproteinases, plasmin could contribute to plaque instability. Urokinase-like plasminogen activation is co-localized with thrombosis on the surface of an atherosclerotic plaque, and the theory of plasminogen system involvement is supported by extensive studies in knock-out animal models [336, 337]. Furthermore, plasminogen activators and their regulators are upregulated in failing arterialized venous grafts, underlining the possible role of the fibrinolytic system in the events [338]. Also haemorheology may have an especially important role in the high-pressure setting of carotid artery flow and through shear stress forces affect haemostasis, thrombosis, and the growth of plaques. The association between haemorheology and atherosclerosis may be more obvious in men [339].

Cerebral haemodynamics

The CS could give rise to ischaemia by cutting down the blood flow to the brain and causing haemodynamic insufficiency, which used to be a popular explanation for cerebral events [293]. However, the blood flow through the stenosis is not affected until the stenosis degree exceeds 50 %, and substantial reduction does not occur until the high-grade levels (Figure 6) [340].

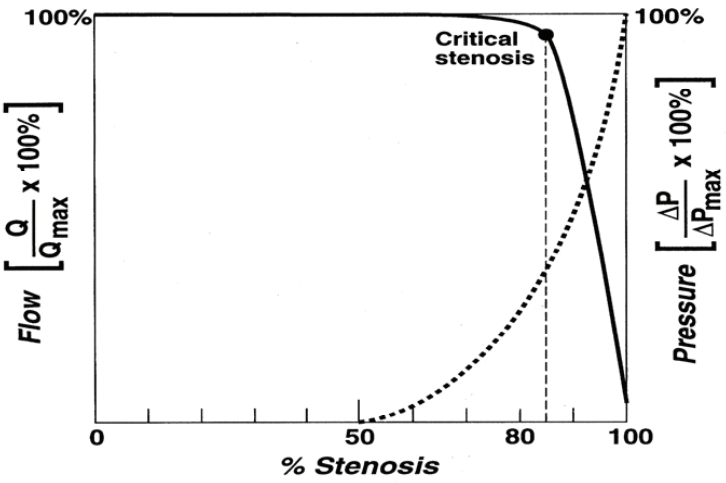


Figure 6. Changes of pressure gradient and flow through progressive luminal obstruction of a vessel (reproduced with permission from Hademenos et al., *Stroke* 1997;28:2067-2077)

By way of autoregulation, the cerebral perfusion pressure may still be maintained within normal limits. A considerable drop in blood pressure does not often cause cerebral symptoms, and when occurring, the symptoms tend to be nonfocal, such as presyncopal signs. However, if the collateralization is defective as a result of anatomy or acquired disease, autoregulatory reserves may be exhausted so that CBF is affected, causing a gradual rise in oxygen extraction fraction, and probably leading to an increased stroke risk, at least in symptomatic stenoses or occlusions [75, 341-345]. Haemodynamic compromise is not regarded as a major pathogenetic mechanisms of ischaemia in carotid occlusive disease, but in a minority of patients the pattern of ischaemia follows borderzones between arterial territories, as a potential sign of a haemodynamic etiology [282, 346]. The radiological diagnosis of a borderzone or watershed infarction is not accurate, not only because of the considerable variation of watershed zones but also because some of these infarctions apparently result from embolism [293]. Nevertheless, prevalence of carotid occlusive disease is high in patients with an observed borderzone infarction, both cortical and especially internal [347]. Haemodynamic etiology is suggested also by precipitation of stroke symptoms by sudden haemodynamic change such as systemic hypoperfusion during cardiopulmonary bypass, severe haemorrhage, or as a result of autonomic failure or overzealous antihypertensive treatment [348-350].

Both embolic and haemodynamic mechanisms may in fact interact: haemodynamic factors may determine whether an embolization leads to occlusion of vasculature or is 'washed out' with reperfusion of the tissue [347, 351]. This could partly explain the variance of outcome in carotid occlusions, when the embolus either causes a permanent vessel occlusion or is fragmented with reperfusion of the vessel, and the co-occurrence of embolic and haemodynamic stroke patterns [347]. Overall, considering the diagnostic difficulties, it is currently held that the significance of low flow in cerebral ischaemia is not fully understood [293]. It is also notable that in discussions 'symptomatic' state usually denotes focal clinical manifestations, whereas long-term effects, such as the effect of potentially increased MES loads over longer periods of time because of diminished washout, or chronic relative hypoperfusion, are controversial or unknown.

White matter changes

Leukoaraiosis (LA) or white matter lesions (WML) refer to bilateral and either patchy or diffuse areas of hypodensity of the WM on CT or hyperintensity on T2-weighted MRI [13, 352]. Its frequency in older patient groups has ranged between 21% and 100% depending on the imaging method and the study population [353]. In a study population representing young and healthy working-age individuals, the prevalence of WML was reported as 5.3 % [354]. Overall, the figures are relative as they are based on variable rating scales, and the results are dependent on the applied MR technology, the very basis of WM research [355-358]. Consistently, the risk of developing WML increases with age, and the finding is often referred to not only as WM lesions or hyperintensities (WMH) but also as age-related WM changes [353, 359]. Still, WML are seen also in younger individuals and stroke patients [354, 360, 361]. Customarily, WMH have been divided into periventricular (PVH) and deep hyperintensities (HI) by topography, and punctate, early confluent or confluent by nature and extent. A population-based topographical study on healthy individuals aged 60 - 64 has confirmed that the periventricular WM has the highest frequency of hyperintense lesions, closely followed by deep HI particularly in occipital and frontal lobes, some degree of WMH being present in every subject [362]. Susceptibility to development of LA and the lesion volume seem genetically influenced [363, 364]. Vice versa, pronounced LA is the hallmark of several hereditary diseases, such as leukodystrophies, and especially CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) [353]. The tendency of WML to progress over time seems associated with the initial severity of the lesions, presence of lacunes and previous strokes, diabetes and blood glucose levels, and increases in diastolic and systolic blood pressure [365-369]. Also elevated homocysteine levels correlate with the degree of

LA, and homocysteine has been considered a marker of endothelial dysfunction [370-372]. Even birth parameters such as lower birth or placental weight have been suggested to affect the proneness to LA [373].

In LA pathology, the most conspicuous findings are gliosis, axonal loss, myelin pallor, and enlargement of perivascular spaces [352, 374]. The ischaemic appearance is most consistent in extensive confluent lesions, whereas PVH appear rather non-ischaemic with subependymal gliosis and ependymal discontinuity, enhanced by disturbed flow of cerebrospinal fluid [14, 375]. In pathological studies, chronic ischaemia, myelin degradation, apoptosis, and axonal transport failure have appeared as integral parts of pathophysiology [376-378]. Thus, chronic cerebral ischaemia and hypoperfusion have been regarded as the main etiology for LA, but its pathogenesis remains incompletely understood and the terms controversial [14]. The cerebral WM is supplied mainly through long penetrating arteries stemming from branches of the major cerebral arteries on the pial surface with few anastomoses. In cases of small vessel disease, the structure of the vessels changes with arteriolosclerosis, hyaline thickening, elongation and increased tortuosity, leading to altered blood supply and either localized necrosis and cavitation or diffuse rarefaction, LA [14, 379, 380]. In terms of pathology, LA may be considered a diffuse manifestation of small vessel disease. It may be accompanied with focal isolated lacunar infarctions, and either focal or diffuse manifestation can predominate. Notably, small vessel disease occurs also without arterial hypertension, as does LA [14, 379]. Consequently, it has been postulated that mere alterations in blood pressure regulation could contribute to the pathogenesis of LA, since patients with LA display more variation in BP and possibly poorer autoregulation [14]. CBF reductions have been detected in LA regions, and even a steal phenomenon has been described [381-384]. However, it is possible that the decrease in CBF is an effect rather than a cause, or an epiphenomenon. Still, lower CBF has been reported also in the normal-appearing white matter of subjects with LA, in the same way as lower fractional anisotropy and higher mean diffusivity and ADC_{av} values on diffusion tensor imaging and DWI [120, 171, 384].

Apart from ischemic hypothesis, it has been suggested that disruption of blood-brain barrier could lead to WM damage through extravasation of plasma proteins [385, 386]. A unifying theory could be offered by endothelial dysfunction and a systemic failure in arteriolar function [370, 387].

Clinical consequences of LA are evident and manifold, although LA may at times be considered asymptomatic or its effects go unnoticed. Firstly, it is associated with cognitive

impairment that is especially related to frontal-lobe performance with deficits in executive functions and information processing speed [388-394]. Some data suggest that WM hyperintensities predict dementia, and it has long been evident that LA often coexists and interacts with Alzheimer's disease, sharing many risk factors with it and modifying the overall cognitive profile of the patients [395, 396]. LA is also associated with late-onset depressive symptoms [397]. Subjects with advanced LA have problems with gait and a poorer balance, and there is evidence of an increased risk of falls and urinary complaints [398-400]. LA is a risk factor for stroke and vascular events, symptomatic haemorrhagic transformation after thrombolysis of acute ischemic stroke, and poorer outcome and death after stroke [401-406].

In a high-grade CS, ensuing relative hypoperfusion could in principle be associated with subclinical changes in the parenchyma, especially in the WM. Presence of LA with a carotid stenosis has predicted stroke events, especially lacunar, during follow-up [407, 408]. At least partly reversible metabolic changes such as diminished N-acetyl aspartate and elevated lactate in MR spectroscopy in hypoperfused ipsilateral brain have been described in patients with CS, but the results are variable [409-411]. Experimentally produced chronic hypoperfusion has caused widespread changes in the WM and cognitive disturbance in animals [378, 412]. Consequently, an increased propensity to ischemic WM degeneration could be expected in a high-grade CS with a haemodynamic compromise also in humans, and the decreased reactivity and perfusion in LA could make the WM more susceptible to transient ischaemia and myelin rarefaction [381, 384]. Recent data have given support to the hypothesis, as well as suggested an association between the carotid plaque characteristics, namely intraplaque haemorrhage and lipid content, and WM hyperintensities [413, 414].

Cognitive function

As a risk factor for stroke, CS is inevitably associated with cognitive decline and dementia. CS is a known risk factor for lacunar infarctions, part of which are silent, and they are known to interfere with cognitive performance [415]. Also subclinical parenchymal changes associated with continuous silent microembolization or a haemodynamic deficit in a high-grade CS could give rise to cognitive impairment, although the stenosis would clinically be categorized as an asymptomatic one. Indeed, in two cross-sectional studies, the subjects with high-grade asymptomatic carotid stenoses were found to have impaired cognition in comparison with subjects without stenoses [416, 417]. The study with a more detailed neuropsychological protocol found the impairments in the domains of attention, psychomotor speed, memory, and motor functioning. Apart from lacunar infarctions, the CS group had no more MR lesions, which did

not support the notion of silent embolization [417]. Also the other study with a follow-up design found the association regardless of MR findings and after adjustment to vascular risk factors, supporting the notion of asymptomatic CS as an independent risk factor for cognitive impairment and decline [416]. A recent report suggested that reduced cerebrovascular reactivity could explain some cognitive decline in these patients [418].

Impaired haemodynamics due to heart failure is associated with impaired cognition, in a similar way, and cerebral hypoperfusion may precede and even contribute to onset of clinical dementia [419-421]. There is also some evidence that the effect of constitutional hypotension might not always be offset by autoregulation but give rise to cognitive deficits, primarily those of attention and memory [422]. Thus, the fraction of patients with a high-grade CS and insufficiently compensated cerebral circulation could be expected to be at risk of cognitive effects.

2.4 Treatment of carotid stenosis

The understanding of the carotid pathology as an etiology of stroke improved greatly during the last century, which paved the way for the development of efficient medical treatment of the risk factors associated with carotid atherosclerosis as well as the surgical and endovascular techniques for stroke prevention. Medical treatment may be regarded as the backbone of treatment for all patients whereas carotid interventions are selectively indicated.

2.4.1 Carotid endarterectomy (CEA)

The first successful surgical removal of the stenosing plaque (CEA) was performed in 1953 but not reported until 1975 [423]. The main impetus to a more widespread use were given by the early reports, leading eventually to a vast and variable surgical practice [424, 425]. Five randomized controlled trials have been performed on the safety and efficacy of surgery on symptomatic CS [81, 83, 426-430]. The early two studies with limited sample sizes did not produce conclusive evidence on the value of surgery, unlike the latter trials, of which the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), complemented with a minor population from the Veterans' Administration Cooperative Symptomatic Carotid Stenosis Trial, altogether with 6092 patients and 35 000 years of follow-up, form the main body of evidence which the present guidelines and practice are largely based upon [232].

In symptomatic CS, appropriate CEA is an efficacious means of prevention. In symptomatic patients with 70-99 % stenosis, CEA can decrease the risk of stroke by more than 60 % (relative risk 0.39, CI 0.28-0.51), and in those with moderate stenosis (50-69%) by 25 % (relative risk 0.75, CI 0.56-0.94) [254]. Absolute 5-year reduction of risk of any stroke or death was 15.3 % (CI 9.8-20.7) in patients with 70-99 % stenosis and 7.8 % (CI 3.1-12.5) in patients with 50-69 % stenosis. No 5-year benefit was seen in near-occlusions, however, possibly indicating the presence of good collateralization, neither did patients with < 50% stenosis benefit from surgery. Risk reduction figures were essentially similar for disabling stroke. Of the subgroup analyses of pooled data, it appeared that in addition to the degree of stenosis, also age, sex, and time from the last event modified the efficiency. Men had the most benefit as well as patients of age 75 years or more and those randomized within two weeks since symptoms. Women with a stenosis of moderate degree (50-69 %) did not benefit from surgery, partly because of lower stroke risk on medical treatment and higher surgical risks, whereas in the high-grade stenosis group, the benefit was clear [431]. Timing of CEA has become an important factor as the stroke risk is known to be high in the early phase after symptoms, and the benefit appears to wane after two-week delay, essentially vanishing in moderate stenoses after this period and in high-grade stenoses by three months. The guidelines have adopted this recommended timeframe, although it is obvious that at present the delays tend to be longer [432-434]. The operative risks are highest in emergency CEAs, but early CEA in stable patients with minor stroke or TIA does not seem to have higher risk than delayed surgery [435]. In the pooled analysis, the perioperative risk of stroke or death was 6.2 % [232].

In asymptomatic CS, the benefit of surgery is considerably smaller. Of altogether seven trials, three major comparable ones were included in the latest systematic review [8, 436-438]. In this review, the relative risk reduction in the surgical group was 31 % (RR 0.69, CI 0.57-0.83) for any stroke or death. Absolute risk reduction was 3.0 % over a mean follow-up of approximately 3 years. The overall perioperative complication rate was 2.9 %. Subgroup analyses were performed in the two large trials showing a greater benefit from CEA in men, and in women the benefit within the follow-up time was not significant [8]. In contrast to symptomatic CS, the benefit of surgery in asymptomatic CS did not appear proportional to the degree of stenosis or age, but the data were considered insufficient [8, 232].

2.4.2 *Medical treatment*

The mainstay of secondary prevention is antithrombotic treatment together with modification of risk factors [439]. Antiplatelet drugs are used on the basis of symptom-based stroke prevention trials, mainly acetosalicylic acid (ASA), clopidogrel, or dipyridamole, mostly in combination with ASA. No stroke prevention studies have focused exclusively on patients with carotid stenosis, and the evidence is elicited from non-cardioembolic stroke prevention studies. In secondary prevention, ASA may reduce the relative risk of vascular events by 13-22 %, and the effect may even be doubled by combining extended-release dipyridamole [440-442]. Clopidogrel is not inferior to the combination and may be better in comparison with mere ASA for vascular events [443, 444]. In the setting of a symptomatic CS, administration of ASA is associated with less microemboli, and also clopidogrel given prior to CEA has reduced postoperative embolization rate [103, 445]. Also combination of ASA and clopidogrel seems to reduce MES in recently symptomatic CS but cannot be recommended owing to the reported increase in major bleeding risk in stroke patients [105, 446, 447]. ASA has been recommended even for primary prevention in patients with asymptomatic CS, based on the regular ASA use in the medical arm of the major carotid trials, in which the ASA use was associated with fewer myocardial infarcts [448]. Anticoagulants are effective in stroke prevention in patients with atrial fibrillation, but in non-cardiogenic stroke anticoagulation provides no extra benefit over antiplatelet treatment [449, 450]. In carotid stenosis, anticoagulation has been used in the clinical practice in cases of crescendo TIA or progressing stroke, or in an assumed symptomatic low-flow state, without specific evidence to support the practice.

Statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) used for lipid-lowering in patients with coronary heart disease have considerably reduced the incidence of fatal and non-fatal stroke, albeit that cholesterol has previously been considered a weak risk factor for stroke [451]. A comprehensive meta-analysis of the earlier statin trials up to 2003 found a relative risk reduction of 21 % for stroke without heterogeneity between the studies, and a consistent correlation between low-density lipoprotein cholesterol decrease (LDL-C) and stroke risk reduction as well as progression of carotid intima-media thickness [452]. The only statin trial designed primarily for secondary prevention of stroke showed a clear risk reduction of both fatal and non-fatal strokes with an aggressive treatment (atorvastatin 80 mg) in patients with TIA or minor stroke and no history of coronary heart disease [453]. Apart from the LDL-C reduction which seems to be the main driving force behind the decrease in stroke risk, statins may act through anti-inflammatory, antiatherothrombotic, neuroprotective, and plaque-stabilizing properties and effect on endothelial function, which might be beneficial

especially in CS [452, 454-456]. In the atorvastatin stroke trial, a secondary analysis supported the notion of special benefit in the carotid stenosis subgroup with a 56 % reduction of subsequent carotid revascularization in the group randomized to atorvastatin [457]. Consequently, although the absolute stroke risk reduction with statins is modest in general, they are an essential part of medical treatment in CS patients, at least in those with less than optimal lipid profile.

Antihypertensive treatment is needed in the majority of patients with CS, and it is one of the cornerstones of medical treatment. There is evidence that the choice of antihypertensive agent may make a difference in secondary prevention, centering on the renin-angiotensin system: treatment with angiotensin-converting enzyme (ACE) inhibitor perindopril with indapamide was associated with better outcome in patients with previous stroke or TIA, and treatment with angiotensin receptor blocker losartan was associated with 25 % relative risk reduction for stroke in comparison with patients on atenolol despite identical blood pressure control [458, 459]. Also candesartan has been associated with significantly less non-fatal strokes [460]. Based on the evidence, prevention guidelines have adopted the recommendation to favour ACE inhibitors or angiotensin receptor blockers in antihypertensive treatment, if possible [432]. Since there are no antihypertensive trials specifically in patients with CS, the particular benefit in this group is not known. However, some preliminary findings support the antiatherogenic and endothelial function improving effect of ACE inhibition also in human carotids [461].

2.4.3 Effects of CEA on the functioning of the brain

CEA may be considered protective of cerebral functions, as it is an effective means of stroke prevention. Still, it is also a risk factor for stroke, since a complicated course of surgery may produce the unwanted result, especially in unstable patients [435]. The frequency of stroke and death in recent large reports have been not dissimilar to the pooled analysis of the previous large CEA trials, being 5.6-7.9 % for those operated on for TIA or stroke [232, 462]. Apart from frank strokes, perioperative ischaemia is more often clinically silent, and postoperative DWI lesions are detected in at least one-tenth of patients [16, 17, 107, 463, 464]. Nevertheless, cognitive decline may not be recognized in this group in the clinical practice.

At least transient cognitive decline seems to occur in a substantial proportion of patients undergoing CEA [16-18, 465, 466]. Postoperative decline has been more common in aged individuals, diabetics, and carriers of apolipoprotein E-ε4 allele, and it has occurred regardless of whether general or regional anesthesia was applied [18, 465, 467]. The decline may mostly be DWI-negative [17]. All the same, it is often attributed to diffuse perioperative embolization or

haemodynamic instability or dysregulation [468, 469]. However, the studies have had limited sample sizes to verify a relationship between HITS or dysregulation and cognitive impairment [466, 468-470]. Despite a single positive report on the association of gliofibrillar protein S-100B levels with subtle cognitive decline, the biochemical markers have not been useful indicators in CEA [471-473]. Not only embolization and hypoperfusion but also postoperative cerebral hyperperfusion may be associated with long-term cognitive decline that can be detectable without structural signs of damage in MR imaging and be persistent over a half-year follow-up [474, 475]. Overall, the long-term course and significance of the postoperative cognitive decline is undetermined.

Since the advent of carotid endarterectomy as an established treatment method, many subjects having had carotid surgery have themselves reported subsequent cognitive improvement, which has probably been readily explained by improved cerebral circulation after revascularization. However, the results of the earlier studies attempting to objectively evaluate the neuropsychological effects of the carotid surgery and the improvement of perfusion have reported highly controversial results, the early studies tending to report improvement, the recent ones being more neutral or reporting decline [15, 476]. The variance of results has been partly explained by methodological problems, e.g. lack of controls, insufficient control of confounding factors such as learning or practice effect, heterogeneity of samples, as well as natural recovery from the index event, and finally, the number of patients in most of these studies has been limited. Laterality of cerebral functions also brings about variation [108]. Furthermore, it is possible that the proneness of asymptomatic and symptomatic populations to cognitive change is different. The earlier studies rarely correlated their findings to other functional methods such as imaging. Even in a study reporting postoperative cognitive improvement and cerebral circulation, the finding could not be attributed to increased cerebral blood flow [477]. Judging by the data available at the time, a systematic review concluded a decade ago that although majority of the studies reported a postoperative cognitive improvement, no conclusion can be drawn on the effect of CEA on cognition because of the methodological issues [15]. A recent systematic review found few studies published after 1990 showing any clear improvement in cognition after CEA, and ended up with the same conclusion that no substantial effect on cognition can be elicited, although most studies are still underpowered with a high risk of false negative results [476]. Yet, two small studies utilizing functional imaging (SPECT) and a moderate-sized study with TCD diagnostics, all with limited cognitive examination batteries, suggest the existence of a haemodynamically compromised subpopulation that could benefit from CEA in terms of cognition [478-480].

3. AIMS OF THE STUDY

The purpose of this study was to combine new MR methodology to find out whether a high-grade carotid stenosis, clinically symptomatic or asymptomatic, and surgical treatment of such a stenosis are associated with changes in brain microcirculation and diffusion, and whether the changes are associated with the neuropsychological performance of the patients.

The aims can be divided in four sections:

I to evaluate brain diffusion with MRI in asymptomatic and symptomatic patients with carotid occlusive disease before and after endarterectomy, and to compare the results with those of healthy controls [paper I]

II to evaluate cerebral perfusion and vasoreactivity in patients with carotid occlusive disease before and after endarterectomy, and to determine if the responses differ in symptomatic and asymptomatic patients, using MRI and transcranial Doppler ultrasound (TCD) [paper II]

III to evaluate cognitive functions in patients with carotid occlusive disease and compare their performance with that of healthy controls; to evaluate the cognitive change after endarterectomy and analyze whether the change is associated with cerebral perfusion or diffusion findings or whether the change is different in asymptomatic and symptomatic subgroups [paper III]

IV to find out if some parameters of blood coagulation, fibrinolysis and haemorheology differ between asymptomatic and symptomatic patients with a high-grade stenosis [paper IV]

4. SUBJECTS AND METHODS

4.1 Subjects

The study protocols for the Helsinki Carotid Endarterectomy Study (HeCES) were approved by the Ethics Committee of the Departments of Neurology and were carried out according to the principles of the Declaration of Helsinki and the institutional guidelines. We recruited 92 consecutive consenting patients fulfilling the inclusion criteria who had been referred to the neurological or the surgical department of our university teaching hospital for treatment of their high-grade carotid stenoses. Six patients had both carotid arteries operated in the study, making the total number of endarterectomies 98. The subjects had to be independent in daily life (modified Rankin scale $\leq$ 2), without potential cardiogenic origin of emboli, with no history of previous ipsilateral carotid endarterectomy (CEA) or radiotherapy, and with a surgically accessible carotid stenosis measured 70 % or more in digital subtraction angiography according to NASCET criteria [426]. After giving their written informed consent, they underwent a thorough clinical examination and detailed interview by a stroke neurologist for classification and assessment of risk factor profile (Table 1).

The total study population was used for the laboratory analyses in the study IV. Apart from the neurological symptoms and the female predominance in the asymptomatic group, demographics of the two groups did not differ (Table 1). On the whole, 74 had had cerebral symptoms: 54 had had a recent minor hemispheric stroke, TIA or amaurosis fugax in the territory of the stenotic artery (median 41 days, interquartile range 22-80 days), whereas in 20 cases the symptoms were attributed to another cerebral territory, rendering the operated plaque asymptomatic (median 106 days, interquartile range 59-198). The remaining 18 patients were totally free of cerebrovascular symptoms. In the symptomatic plaque group, 19 patients had an ongoing anticoagulant medication, and so had one patient in the 'other symptoms' group. The average time from symptoms to operation was 77 days (median 58) in the non-anticoagulated and 55 (median 38) in the anticoagulated patients. The data of the patients and their removed plaques were analyzed comparing both symptomatic vs. asymptomatic patients as well as plaques. Separate analyses were made for patients with and without anticoagulation and for patients on or off statin or ACE inhibitor treatment .

The populations of the substudies I-III were limited by the availability of scanning facility and the study neuropsychologist, or by the presence of a contraindication to imaging, as well as the patient's individual consent to participate in the substudies [481].

Table 1. Demographic and clinical profiles of asymptomatic and symptomatic subgroups in study IV (n = 92; means and 95 % confidence intervals for continuous variables).

	TOTALLY ASYMPTOMATIC (n=18)	SYMPTOMATIC, OTHER (n=20)	SYMPTOMATIC PLAQUE (n=54)
Gender: female/male (%)	10/8 (44%) *	7/13 (65 %)	15/39 (72 %)
Age (years)	65.0 (60.7-69.2)	65.0 (61.5-68.5)	64.4 (62.1-66.7)
Body Mass Index (kg/m^2)	26.5 (24.3-28.7)	26.1 (24.5-27.7)	27.8 (26.6-29.0)
Carotid stenosis (%, NASCET)	76.3 (72.7-79.9)	76.7 (73.4-80.1)	78.7 (76.2-81.2)
Coronary heart disease	8 (44 %)	9 (45 %)	17 (31.5 %)
Peripheral arterial disease	5 (28 %)	8 (40 %)	15 (28 %)
Arterial hypertension	11 (61 %)	13 (65 %)	38 (70 %)
Diabetes mellitus	4 (22 %)	6 (30 %)	13 (24 %)
Dyslipidemia	9 (50 %)	16 (20 %)	32 (59 %)
Smoking			
Current	4 (22 %)	7 (35 %)	17 (31 %)
Former	10 (56 %)	10 (50 %)	27 (50 %)
Stroke	-	13 (65 %)	26 (48 %)
Preoperative TIA	-	13 (65 %)	28 (52 %)
Statin use	7 (39 %)	10 (50 %)	22 (41 %)
ACE inhibitors	2 (11 %)	6 (30 %)	12 (22 %)
Antiplatelet agents	15 (83 %)	16 (80 %)	32 (59 %)
Anticoagulation	1 (5.6 %)	3 (15 %)	21 (39 %)
Time since symptoms (days)	-	158 (75-240)	55 (42-67)

(* $p < 0.05$, χ^2 test)

4.2 Controls

Two sets of control populations were selected. For the study I, the age- and sex-matched controls (n = 45, mean age 61.9 ± 10.8, range 42-85 years) were chosen from a strictly healthy population. They had to fulfill the following criteria: no symptom, sign or history of any neurological disease or a systemic disease with a potential brain involvement; no family history of dementia or multiple sclerosis; no regular medication except for hormonal substitution or topical therapies, and no history of excessive alcohol intake over longer periods. All subjects were white and Finnish in origin. They underwent scanning in an MR imaging study of healthy humans with normal scanning results and no sign of carotid stenosis [173, 482].

A control population was chosen also for serial neuropsychological assessment, and their results were used as reference values in the study III. The group consisted of strictly healthy volunteers who were recruited by word of mouth. Half of them were a part of the aforementioned larger control population set undergoing MR imaging. The control persons were selected by age, sex, education, and social class. After sorting the patients by the respective criteria, we selected a matching control person for every second surgical patient, ending up with 22 control persons. Controls were matched for age (± 5 years), sex, and education and/or social class classified with three-category scales [483] (Table 2).

Table 2 . Clinical profiles of the patients and controls at baseline (± SD) in Study III.

	Patients	Controls
Age	65.3 (± 8.4)	67.0 (± 8.9)
Body mass index	26.4 (± 4.2)	25.5 (± 4.2)
Cerebrovascular events		
Stroke	7 (16 %)	0
TIA	14 (33 %)	0
None	23 (51 %)	22 (100 %)
Gender (female/male)	16/28	9/13
Education (years)	9.6 (± 3.2)	10.2 (± 4.8)
Higher	5 (11 %)	4 (18 %)
Secondary	16 (36 %)	8 (36 %)
Basic	23 (52 %)	10 (45 %)
Social class		
Non-manual	12 (27 %)	6 (27 %)
Skilled manual	20 (46 %)	11 (50 %)
Unskilled manual	12 (27 %)	5 (23 %)
Arterial hypertension	16 (70 %)	0
Coronary heart disease	9 (39 %)	0
Diabetes	8 (35 %)	0
Peripheral arterial disease	7 (30 %)	0

4.3 Methods

4.3.1 Imaging techniques

MRI

All MR images were acquired on a Siemens Magnetom Vision whole-body clinical scanner (Siemens Medical Systems) operating at 1.5 Tesla, with a standard head coil. All imaging studies were completed without complications. The first imaging (n = 45) was performed in the evening on the day before surgery, and the scanning was repeated 3 days (postoperative) (n = 42) and 100 days (chronic) (n = 37) after CEA. Control subjects (n = 45) for the diffusion MR study were imaged once. No adverse effects occurred during the scanning procedure.

DWI was performed with a spin-echo echo-planar imaging sequence having a repetition time of 4000 ms, an echo time of 103 ms, and a gradient strength of 25 mT/m covering 19 five-mm-thick slices (interslice gap 1.5 mm, field of view 230 x 230 mm^2, and matrix size 96*128 interpolated to 256*256). Diffusion was measured in three orthogonal directions (x, y, and z) with 2 b-values (b = 0 and b = 1000 s/mm^2).

In addition to axial DSC-MRI, conventional T2- and proton-density-weighted images were obtained. The first imaging was performed in the evening on the preoperative day, and it was repeated 3 days and 100 days after CEA.

DSC-MRI was performed with a gradient-echo echo-planar imaging sequence with a repetition time of 1.2 ms, an echo time of 42.1 ms, flip angle 90°, and a gradient strength of 25 mT/m covering five 5-mm-thick slices (interslice gap 1.5 mm, field of view 230 x 230 mm^2, and matrix size 128*128). The centermost slice was leveled with corpus callosum and anatomical landmarks to keep the slicing constant. The slices were imaged one per second a total of 60 times. After collection of 7 baseline images, gadopentetate dimeglumine (GD-DTPA, Magnevist, Schering AG, 0.15 mmol/kg) was injected into the antecubital vein via an 18-gauge catheter at a speed of 5 mL/s using an MR compatible power injector (Spectris, Medrad), followed by a 10 mL flush of saline. The DSC-MRI data was analyzed as described in detail previously [484].

Transcranial Doppler ultrasound

For the transcranial Doppler ultrasound the patient was examined in supine position in a quiet room. The recordings were made from ipsilateral MCA through the transtemporal window. A commercially available equipment (Nicolet EME Pioneer TC 4040) was used, and the 2-MHz pulsed-wave transducer was held in position by an external device. The baseline assessment was done within a few hours before surgery, and the postoperative one prior to the second MR imaging three days after surgery. Cerebral vasomotor reactivity was determined ipsilaterally by means of a breath-holding index as described previously, as well as Gosling's pulsatility index (p. 24). Microembolic signals were recorded by insonating middle cerebral artery at 50 mm depth. The audible Doppler shift and transformed spectra were monitored on-line for 45-60 minutes. High-intensity transients that fulfilled the criteria of international recommendations were interpreted as microembolism (MES): short unidirectional signals occurring within the blood flow spectrum together with the characteristic sound without association to any potentially artefactual event [485].

4.3.2 Imaging data analyses

In each hemisphere, 11 distinct neuroanatomical structures were selected for the analysis (normal-appearing frontal, parietal, temporal, and occipital grey and white matter, and the watershed regions between the territories of middle cerebral artery and anterior and posterior cerebral artery (Fig. 7). T2 images were used to identify the relevant anatomical structures. ROIs were subsequently drawn manually on the CBF maps and transferred to the equivalent maps of absolute CBV and MTT. For each ROI, the following parameters were recorded: the surface area (40-120 pixels), the mean, standard deviation (SD), and range of the given values. The ROIs were analyzed blindedly with a commercially available image analysis software (Alice, Hayden Image Processing Group, Perceptive Systems Inc.).

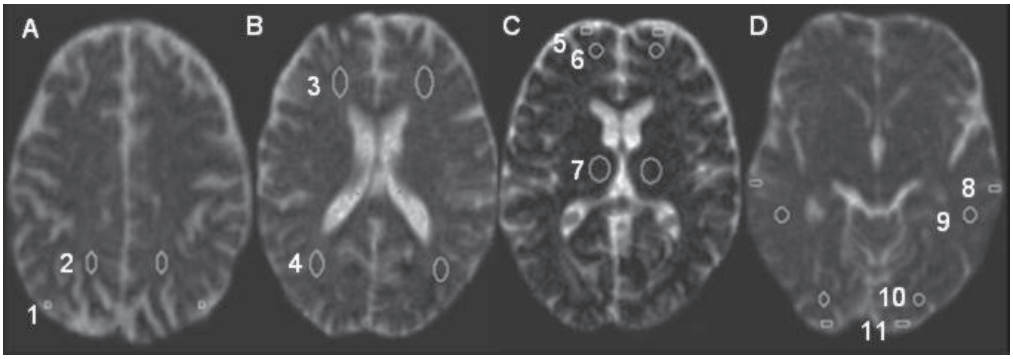


Figure 7. All regions of interest superimposed on average apparent diffusion coefficient maps.

A) the parietal grey (1) and white matter (2), **B**) the anterior watershed (3) and posterior watershed region (4), **C**) the frontal grey (5) and white matter (6), the thalamus (7), **D**) the temporal grey (8) and white matter (9), the occipital grey (10) and white matter (11).

Two observers independently and blindedly evaluated the baseline and postoperative MTT maps for presence of a perfusion deficit (Figure 8). Digital subtraction angiographies were analyzed by NASCET criteria by one experienced neuroradiologist (O.S.) blinded to the clinical data [426].

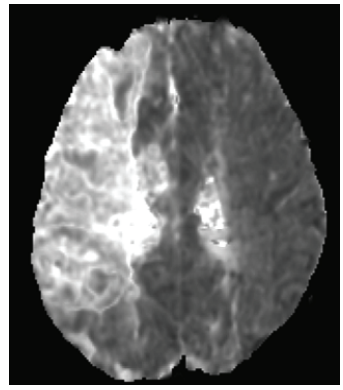


Figure 8. Large perfusion deficit on MTT map

4.3.3 Neuropsychological assessment

The cognitive assessment was done on the day before CEA, 4 days after the operation (5.0 days after baseline), and at approximately 100 days (mean 102), in the same quiet room at approximately the same daytime, by either of two certified neuropsychologists. The control population was examined thrice with the same timing. The same examiner was used for repeated evaluations, and all controls were examined by the same examiner at all stages. The comprehensive neuropsychological test battery was completed in the same order, using parallel forms of tests in a randomly crossed fashion when applicable.

The test battery was designed using validated tests [486]. Language domain was assessed by The Boston Naming Test (BNT) as naming and recognition of common objects (60), and Word fluency with the letter and category naming with one-minute generation of words by a letter (WF-L) or by a category (WF-C). Verbal memory and learning were evaluated by Auditory Verbal Learning Test with 5 trials to learn 10-word lists, scoring both sum score of trials (AVLT-SUM) and delayed memory recall (AVLT-D) and immediate verbal memory with WAIS-R Digit Span forwards and backwards (W-VESP). Visual memory and learning by Rey Visual Learning Test scoring the sum of five trials as well as delayed recall (RVLT-SUM, RVLT-D), and immediate visual memory was evaluated with Corsi Blocks visual span forwards and backwards (CB-VISP). Motor dexterity was evaluated with Purdue Pegboard, scoring performance of the hand contralateral to the stenosis (PP-CONTRA). Attention was assessed with Letter Cancellation Task (LCT) and Trail Making A (TMA). Executive functions were assessed with The Trail Making and Stroop tests, making use of the differences of performance times in Trail Making A and B (TMB-TMA) as well as the word and colour naming in Stroop test (STROOP-INT) divided by the time spent on the first task. Mood was evaluated with Beck Depression Inventory.

The distributions of the raw scores were studied, and logarithmic transformation was applied to BNT and TMB-TMA, and square root transformation to STROOP-INT. The individual raw scores were standardized into Z scores using the controls' baseline performance as the norm for the mean and standard deviations, and inverted for the time-based tasks for the increase of score to consistently indicate improvement of performance and decrease worsening. Domain scores were derived as average Z scores of the subtests. Compound cognitive score (CCS) was calculated by summing up the individual z scores and dividing by the standard deviation (SD) of summed scores. Cognitive change scores were calculated by subtracting the baseline scores from the timely score, and then by subtracting the average learning effect of controls from this result and by dividing the result by the SD of the control group [487, 488]. A worsening of more than one standard deviation of CCS was considered dysfunctional.

4.3.4 Laboratory analysis

Free flowing blood samples were collected from antecubital vein closely prior to operation at 8-10 a.m. into polypropylene and siliconized glass tubes for determination of fibrinogen (Clauss), thrombin-antithrombin complex (ELISA, Behring), prothrombin fragments PF 1 and 2 (ELISA, Behring), tPA antigen (Biopool, TintELIZA) and activity (Biopool, chromogenic assay) and PAI-1 antigen (Biopool, TintELIZA) and activity (Biopool, one-stage chromogenic assay). D-dimer was determined by ELISA assay (Asserachrom® D-Di, Diagnostica Stago, Asnieres Sur Seine, France). Plasma was separated immediately, centrifuged and processed. Description of the procedure as well as plasma processing conditions and intra- and interindividual variabilities of our assays have been published previously [489]. Plasma total homocysteine was measured using a standard competitive immunoassay method (Immulite® 2000) from plasma sample stored at -70°C. Haemoglobin, hematocrit, and platelet count were obtained using an ordinary autoanalyzer. Serum cholesterol and triglycerides were assessed by immunochemical methods, and serum calcium photometrically. High-sensitivity CRP assays were made with a sandwich enzyme immunoassay (UC CRP ELISA, Eucardo Laboratory, San Diego, CA).

4.3.5 Carotid endarterectomy

All standard CEAs were performed by one experienced vascular surgeon (E.S.). The operator systematically recorded the morphology of the plaque at the operation denoting the general appearance: smooth vs. ulcerated plaque, presence and degree of calcification, loose atheroma, and intraplaque haemorrhage.

4.4 Statistical analyses

Distributions of the variables were studied with Shapiro-Wilk W test. Interhemispheric and regional variation as well as comparison between asymptomatic and symptomatic patient groups were studied with repeated-measures analysis of variance or covariance using symptomaticity as the between-subjects variable. The variance homogeneity was studied using Box M test and sphericity evaluated with Greenhouse-Geisser ε values [490]. Pairwise comparisons were made with Student's t test, correcting for multiple comparison. The χ^2 test or Fisher's exact test was applied to univariate dichotomous variables. Correlations were studied with Spearman's rank correlation. The values are given as means and 95%

confidence intervals or standard deviations. A two-tailed value of $p < 0.05$ was considered significant.

The levels of coagulation and fibrinolytic markers between the groups were compared with Mann Whitney U test and Kruskal-Wallis analysis of variance. χ^2 test was applied in case of frequencies of discrete variables. Analysis of covariance was used in comparison of hematocrit. Backward stepwise logistic regression was applied with a core set of the studied haematological variables with the status of symptomatic stenosis as the dependent variable. Hosmer and Lemeshow test was used in evaluation of goodness-of-fit. The values are given as medians and interquartile ranges or means and 95 % confidence intervals.

5. RESULTS

5.1 Changes in brain diffusion

All ADC_{av} values are given in $10^{-3}mm^2/s$. The ADC_{av} values of ipsilateral and contralateral hemispheres at different time points, in various regions of brain, and in different subgroups are presented in the Table 3 .

5.1.1 Patients with carotid stenosis

At baseline, ADC_{av} values of the WM and watershed regions in the lobes of the hemisphere ipsilateral to the CS were higher than those of the contralateral side ($p < 0.001$, two-way ANOVA). Such an asymmetry was not detected in GM ($p = 0.2$) or thalamus ($p = 0.8$) (Table 3). The surface area of regions with leukoaraiosis was larger in the ipsilateral than in the contralateral hemisphere ($p < 0.04$, Student's t test). The ADC_{av} values of these regions were not different between hemispheres (0.95 ± 0.12 vs. 0.95 ± 0.11, $p = 1.0$, Student's t test).

At the postoperative and chronic stages, the ipsilateral hemispheric WM and watershed regions had resumed lower ADC_{av} levels not significantly different from the contralateral hemisphere (postoperatively, WM: $p = 0.5$; watershed regions: $p = 0.9$; at the chronic stage, WM: $p = 0.5$, watershed regions: $p = 0.4$; ANOVA) (Table 3).

The lobar WM ADC_{av} values were consistently different from one another at the three stages in each hemisphere (Figure 9). At the preoperative stage, the frontal and occipital lobes displayed higher values than occipital and temporal ($p < 0.05$, Scheffé test). The symptomatic group did not differ from the asymptomatic in ADC_{av} values (Table 3). In the cognitively studied subpopulation (III), the ADC_{av} levels (10^{-3} mm^2/s) displayed the same pattern, being higher in the normal-appearing WM ipsilateral to the stenosis in comparison with the contralateral hemisphere (0.69 vs. 0.66, $p < 0.001$), decreasing in successive measurements (0.69 – 0.66 – 0.66) with abolition of the interhemispheric difference. In GM or basal ganglia, there was no difference in baseline ADC_{av} levels (0.91 vs. 0.90, $p = 0.22$ for GM; 0.77 vs. 0.77, $p = 0.80$, for basal ganglia). The levels decreased slightly in GM (0.91 - 0.89 - 0.90, $p = 0.03$) with no interhemispheric difference. Two patient scans revealed new DWI lesions compatible with a minor watershed stroke, and a haemorrhagic lesion probably caused by postoperative hyperperfusion.

Table 3. ADC_{av} values of the regions in the subgroups (values mean ± SD, 95 % confidence interval, unit 10^{-3} mm^2 s^{-1})

	SYMPTOMATIC (n = 22)	ASYMPTOMATIC (n = 23)
GREY MATTER		
Stenotic side		
Preoperative	0.92 ± 0.03 (0.90-0.93)	0.90 ± 0.03 (0.89-0.92)
Postoperative	0.90 ± 0.03 (0.89-0.91)	0.89 ± 0.03 (0.88-0.90)
Chronic	0.90 ± 0.03 (0.89-0.92)	0.89 ± 0.03 (0.88-0.91)
Contralateral side		
Preoperative	0.90 ± 0.03 (0.89-0.91)	0.90 ± 0.02 (0.87-0.90)
Postoperative	0.89 ± 0.03 (0.88-0.90)	0.88 ± 0.02 (0.87-0.90)
Chronic	0.90 ± 0.03 (0.89-0.91)	0.88 ± 0.02 (0.87-0.90)
Controls		0.90 ± 0.05 (0.88-0.91)
WHITE MATTER		
Stenotic side		
Preoperative	0.69 ± 0.04 (0.68-0.71)	0.69 ± 0.04 (0.67-0.71)
Postoperative	0.68 ± 0.04 (0.66-0.70)	0.67 ± 0.04 (0.65-0.69)
Chronic	0.67 ± 0.04 (0.65-0.69)	0.66 ± 0.03 (0.64-0.68)
Contralateral side		
Preoperative	0.65 ± 0.03 (0.63-0.76)	0.66 ± 0.04 (0.64-0.68)
Postoperative	0.67 ± 0.04 (0.65-0.68)	0.67 ± 0.04 (0.66-0.69)
Chronic	0.67 ± 0.04 (0.65-0.69)	0.67 ± 0.04 (0.65-0.69)
Controls		0.63 ± 0.02 (0.63-0.64)
WATERSHED REGIONS		
Stenotic side		
Preoperative	0.74 ± 0.05 (0.72-0.76)	0.73 ± 0.05 (0.71-0.75)
Postoperative	0.70 ± 0.06 (0.67-0.73)	0.70 ± 0.04 (0.68-0.72)
Chronic	0.70 ± 0.06 (0.67-0.73)	0.68 ± 0.04 (0.66-0.70)
Contralateral side		
Preoperative	0.70 ± 0.04 (0.69-0.72)	0.70 ± 0.05 (0.68-0.72)
Postoperative	0.69 ± 0.06 (0.67-0.72)	0.71 ± 0.06 (0.68-0.74)
Chronic	0.68 ± 0.06 (0.65-0.70)	0.71 ± 0.06 (0.68-0.74)
Controls		0.65 ± 0.04 (0.64-0.66)
THALAMUS		
Stenotic side		
Preoperative	0.77 ± 0.06 (0.74-0.79)	0.75 ± 0.06 (0.72-0.77)
Postoperative	0.78 ± 0.07 (0.75-0.81)	0.76 ± 0.06 (0.73-0.78)
Chronic	0.77 ± 0.06 (0.74-0.80)	0.74 ± 0.06 (0.71-0.77)
Contralateral side		
Preoperative	0.77 ± 0.06 (0.74-0.80)	0.76 ± 0.07 (0.73-0.79)
Postoperative	0.76 ± 0.06 (0.73-0.79)	0.75 ± 0.06 (0.72-0.78)
Chronic	0.78 ± 0.09 (0.73-0.82)	0.73 ± 0.05 (0.71-0.76)
Controls		0.74 ± 0.04 (0.73-0.75)

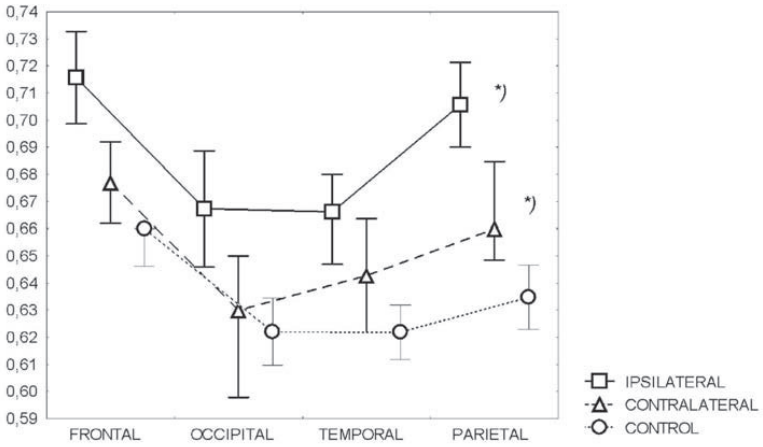


Figure 9. Lobular mean white matter average apparent diffusion coefficient (ADC_{av}) values (with 95% CI) of ipsilateral and contralateral sides compared with lobular white matter ADC_{av} values of healthy control subjects. *) p = 0.001 (two-way analysis of variance, main effect, in comparison with the control population).

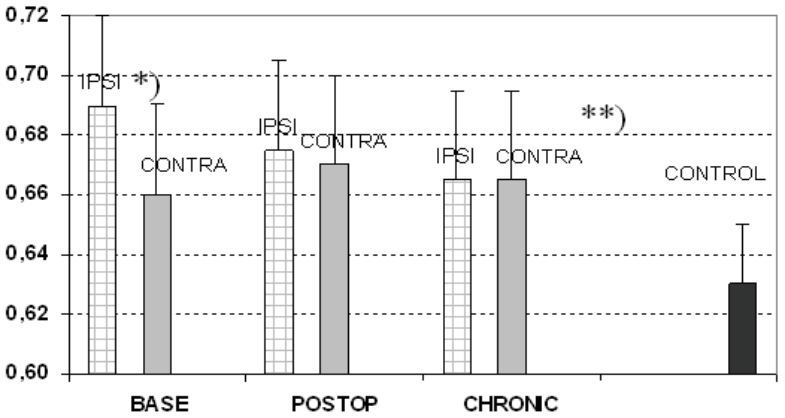
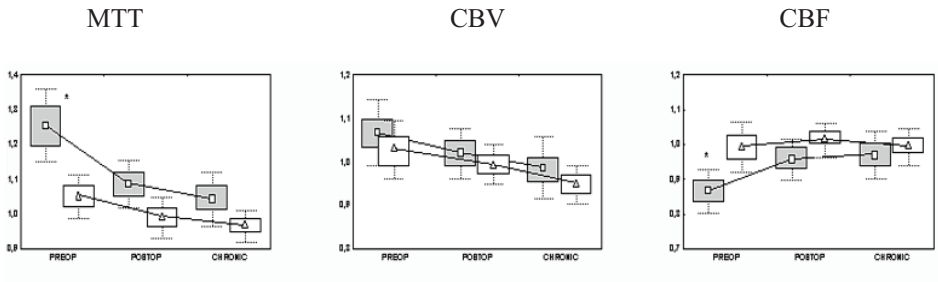
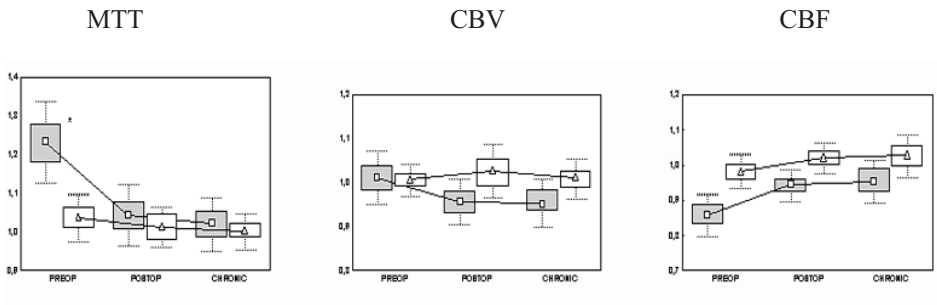


Figure 10. ADC_{av} levels (+ 95% CI) in white matter at the three stages in comparison with values of healthy population. IPSI = ipsilateral hemisphere; CONTRA = contralateral hemisphere; CONTROL = healthy population; BASE = baseline, preoperative stage; POSTOP = postoperative stage; CHRONIC = chronic stage.
*) $p < 0.001$ (paired t test), **) $p < 0.01$, two-way repeated measures ANOVA

Watershed regions:



White matter:



Grey matter:

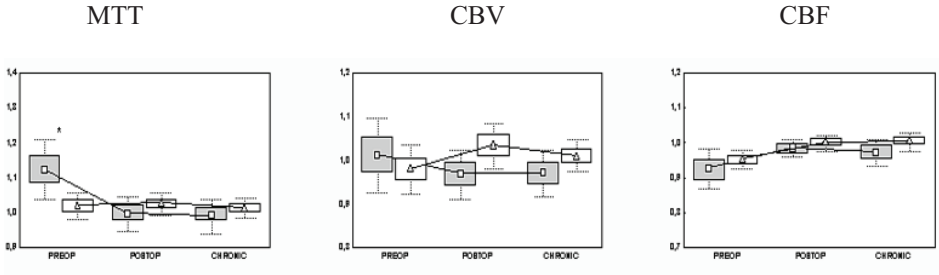


Figure 11. Interhemispheric ratios for perfusion parameters in asymptomatic (open box) and symptomatic (hatched box) patients (box: SEM; whiskers: 95% CI). *$P < 0.05$, repeated-measures ANOVA.
MTT = mean transit time; CBV = cerebral blood volume; and CBF = cerebral blood flow

5.1.2 Patients vs. controls

Preoperative ADC_{av} values in WM and watershed regions ipsilateral as well as contralateral to CS were significantly higher in patients than in the control population ($p < 0.001$, two-way ANOVA), whereas no difference was detected in GM or thalamic level. Despite the higher ADC_{av} level, the relative lobar differences in the WM of patients were identical to those in controls (Figure 9). Anterior watershed regions had higher ADC_{av} values than posterior, on ipsilateral side (0.76 ± 0.05 vs. 0.71 ± 0.07; $p < 0.001$, one-way ANOVA), as well as on contralateral side (0.73 ± 0.05 vs. 0.67 ± 0.06; $p < 0.001$, one-way ANOVA), and in controls (0.66 ± 0.04 vs. 0.64 ± 0.04; $p < 0.01$, one-way ANOVA). In the course of time at the postoperative stage, the ADC_{av} values had undergone a considerable decrease but remained significantly higher among patients than in controls for ipsilateral and contralateral WM and watershed regions ($p < 0.001$, two-way ANOVA) (Figure 10).

5.2 Changes in brain perfusion

5.2.1 Interhemispheric, within-group differences

In the symptomatic CS group, the preoperative ipsilateral hemispheric MTT values were intraindividually higher than contralateral in WM and watershed regions ($p < 0.001$ for each, paired t-test), and marginally in GM ($p = 0.05$, paired t-test), but not in the asymptomatic group (Table 4). Correspondingly, the preoperative ipsilateral CBF values were lower in WM and watershed regions ($p < 0.001$ for each), and marginally in GM ($p = 0.05$, paired t-test) in the symptomatic group only. There were no differences in the asymptomatic CS group, notwithstanding the preoperative CBF values in GM, where the ipsilateral value was lower also in the asymptomatic group ($p < 0.05$). In CBV values, there were no significant interhemispheric differences in either group at any stage (Fig. 11). The evolution of the interhemispheric ratios is depicted in Figure 11, showing the abolition of interhemispheric asymmetry by CEA and the significance of group × time interaction. In watershed regions, there was no difference between the anterior and posterior territories.

Table 4. Quantitative perfusion parameters at different timepoints with 95% confidence intervals (preop: baseline, postop: 3 days after CEA; chronic: ≥ 3 months after CEA). P value is for two-way analysis of variance (group × time)

MTT (s)	IPSILATERAL			CONTRALATERAL		
	symptomatic	asymptomatic	P	symptomatic	asymptomatic	P
GREY MATTER						
preop	4.8 (4.3-5-3)	4.3 (3.6-5.0)		4.2 (3.8-4.7)	4.1 (3.5-4.7)	
postop	4.4 (4.0-4.8)	3.9 (3.4-4.4)		4.4 (4.0-4.8)	3.8 (3.3-4.2)	
chronic	4.0 (3.6-4.4)	4.3 (3.8-4.8)	***0.05***	3.9 (3.6-4.2)	4.3 (3.7-4.8)	***0.04***
WHITE MATTER						
preop	6.5 (5.7-7.2)	5.6 (4.9-6.2)		5.1 (4.6-5.5)	5.3 (4.6-5.9)	
postop	5.5 (4.9-6.1)	4.5 (4.0-5.0)		5.0 (4.6-5.5)	4.4 (3.9-4.8)	
chronic	4.8 (4.3-5.3)	5.2 (4.7-5.8)	***<0.001***	4.6 (4.2-4.9)	5.2 (4.7-5.8)	***0.004***
WATERSHED						
preop	6.7 (5.9-7.4)	5.4 (4.8-6.1)		5.2 (4.7-5.7)	5.1 (4.5-5.6)	
postop	5.6 (5.0-6.2)	4.5 (4.1-4.9)		5.0 (4.6-5.4)	4.4 (4.0-4.8)	
chronic	5.0 (4.5-5.5)	5.0 (4.5-5.5)	***0.02***	4.6 (4.2-4.9)	5.2 (4.7-5.8)	***0.01***

CBV (mL/100 g)	IPSILATERAL			CONTRALATERAL		
	symptomatic	asymptomatic	P	symptomatic	asymptomatic	P
GREY MATTER						
preop	4.6 (4.1-5-1)	4.6 (4.0-5.2)		4.6 (4.1-5.1)	4.6 (4.1-5.1)	
postop	4.7 (4.4-5.1)	4.5 (4.0-5.0)		5.0 (4.6-5.3)	4.3 (3.9-4.7)	
chronic	4.3 (3.8-4.8)	4.6 (4.2-5.0)	***0.37***	4.3 (3.9-4.6)	4.6 (4.2-5.1)	***0.03***
WHITE MATTER						
preop	1.9 (1.6-2.1)	1.9 (1.6-2.2)		1.8 (1.6-2.0)	1.9 (1.6-2.1)	
postop	1.8 (1.5-2.1)	1.7 (1.5-1.9)		1.8 (1.5-2.1)	1.6 (1.4-1.8)	
chronic	1.6 (1.4-1.8)	1.7 (1.5-2.0)	***0.60***	1.7 (1.4-1.9)	1.7 (1.5-2.0)	***0.41***
WATERSHED						
preop	1.9 (1.6-2.2)	2.0 (1.8-2.3)		1.9 (1.6-2.1)	2.0 (1.7-2.3)	
postop	1.8 (1.5-2.1)	1.8 (1.6-2.1)		1.8 (1.5-2.0)	1.8 (1.6-2.1)	
chronic	1.7 (1.4-1.9)	1.8 (1.5-2.0)	***0.99***	1.7 (1.4-2.0)	1.8 (1.6-2.1)	***0.99***

5.2.2 Between-groups differences

The longer ipsilateral MTT in symptomatic CS patients before CEA, most pronounced in watershed regions and WM, improved in subsequent measurements, whereas in the asymptomatic group the improvement was marginal or transient (Table 4). In CBF, there was a trend for slightly lower preoperative values in the symptomatic group, and CBV levels remained essentially homogeneous. None of the parameters showed significant groupwise differences after correction for multiple comparison. The p values in the study of the two-way interaction (group × time) for each hemisphere are shown in the table 4. Results of between-group analyses were not altered by having blood viscosity or degree of stenosis as covariates.

Altogether 14 patients had a visible perfusion deficit in the ipsilateral carotid territory, with a perfect interobserver agreement ($\kappa = 1.0$). Of the patients with a visualized hypoperfusion, 12 were in the symptomatic group ($p = 0.003$, Fisher's test). In the population with a visualized deficit, the mean MTT values for ipsilateral GM was 5.5 s (4.9 - 6.2 s, 95% CI), for WM 7.5 (6.7 - 8.3 s), and watershed regions 7.2 (6.2 - 8.2) s. The respective values for the subpopulation without a deficit were 4.1 s (3.7 - 4.6 s ; $p = 0.001$), 5.4 s (4.9 - 6.0 s; $p < 0.0001$), and 5.5 s (5.0 - 6.1 s; $p = 0.002$, t test). The interhemispheric MTT ratio was in visually hypoperfused subjects 1.28 (1.13 - 1.42) for GM, 1.46 (1.32 - 1.60) for WM, and 1.39 (1.21 -1.56) for watershed regions. In subjects without deficit, the respective values were 1.02 (0.98 - 1.06) s, 1.06 (1.01 - 1.11) s, and 1.09 (1.04 - 1.15) ($p < 0.0001$ for all comparisons, t test). The patients with a visible deficit represented higher grades of stenosis [85% (81 - 90%) vs. 76% (73 - 79%), $p = 0.001$, t test]. The lowest degree of stenosis with a visually detected perfusion deficit was 71 % (2 subjects). In the postoperative maps, no hypoperfusion was seen.

In the subpopulation undergoing cognitive studies, the preoperative MTT values were higher in the WM (6.0 s vs. 5.2, $p < 0.001$, t test) as well as in the GM (4.5 s vs. 4.2, $p < 0.01$, t test) ipsilateral to the stenosis. The difference was more pronounced in the symptomatic group, in which the WM MTT was longer than in the asymptomatic group (6.6 vs. 5.4, $p = 0.02$, t test). After CEA, the MTT shortened with disappearance of the within-subject interhemispheric difference ($p < 0.02$, ANOVA). In the cognitive substudy, there were 10 patients with a visible perfusion deficit in the ipsilateral carotid territory in MTT map, and 8 of these were symptomatic ($p < 0.01$, Fisher's test). The observed deficits covered the arterial territory of the MCA (in two patients also ACA).

The ipsilateral PI was initially significantly lower in the symptomatic subjects, undergoing a similar pattern of improvement with no significant postoperative difference (Figure 12). The change in PI after CEA correlated with the improvement of the interhemispheric ratios of perfusion parameters. The association was significant for all parameters in WM (MTT, R = -0.64, p < 0.0001; CBF, R = 0.42, p = 0.01; CBV, R = -0.46, p = 0.006) and for two parameters in watershed regions (MTT, R = -0.55, p = < 0.001; CBF, R = 0.46, p < 0.01; CBV, R = -0.10, p = 0.59), but not in GM (highest in MTT, R = -0.29, p = 0.09, Spearman rank correlation).

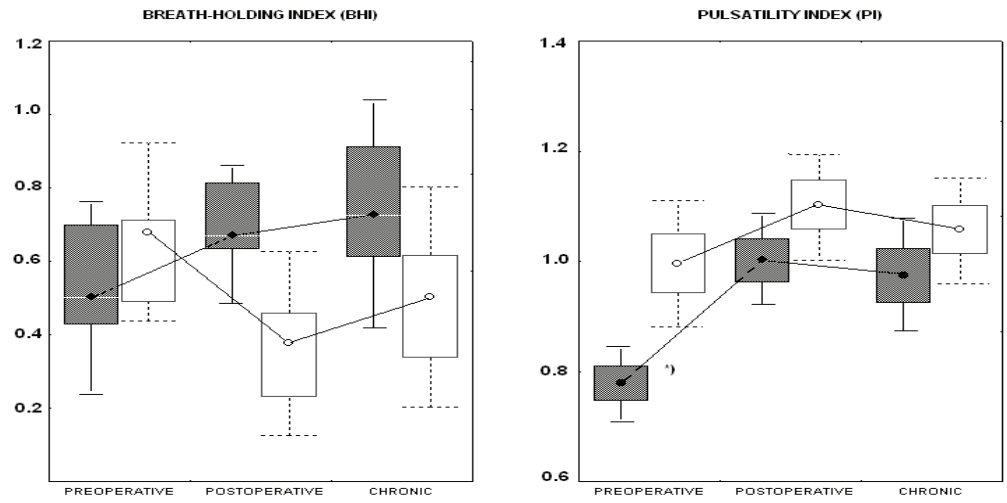


Figure 12. Ipsilateral findings on TCD measurement in asymptomatic (open box) and symptomatic (hatched box) patients (box: standard error of mean; whiskers: 95% confidence interval).
*) $P < 0.05$, t test.

The breath-holding index was comparable in the two groups at baseline, but only the symptomatic group improved postoperatively (group × time interaction, p = 0.02, ANOVA) (Figure 12). The postoperative change in BHI was associated with improvement in interhemispheric ratios in MTT (WM, R = -0.53, p = 0.001; watershed regions, R = -0.34, p = 0.04, GM, R = -0.34, p = 0.04), and in CBV, for WM (WM, R = -0.48, p < 0.005). Improvement of CBF was positively associated with change in BHI only in watershed regions (R = .46, p < 0.01).

5.3. Cognitive changes

The baseline cognitive performance tended to be lower in patients in most domains, with no difference between asymptomatic and symptomatic groups (Table 5). The overall cognition was lower in subjects with higher degrees of leukoaraiosis as measured by both periventricular and disseminated WM hyperintensities ($p = 0.02$, group effect, repeated-measures ANOVA). However, the degree of leukoaraiosis did not affect the cognitive change scores, and in repeated-measures ANOVA, there was no significant difference in the overall course (time × domain × dichotomized WMH effect). The patients were slightly more depressed than controls at all stages (average Beck scores 4.6 -4.8 vs. 1.6-2.2, $p = 0.01$).

Table 5. Neuropsychological performance of the patients in SD units at baseline (controls = 0.00).

		symptomatic	asymptomatic	P	P (controls)
Language		**-0.17**	**-0.29**	**.58**	**.24**
	WF-L	-0.44	-0.71	.37	.03*
	WF-C	0.04	-0.03	.83	.98
	BNT	-0.10	-0.12	.92	.66
Verbal memory		**-0.39**	**-0.46**	**.81**	**.07**
	AVLT-SUM	-0.61	-0.63	.97	.07
	AVLT-D	0.02	-0.24	.38	.68
	W-VESP	-0.57	-0.49	.78	.03*
Visual memory		**-0.45**	**-0.51**	**.86**	**.07**
	RVLT-SUM	-0.43	-0.45	.94	.12
	RVLT-D	-0.35	-0.52	.68	.18
	CB-VISP	-0.56	-0.55	.90	.03*
Motor dexterity	PP-CONTRA	**-0.32**	**-0.67**	**.28**	**.08**
Attention		**-0.33**	**-0.55**	**.59**	**.16**
	LCT	-0.57	-0.75	.76	.14
	TMA	-0.28	-0.49	.60	.24
Executive functions		**-0.66**	**-0.55**	**.82**	**.10**
	TMB-TMA	-0.77	-0.31	.45	.21
	STROOP-INT	-0.13	-0.07	.87	.75
Compound cognitive score (CCS)		**-0.70**	**-0.92**	**.64**	**.02***

BNT=Boston Naming Test; WF-L= Word Fluency, Letter; WF-C=Word Fluency, Category; RVLT-SUM = Rey Visual Learning Test, sum of attempts; RVLT-D= Rey Visual Learning Test, Delayed Recall; AVLT-SUM= Auditory Verbal Learning Test, Sum of attempts; AVLT-D= Auditory Verbal Learning Test, Delayed recall; CB-VISP= Corsi Blocks, Visual Span; W-VESP= WAIS Verbal Digit Span; WR-SIMIL= WAIS-R Similarities, Incidental learning; PP-SUM= Purdue Pegboard, sum of hand scores; LCT= Letter Cancellation Test; TMB-TMA= difference of Trail Making A and Trail Making B time; STROOP-INT= Stroop Interference, difference of colours/words time; CCS= Compound Cognitive Score

P: P value for comparison of performance of asymptomatic and symptomatic patients (uncorrected)
P (controls) : P value for comparison of patients vs. controls (uncorrected)

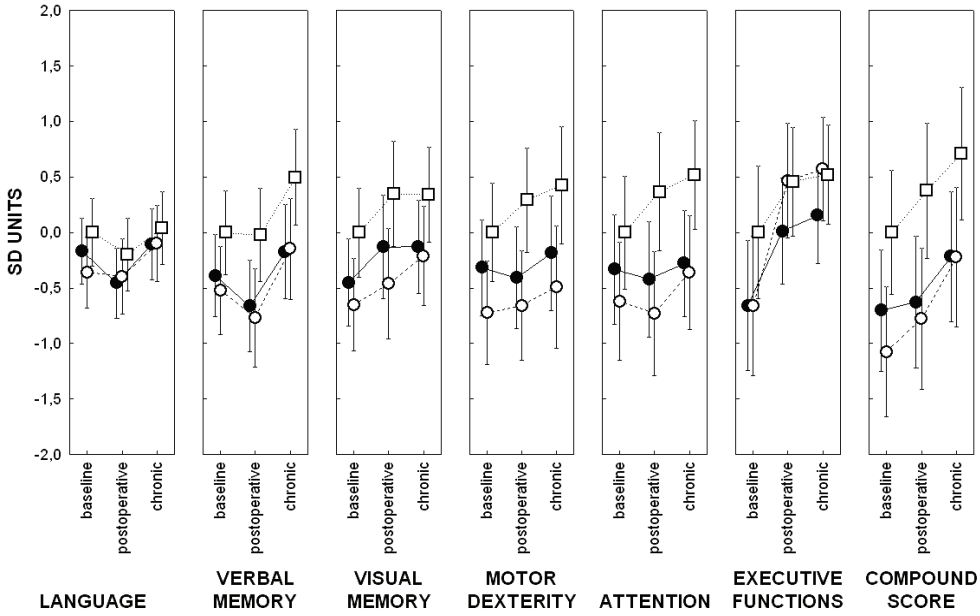


Figure 13. Groupwise cognitive scores at the three timepoints [controls vs. patients, $p < .01$ for group effect, repeated-measures ANOVA]. ○ asymptomatic stenosis; ● symptomatic stenosis; □ controls.

The overall cognitive performance (compound cognitive score) improved equally in controls and in patients ($p = 0.44$, repeated-measures ANOVA, times × group effect) (Figure 13). In univariate analysis, the standardized change score was 0.16 SD lower in patients at the postoperative stage ($p = 0.53$), and 0.04 SD lower at the chronic stage ($p = 0.91$). The cognitive change scores did not correlate with the ADC or MTT changes at postoperative stage, but a weak inverse correlation to MTT was seen at the chronic stage (for GM, $R = -0.35$, $p = 0.03$; for WM, $R = -0.34$, $p = 0.04$), the best domain being executive functions ($R = -0.43$, $p < 0.01$). Patients with a visible perfusion deficit at baseline tended to improve more in successive assessments ($p < 0.04$, repeated measures ANOVA) (Figure 14). Controlling for age or mood did not alter the findings. Correspondingly, in univariate analysis the cognitive change score of patients with an initial perfusion deficit was higher (postoperatively + 0.43 SD vs. + 0.10 SD, $p = 0.11$; at the chronic stage + 1.13 SD vs. + 0.48 SD, $p = 0.01$). The improvement was marked in the domain of executive functions (postoperative + 1.46 vs + 0.70, $p = .08$; chronic + 1.81 vs + 0.74, $p = 0.04$), and a trend was seen in visual memory and language.

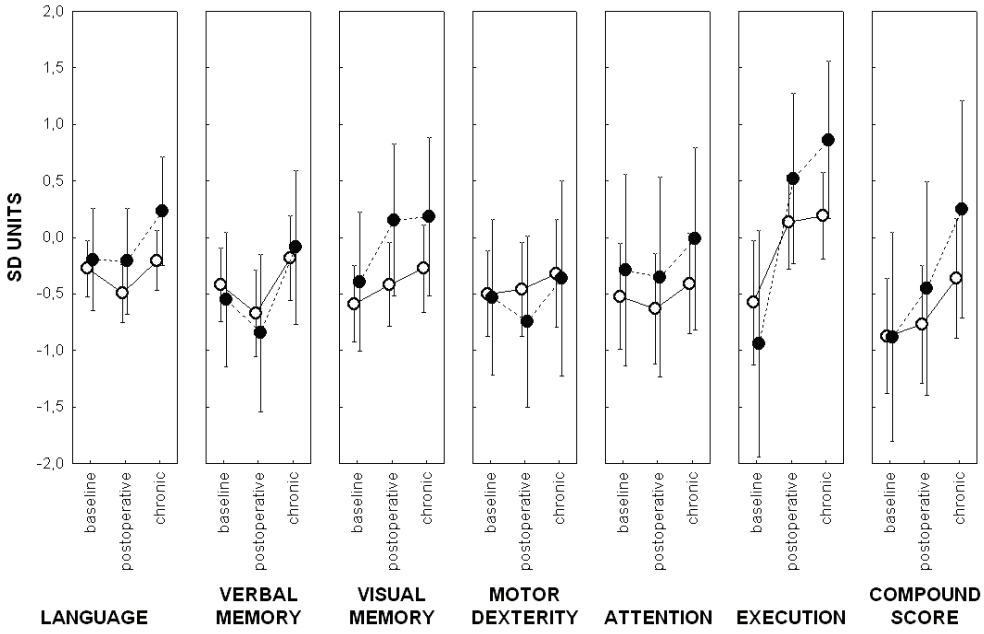


Figure 14. Cognitive scores in patients with a baseline perfusion deficit vs. patients without a visible deficit ($p < 0.05$, time × group interaction, repeated-measures ANOVA) ● initial perfusion deficit; ○ no perfusion deficit. [$p < 0.01$ for group effect, repeated-measures ANOVA].

On an individual level, there were 9 patients with a postoperative impairment of the compound cognitive score of one SD or more, and one patient with that of 2 SD. In the control group, 4 subjects had a total performance impaired by 1 SD or more, and none over 2 SD. At the chronic stage, 5 patients were impaired by 1 SD, one of these as a result of a sizable frontal haemorrhage and one because of another unrelated emergent disease, and in the control group, none were impaired by 1 SD. The most sensitive domains to postoperative impairment were attention, motor dexterity, and verbal memory. In attentional tasks, 21 patients (48 %) vs. 4 control persons (18 %) had an impairment over 1 SD ($p = 0.03$), the only difference reaching statistical significance, and in two patients the impairment exceeded 2 SD. In motor dexterity, 14 patients and 4 control persons had a postoperative impairment over 1 SD ($p = 0.38$), exceeding 2 SD in one patient. Notably, the two patients with new DWI lesions at the postoperative imaging showed no cognitive decline.

5.4 Change in blood coagulation, fibrinolysis, and haemorheology

5.4.1 General clinical and coagulation and fibrinolysis-associated variables

The demography and risk factor profiles of the groups are given in Table 1 (p. 52), and the general laboratory and blood count variables in Table 6. Age was positively correlated to D-dimer ($R = 0.32$, $p < 0.01$), plasma homocysteine ($R = 0.29$, $p < 0.01$), erythrocyte sedimentation rate ($R = 0.28$, $p < 0.01$), fibrinogen ($R = 0.22$, $p = 0.04$), and tPA activity ($R = 0.24$, $p = 0.02$). Body mass index correlated strongly with PAI-1 antigen ($R = 0.60$, $p < 0.001$), PAI-1 activity ($R = 0.59$, $p < 0.001$), and tPA antigen ($R = 0.50$, $p < 0.001$), and inversely with tPA activity ($R = -0.59$, $p < 0.001$). Smoking habits were unrelated to coagulation and fibrinolysis-associated variables, and so was the type of the vascular event (stroke or transient ischemic attack). An estimate for viscosity, calculated from its principal determinants was higher in the symptomatic patients (Table 6) [319]. Median high-sensitivity CRP levels were not different between the asymptomatic, symptomatic, and the symptomatic plaque groups (3.8 mg/L, 5.4 mg/L, 3.7 mg/L, $p = 0.34$).

Table 6. Laboratory variables and microembolic signals (MES) of asymptomatic and symptomatic subgroups. Numbers are given as means ± 95 % confidence intervals, and p values for a three-way comparison (Kruskal-Wallis analysis of variance, if not otherwise indicated)

	ASYMPTOMATIC (n = 18)	SYMPTOMATIC, OTHER (n = 20)	SYMPTOMATIC, PLAQUE (n = 54)	
ESR (mm/h)	23 (12-34)	21 (15-26)	21 (17-24)	0.88
Haemoglobin (g/L)	137 (130-144)	138 (132-144)	140 (138-143)	0.39
Hematocrit (%)	39.0 (37.5-40.8)	40.8 (39.2-42.5)	42.0 (41.1-42.9)	0.04*)
Platelets (E9/L)	246 (214-278)	265 (238-298)	246 (227-266)	0.32
Creatinine (µmol/L)	96 (83-109)	92 (83-100)	92 (87-96)	0.93
Calcium (mmol/L)	2.33 (2.24-2.41)	2.32 (2.29-2.36)	2.32 (2.30-2.34)	0.58
Homocysteine (µmol/L)	10.0 (8.0-11.9)	10.9 (9.0-12.8)	11.5 (10.2-12.8)	0.34
Cholesterol (mmol/L)	5.2 (4.8-5.7)	5.5 (5.1-6.0)	5.5 (5.2-5.9)	0.51
LDL cholesterol	3.0 (2.6-3.5)	3.3 (2.8-3.8)	3.4 (3.1-3.7)	0.38
HDL cholesterol	1.5 (1.2-1.7)	1.3 (1.0-1.5)	1.3 (1.2-1.4)	0.22
Triglycerides (mmol/L)	1.58 (1.25-1.91)	2.13 (1.53-2.72)	1.85 (1.49-2.21)	0.55
Glucose (mmol/L)	6.1 (5.0-7.3)	6.4 (5.2-7.6)	6.1 (5.4-6.8)	0.98
Calculated viscosity [Fibr x $(Hct)^3$]	0.23 (0.19-0.27)	0.27 (0.23-0.31)	0.29 (0.27-0.31)	0.04*)
MES (/hour), all	1 (0-2)	4 (0-8)	6 (2-9)	0.15
(without anticoagulation)		4 (0-9)	7 (2-12)	0.14

(*)Analysis of covariance, adjusted for gender)

5.4.2 Comparison between symptomatic and asymptomatic patients

The measured markers of coagulation and fibrinolysis showed no statistically significant difference in three-way univariate comparison, although tPA antigen values in symptomatic group tended to be higher (Table 7), and there was a trend for a higher MES count, particularly in cases of symptomatic plaques in comparison with the rest of the patients ($p = 0.07$, Mann-Whitney U test). Uncorrected comparison between asymptomatic and ipsilaterally symptomatic CS reached significance for Hct and tPA antigen ($p < 0.01$ and < 0.05, respectively, Table 7). No significant correlation was found between MES counts and the measured markers in any subsets, nor did the markers correlate with the time elapsed since onset of symptoms.

Table 7. Coagulation- and fibrinolysis-related laboratory values in asymptomatic and symptomatic subgroups; medians with interquartile ranges (w/a: patients without anticoagulation).

	ASYMPTOMATIC (n = 18)	SYMPTOMATIC, OTHER (n = 20)	SYMPTOMATIC PLAQUE (n = 54; w/a 35)	*P VALUE*
Fibrinogen	3.9 (2.9-4.8)	4.0 (3.4-4.6)	4.0 (3.2-4.5)	0.94
(w/a)		4.0 (3.4-4.6)	3.6 (2.7-4.4)	0.79
tPA activity	0.6 (0.2-1.0)	0.7 (0.3-1.1)	0.6 (0.3-1.0)	0.27
(w/a)		0.7 (0.4-1.1)	0.5 (0.3-0.9)	0.14
tPA antigen	7.0 (4.1-9.6)	7.8 (3.8-14.9)	8.9 (7.3-10.7)	0.12
(w/a)		7.8 (6.3-10.7)	8.6 (7.4-10.7)	0.07
PAI-1 activity	7.0 (4.5-16.8)	8.3 (3.9-14.4)	10.1 (6.7-14.1)	0.56
(w/a)		8.3 (3.9-14.4)	10.5 (6.3-14.7)	0.09
PAI-1 antigen	15.6 (6.4-25.9)	12.9 (8.2-20.0)	15.7 (11.1-19.7)	0.98
(w/a)		12.9 (4.7.9-22.2)	14.8 (10.6-19.5)	0.96
D-dimer	0.5 (0.4-0.9)	0.4 (0.3-0.8)	0.4 (0.3-0.6)	0.64
(w/a)		0.5 (0.3-0.8)	0.5 (0.4-0.8)	0.89
thrombin-antithrombin	4.0 (2.5-11.8)	4.6 (2.6-10.4)	2.2 (1.8-4.1)	0.006
(w/a)		5.8 (2.7-10.4)	2.6 (1.9-4.9)	0.05
PF 1 and 2	1.2 (0.8-2.1)	1.0 (0.8-1.5)	0.7 (0.4-1.2)	0.06
(w/a)		1.1 (0.9-1.5)	1.1 (0.7-1.3)	0.64

In backward stepwise logistic regression analysis taking into account all the studied variables pertaining to coagulation and fibrinolysis as independent and the symptomatic plaque as the dependent variable, tPA antigen remained in the model as the only significant predictor (OR 1.27, 95% CI 1.04 -1.55, $p = 0.02$). When hematocrit was included in the variables, it remained in the model (OR 1.22, 95% CI 1.05 -1.45, $p = 0.04$) together with tPA antigen (OR 1.31, 95% CI 1.03 -1.66) and PF 1 and 2 (OR 0.64, 95% CI 0.46 -0.89).

5.4.3 Effect of medication

Only four patients had neither antiplatelet nor anticoagulant treatment. Anticoagulation with warfarin ($n = 22$) had expectedly a powerful lowering effect on thrombin-antithrombin complex (3.4 vs. 5.9, $p < 0.01$), PF 1 and 2 (1.2 vs. 1.7, $p < 0.01$) and D-dimer (0.34 vs. 0.50, $p < 0.01$, Mann-Whitney U test), associated with lower prothrombin time (27 vs. 117, $p << 0.01$) and a fraction higher activated partial thromboplastin time (43.5 vs. 31.5, $p < 0.01$). Fibrinolytic marker levels and platelet counts were uniform in the anticoagulated and non-anticoagulated groups. Statin users had apart from significantly lower total and LDL cholesterol levels also lower ESR (18 vs. 24, $p = 0.02$) and a trend for fewer MES (3.1 vs. 5.3, $p = 0.10$). There were no differences in the measured variables between statin or ACE inhibitor users and non-users.

5.4.4 Degree of carotid stenosis

Degree of stenosis had an overall trend for negative correlation to variables PF 1 and 2, D-dimer, and tPA activity. The trend was strongest in ipsilateral symptomatic patients without anticoagulation ($n = 33$; for PF 1 and 2, $R = -0.32$, $p = 0.02$; for D-dimer, $R = -0.41$, $p = 0.02$; for thrombin-antithrombin complex, $R = -0.20$, $p = 0.15$; for tPA activity $R = -0.30$, $p = 0.03$, Spearman Rank correlation), and was lacking in asymptomatic CS. Correspondingly, an overall trend for positive correlation was seen in tPA antigen, PAI-1 antigen and activity, and the phenomenon was most pronounced in ipsilateral symptomatic CS patients (for tPA antigen, $R = 0.58$, $p < 0.01$; for PAI-1 antigen, $R = 0.49$, $p = 0.03$, and PAI-1 activity, $R = 0.33$, $p = 0.15$). Fibrinogen had no association with the degree of stenosis, whereas hematocrit was positively correlated to it in both asymptomatic and symptomatic groups ($R = 0.32$, $p < 0.01$ for total population)

5.4.5 Plaque characteristics

With smooth plaques the MES counts tended to be lower and with ulcerated plaques higher (for both, 3.7 vs. 5.2, p = 0.03, Mann-Whitney U test) (Table 8). Intraplaque haemorrhage tended to associate with higher degree of stenosis (79.6 vs. 75.5 %), reduced platelet count (238 vs. 261 E9/L) and elevated hematocrit (41.9 % vs. 40.3 %, $p < 0.05$ for all, Mann-Whitney U test) but not with the variables of coagulation and fibrinolysis (data not shown). Anticoagulated ipsilaterally symptomatic patients had fewer haemorrhagic plaques than non-anticoagulated (9 (42 %) vs. 23 (70 %) , p = 0.05, χ^2 test).

Table 8. Macroscopic characteristics of the plaque at surgery

PLAQUE	ASYMPTOMATIC (n=18)	SYMPTOMATIC, OTHER PLAQUE (n=20)	SYMPTOMATIC (n=54)
smooth	13 (72 %)	15 (75 %)	27 (53 %) *)
ulcerated	5 (28 %)	6 (30 %)	29 (54 %) *)
calcified	14 (78 %)	11 (55 %)	31 (57 %)
loose atheroma	2 (11 %)	4 (20 %)	14 (26 %)
haemorrhage	8 (44 %)	8 (40 %)	32 (59 %)

*) $p < 0.05$, χ^2 test

6. DISCUSSION

6.1 Changes in brain diffusion

In the diffusion study, the ADC_{av} values were found to be elevated in the WM and the watershed areas of the hemisphere ipsilateral to a high-grade CS; furthermore, removal of the stenosis brought the values promptly back to the same level as in the contralateral hemisphere. The finding was consistent in the asymptomatic and the symptomatic subgroups. Yet, the ADC_{av} values of GM and thalamus displayed neither interhemispheric nor postoperative variation, and, despite the postoperative decline, the ADC_{av} values of WM and watershed regions of patients remained higher than those of the controls regardless of the hemisphere or time point. Although the magnitude of the ADC_{av} change was small, it was consistent enough both among the patients and between the different lobes of the brain as to make is statistically clearly significant, and thus chance variation remains an improbable explanation.

Rise of ADC levels indicates less restriction to diffusivity in the tissue. Chronically increased diffusion implies a structural change which may be a form of permanent damage, such as chronic ischemic stroke or presumably LA. In case of tissue destruction, the ADC elevation can be assumed to be irreversible. The ADC elevation may be sensitive to a 'subclinical' level of change in tissue structure as shown in the normal-appearing WM patients with advanced WM lesions [171]. A more informative way to characterize the structural change or damage change would be diffusion tensor imaging capable of producing multiple indices, especially, fractional anisotropy, which is inversely proportional to ADC levels [491]. Several studies have confirmed the change in the normal-appearing WM in patients with WM lesions, and some of the studies have been able to show a correlation to the degree of cognitive dysfunction, mainly in the domain of executive functions [120, 492, 493]. WM has appeared the most vulnerable in experimentally induced chronic hypoperfusion; moreover, human studies with DSC MRI and positron emission tomography have detected hypoperfusion in association with WM lesions, which is consistent with the notion of a low-grade perfusion deficit [378, 383, 484, 494, 495]. Yet, it remains in question whether hypoperfusion is the cause or the effect in case of the WM lesions. In our study, the perfusion sequences revealed diminished perfusion ipsilateral to the stenosis in a considerable proportion of the patients, and so it is prudent to ask what kind of an effect the perfusion deficit would technically have on the ADC_{av} values. Since the rate of perfusion is estimated to constitute a few percent of the ADC_{av} values of the brain tissue, the expected consequence of a perfusion deficit *per se* would be a minor ipsilateral ADC_{av}

decrease [180]. As the ipsilateral ADC_{av} values, to the contrary, were significantly higher than in controls, it is evident that other physiological mechanisms and consequences predominate over the short-term direct effect of reduced perfusion. What is more, also the contralateral ADC_{av} values were higher in the patients than in controls, which underscores the pivotal differences between patient and control populations and probably reflects the patients' greater propensity to WM changes in comparison to a population without cerebrovascular risk factors.

Reversible elevations of the ADC may be encountered in vasogenic oedema, e.g. hypertensive encephalopathy, eclampsia, or posterior reversible encephalopathy syndrome [160, 167, 496, 497]. In these cases, the permeability of the blood-brain barrier is altered, and intra- and extracellular water is redistributed so that excess water is found in the interstitium. When CS is sufficiently tight to cause relative hypoperfusion, the expected haemodynamic change would be vessel dilatation and an increase in cerebral blood volume (CBV). After CEA, the ipsilateral flow increases, and the blood volume would be expected to either decrease or remain unchanged [498, 499]. Perfusion would thus improve, which could induce a slight elevation of ADC_{av} values. In our study, no significant alteration in CBV was detected at any of the three stages; however, it is possible that the magnitude of change needed to be reflected in ADC values is greater, and the sensitivity of the perfusion imaging methodology used in this study may be insufficient for detection of a minor difference. At any rate, the detected postoperative ADC_{av} decrease is contrary to the change that would be expected solely on the basis of the altered perfusion.

The contralateral hemisphere had unaltered diffusion after the operation, neither did the ADC_{av} values of GM or thalamus change in either hemisphere. These entities are not only structurally different from WM but their inflow of blood has other sources: GM is supplied by leptomeningeal collaterals, and thalamus by vertebrobasilar circulation [500, 501]. The lack of variation is concordant with the observation that the ADC_{av} levels of GM and thalamus were equal in the patients and controls, in contrast to the differing values in WM.

Both asymptomatic and symptomatic subgroups had uniform levels of ADC_{av} values in the ipsilateral hemispheres, and their development was similar in the follow-up. The groups were homogeneous also in terms of the patient characteristics (age, risk factors, and degree of CS) at baseline. Thus, in this context, ADC_{av} measurements did not distinguish the symptomatic from the asymptomatic or shed any light on the question why and how some patients with similar CS become symptomatic. In within-subject analysis, the anterior watershed regions

had higher ADC_{av} values than the posterior watershed area at every time point. This supports the previous study and our own findings of the frontal lobes having the highest ADC_{av} levels [499]. The impact of a stenosis in anterior circulation may have a propensity to accentuate the lobar differences, depending on the degree of subservience by anterior or posterior circulation and the effectiveness of collateralization.

The overall finding of elevated preoperative ADC_{av} values and their partial reversal by CEA, and the fact that they remained higher than in the normal controls even at the chronic stage, suggest that both reversible and irreversible components exist in the impact of a severe CS on the ipsilateral WM. The observed net decrease of ADC_{av} supports the hypothesis of a corrective effect on cellular-level pathophysiological mechanisms, such as chronic ipsilateral relative ischaemia. The finding of a slightly larger volume of LA in the ipsilateral hemisphere may give some support to the notion of LA-inducing potential of CS, in accordance with a previous positron emission tomography study [495].

6.2 Changes in brain perfusion

The most sensitive parameter to the haemodynamic effect of CS in perfusion imaging was MTT, supporting previous findings [484, 502]. MTT values improved not only in the hemisphere ipsilateral to the stenosis but also to some extent in the contralateral hemisphere, which contributed to the significance of the group × time interaction. The baseline MTT maps revealed a visually detectable perfusion deficit in over half of the symptomatic group, and the finding was significantly associated with symptomatic status. On the basis of these data, the threshold for visual detection of the perfusion deficit can be approximated as an MTT prolongation of more than 15-20 % on the affected side. The high prevalence of a chronic perfusion deficit in the symptomatic group needs to be kept in mind as a potential confounder in the setting of acute ischaemia, as it may erroneously be regarded as tissue-at-risk [503, 504]. In such cases, more comprehensive vascular imaging is needed to differentiate the chronic form of hypoperfusion from the acutely emerged one.

The variation of perfusion parameters from the acute to the chronic stage was negligible especially in the asymptomatic patients. This lack of effect in a considerable part of subjects may explain why little long-term change has been detected in previous studies [498, 499]. Our findings also corroborate the greater haemodynamic impairment of WM in comparison to GM [505]. However, the watershed areas did not appear specifically vulnerable to lower perfusion

but resembled the rest of the chosen WM regions of interest, and no perfusion asymmetry was found between the anterior and posterior borderzones [499]. Variation in CBV was lowest of all perfusion parameters, and not more than minute differences between the asymptomatic and symptomatic groups were seen. In principle, CBV parameter should not be sensitive to delay and dispersion of the bolus, but it seems unlikely to be a sensitive indicator of haemodynamic reserve [75, 341, 484, 502].

TCD findings displayed little difference between asymptomatic and symptomatic groups in the preoperative reactivity, but the reactivity improved notably only in the symptomatic patients, suggesting some degree of preoperative haemodynamic compromise. In addition, the correlation between the attenuation of interhemispheric asymmetry of MR parameters and the improvement of BHI underlines the effect of CEA in symptomatic patients. Pulsatility index is proposed to reflect cerebrovascular impedance, and it is influenced by several properties of the vasculature as well as by cardiac function, and it has been applied as an indiscriminate index of vascular resistance [507]. It has been associated with symptomatic status, and it is known to improve after CEA, but its predictive value has been poor [75, 507, 508]. CS decreases pulsatility index by reducing inflow, and retained pulsatility is thought to indicate lower impedance of collateral vessels. In our study, the preoperatively lower pulsatility index and the greater postoperative improvement of pulsatility in the symptomatic patients is in accord with more severe initial haemodynamic impairment and previous findings [507]. However, since pulsatility index is an inaccurate measure of vascular resistance and it is affected by many confounding parameters, its value to a clinician in the context of CS is at least limited. At this stage, the clinical use or benefit of vasoreactivity testing is not established, either. To evaluate its predictive value among other predictors would require a large study population, and it could be beneficial to apply a more exact testing method than breath-holding.

Overall, the perfusion results corroborate that within a homogeneous patient population with a unilateral high-grade carotid stenosis, the patients who develop symptoms have in general a poorer haemodynamic adaptation to the stenosis than the patients who remain asymptomatic. This tendency may be detected as an abnormal interhemispheric ratio of MTT in DSC MRI, which often produces a visible perfusion deficit in perfusion mapping. Consequently, the symptomatic patients also improve more clearly after CEA than the haemodynamically more stable asymptomatic patients whose long-term haemodynamic response was negligible in our study. The better haemodynamic adaptation may partly account for the lesser benefit from surgery in asymptomatic patients.

6.3. Cognitive changes

6.3.1 Cognitive dysfunction

Patient groups with risk factors and CS were consistently inferior in cognitive performance in comparison to a matched group without major risk factors. The long-term inferiority is not surprising, as cerebrovascular disease and cognitive impairment share several risk factors. Although previous cerebrovascular events could explain the difference especially in a symptomatic group of patients, considering the absence of major strokes and the low overall level of MR lesions in the symptomatic group as well as the homogeneous performance level in symptomatic and asymptomatic patients, the patient population seems to differ from the healthy controls irrespective of clinical vascular events. Still, an equal number of lacunar infarctions were detected in both patient groups; these are known to be one of the central mediators of cognitive decline, and here they may serve as markers of the underlying cerebrovascular disease along with the WM lesions [415]. Apart from minor strokes and WM lesions, the cognitive impairment in CS patients could be due to microembolization, regional hypoperfusion, or to other mechanisms. Further information on the mechanisms could have clinical implications and help define appropriate therapeutic interventions.

The cognitive dysfunction after CEA has become a well documented finding during the last decade. In the publications the incidence of dysfunction has attained to or exceeded one-fourth of patients [16, 18, 465, 468]. Considering the primarily preventive nature of the intervention, complications would threaten its aims, and one should be aware of potential subtle cognitive effects, which might easily go unnoticed in the clinical practice and not be taken into account in complication rate assessments of CEA. However, it is to be borne in mind that the reported figures are relative and determined by the set criteria for dysfunction, and thus arbitrary, and not much is known about the long-term effects or the actual 'real-life' significance of the postoperative cognitive decline to the patients' discharge from the hospital, their daily life, recovery, or well-being. Nevertheless, the occurrence of postoperative cognitive decline underlines the importance of identifying high-risk patients, whenever possible, and opting for prevention with appropriate operative and monitoring techniques.

Our study revealed a noticeable postoperative dysfunction in a number of patients, using strict criteria for dysfunction, although the changes were not strongly reflected in group means. When criteria adopted by Heyer et al. were used, there were fewer patients with cognitive deficits than anticipated [16]. The stricter criteria may be more appropriate for the limited

sample size, albeit that the risk of false positive findings becomes substantial, i.e. subjects are classified as having postoperative cognitive decline merely because of the intrinsic variability of the neuropsychological instrument, or the observed decline in test performance is not translated to any considerable disability in daily life. One of the many confounding elements in this setting is general anaesthesia, which decline is at times attributed to, but the recent results do not support its role [465]. Some decline in our material may have been artefactual and due to the intrinsic variability of the instrument, e.g. because of suboptimal parallel test versions, as a transient decline was seen in control group as well (Figure 13). The decline was also a DWI-negative phenomenon, as in previous reports [17, 509]. Furthermore, the subjects with new postoperative DWI lesions were not classified as having cognitive decline by their test performance. The insensitivity of the cognitive assessment to appearance of new DWI lesions can be interpreted as a reminder of the 'non-localizable' network functioning of the brain, expected to be more sensitive to disseminated microembolic loads over time, low-grade regional hypoperfusion, or widespread gradual changes, than punctate lesions.

Finally, considering the generally good performance of the subjects at the three-month time point and the overall clinical impression, the transient cognitive effects could be interpreted as mild and not constituting a clinical problem in this patient group. However, questions on the importance of the finding cannot be answered within this study design but would require a larger study population, a different approach and a longer follow-up time; neither can predictors for postoperative decline be determined within this design.

6.3.2 Cognitive improvement

The overall cognitive improvement of the patients after CEA reflected a learning effect that was as good as in healthy peers regardless of the WM lesion severity. The PWI result suggesting a greater cognitive improvement in patients with visible perfusion deficits tallies with recent reports of a greater cognitive improvement in patients with compromised cerebral vasoreactivity, two of them published after the completion of our study [478-480]. According to previous PWI findings, these patients may represent mainly symptomatic subjects with poorer collaterals and exhausted physiological cerebrovascular autoregulatory buffer. Such a subgroup would be more prone to recurrent ischaemia or spells of inadequate oxygen supply as well as impaired clearance of microemboli [347, 351, 510]. Poorer reserve capacity, on the other hand, could also increase surgical risks.

Preliminary domainwise analysis was possible with our comprehensive study battery, and the improvement was mainly based on better executive functioning. This finding is supported by the recent small study by Fukunaga et al. [479] Executive functions involve planning and goal setting, coordination of multiple tasks while storing information, set shifting between stimulus and response, and deployment of attentional resources; from the point of view of cognitive neuroscience, executive functions require large-scale network functioning of the brain and connectivity, essentially through fronto-subcortical circuits. On the basis of many studies, execution is postulated as the most sensitive cognitive domain to age-related connective integrity and white matter pathology [510, 511]. This sensitivity obviously explains the high incidence of dysexecutive problems in cerebrovascular disease as well.

The finding of cognitive improvement needs to be interpreted with caution; nevertheless, the prospect of improvement in the most hypoperfused individuals deserves further study with larger sample size, preferably with a more hemisphere-specific testing battery dimension. Furthermore, despite the predominance of symptomatic patients in the most hypoperfused group, notably two out of ten in our study were asymptomatic in this substudy. In principle, perfusion status could serve as an accessory criterion in selection of asymptomatic patients that might benefit from CEA, but evidence from controlled trials is needed.

The cognitive score change was not directly correlated with the small but consistent and partially reversible elevation of ADC values detected in the diffusion study. However, should higher ADC levels indicate a step towards WM degeneration, this would provide a link with the long-term cognitive deterioration, which was outside the scope of the design of our study [512]. If the link exists, and WM degeneration is seen as a target for prevention of cognitive decline, CEA would provide a means of preventing cognitive deterioration in the long run also by protecting WM, not only by reducing the risk of stroke.

6.4 Change in blood coagulation, fibrinolysis, and haemorheology

The thrombogenic process in carotid occlusive disease involves blood and plaque properties as well as blood flow conditions. In this cross-sectional study, we chose to compare selected markers of coagulation and fibrinolysis, and the most general factors of viscosity, to see whether they appeared involved in the process transforming an asymptomatic high-grade carotid stenosis into a symptomatic one. Although the study design and the sample size does

not allow firm conclusions, the results support the association of both coagulation-fibrinolysis and haemorheology with generation of symptoms in advanced CS.

Elevated viscosity estimate was associated with the symptomatic state, and it was notably due to increased hematocrit (Hct) levels, not to rise in fibrinogen (Table 6). Otherwise, the subpopulations had uniform risk factor profiles and demography, apart from the female predominance in the asymptomatic group, due to chance or gender-associated difference in plaque constitution, as well as the basic serology including lipid profile and homocysteine (Table 1) [513]. Hct may have an impact as a significant contributor to local shear stress and von Willebrand factor-mediated formation of platelet thrombus, and the shear force and flow conditions have their effects on several mechanisms of thrombosis [514, 515]. Unfavourable haemorheology may not only be a mediator of the initial injury to the vessel wall, giving impetus to atherogenesis, but also a risk factor for generation of symptoms through local shear, thrombus-forming effects on platelets, and greater risk of turbulence and stagnation of flow. CS could be an especially prone site, considering the high-shear and turbulent flow conditions in the carotid arteries in comparison with e.g. coronary arteries. Increased viscosity has been associated with enhanced stroke risk in prospective studies with synergistic effects with other risk factors as well as with carotid intima-media thickness, and elevated viscosity levels have been detected in acute stroke [322, 323, 516-518]. However, rheological studies in acute stroke have detected elevations in fibrinogen rather than Hct, although some studies have documented increased Hct in presence of CS [322, 323, 517]. In principle, haemorheological impairment could give rise to symptoms also through influence on cerebral perfusion in cases of less well-developed collateralization. Yet, the acute cerebrovascular event itself could be a confounding factor in symptomatic CS, as both acute-phase elevations and decreases have been described in patients with a recent thrombosis, in addition to elevated fibrinogen [517, 519, 520]. Our study lacked major infarctions, however, and the baseline levels did not correlate with the time elapsed since symptoms. Although no direct measurements of viscosity were made in this study, the results support the notion that the haemorheological aspect merits further consideration in future studies [521].

Coagulation- and fibrinolysis-related variables showed little difference in univariate analysis, although the trend of higher tPA antigen together with the relatively low tPA activity implies reduced fibrinolytic capacity in the symptomatic group. In multivariate analysis, elevated tPA antigen levels seem to associate with the symptomatic plaque more clearly, in line with previous studies where elevated tPA antigen has appeared as a risk factor and a predictor of future vascular events [316, 522, 523]. A similar association has been reported in severe peripheral

arterial disease and thrombotic events in coronary heart disease, whereas PAI-1 has not consistently displayed an association despite its definite role in fibrinolysis [524-526]. Involvement of the plasminogen system in activation of matrix metalloproteinases and thus eventually plaque instability and tissue remodeling may underlie its importance in this setting [527]. The finding suggests that elevated tPA antigen may be an indicator of endothelial dysfunction and plaque instability as well as reduced fibrinolytic capacity to counteract intraluminal thrombus formation also in advanced carotid disease, thus contributing to the generation of symptoms. An overall 'thrombogenic profile' with higher level of thrombin generation together with impaired fibrinolysis was not detected, suggesting that induction of symptoms by an intrinsically abnormal coagulation-fibrinolysis pattern is not common in this patient group, or it may have been modified before blood samples were collected. The low-level PF 1 and 2, and thrombin-antithrombin complex are likely confounded not only with the active anticoagulant treatment in a major part of the most symptomatic patients but also the time elapsed since the symptomatic stage.

The degree of stenosis revealed a positive association with fibrinolytic factors tPA antigen, PAI-1 antigen and activity especially in presence of an anticoagulant lowering the overall level of thrombin generation. Correspondingly, increasing stenosis was involved with decreasing levels of PF 1 and 2, D-dimer, thrombin-antithrombin complex, and tPA activity, and this phenomenon was evident without the interfering presence of anticoagulation. This supports involvement of the fibrinolytic system in the evolution of atherosclerotic disease into the symptomatic stage, especially as no association of tPA antigen and the grade of stenosis was detected in the asymptomatic group. The correlation between tPA antigen and the stenosis degree was highest in the anticoagulated, ipsilaterally symptomatic stenoses, probably explained by the selective attrition the most symptom-generating and unstable plaques in this subgroup, as their degree of stenosis was not higher *per se*. The expression of markers may also be affected by the flow and perfusion condition, which were found in the perfusion imaging substudy to be better in the asymptomatic patients.

The macroscopic appearance of the symptomatic plaques with more frequent ulcerations and intraplaque haemorrhages was associated with clinical symptoms and MES counts but not with mediators of coagulation and fibrinolysis. This may reflect the importance of plaque ulceration as a nidus for thrombi even in absence of increased thrombogenic potential [301]. The lack of association may also serve as a reminder of the systemic nature of the markers and disease, determined by the extent and nature of the overall burden of atherosclerosis rather than reflecting a local process. This may also explain why CRP levels did not differentiate the groups, which all displayed levels that generally indicate a high risk for

cardiovascular events. The initial approach of attempting to cross-correlate plaque processes related to inflammation and cell death to symptom-associated systemic factors did not produce any robust correlations withstanding the necessary corrections for multiple statistical comparisons. Notably, although the risk factor profiles and grade of stenosis were comparable between the subgroups, the overall atherosclerotic lesion burden was not known. The association of intraplaque haemorrhage with higher hematocrit and calculated viscosity may suggest the impact of higher shear on bleeding tendency and constitute a possible mechanism of symptom generation.

6.5 Limitations of the studies

The fundamental limitations of all substudies are the limited sample size and the relatively short follow-up time. The heavy imaging protocol and the comprehensive neuropsychological battery have made the substudies labour-intensive and curbed the recruitment numbers, which has brought on statistical limitations and precluded many subgroup analyses. Since the follow-up time was barely longer than three months after the baseline, little can be said about the actual long-term effects of CEA.

The imaging studies involve some technical limitations. Firstly, analysis of the various regions of interest is challenging because of the potential contamination risk with neighbouring substance or cerebrospinal fluid, especially in case of GM regions of interest. However, as especially ADC_{av} values were within a very narrow range in this study (Table 3), the contamination seems unlikely, and the same applies in principle to the haemodynamic parameters. Secondly, perfusion imaging and its analysis has intrinsic limitations. Perfusion MRI has not become strictly quantitative, essentially because the basic assumptions concerning the underlying microvascular structure are simplified [189, 190]. Even if the values would be expected to be reasonably proportional to the actual blood flow measured, the premises of the calculation may lead to systematic errors. The fairly low resolution of the images enhances the risk of partial volume effects. These shortcomings could be partially improved by correction algorithms [528]. In this study, the main focus was on comparison and relative values, and we refrained from using correction methods. Potentially greater and even crucial problem in the presence of a CS could be the absolute dependence on arterial input function, which is a prerequisite for quantification. Delay or dispersion in the bolus passage would inevitably introduce error. We selected an arterial input function from the contralateral hemisphere, using a feeding branch of the middle cerebral artery distal to the circle of Willis

for determination as close to the region of interest as reasonable, after the input of main collaterals, even at a somewhat greater risk of partial volume effects. Finally, one of the confounding factors is the variation in the fraction of cardiac output reaching the brain. In this material, the risk may not be substantial as major cardiac diseases were criteria for patient exclusion.

In the study on cognitive functions, neuropsychological assessment as a sensitive tool with a considerable intrinsic variability may be especially prone to confounding elements in repeated testing in the surgical setting [487, 488]. Furthermore, in successive testing within a limited time frame, the subject's performance will inevitably improve in a number of neuropsychological tasks by learning effect. To control for learning, we chose to compare the subjects to healthy peers examined within the same time frame. This group may, however, be suboptimal as the anxiety and motivational levels of healthy people differ from those of the patients. On the other hand, although their cognitive performance was better it was not as far superior as to be cut down by ceiling effect of the subtests, and being strictly healthy they assumedly provided a good measure for the natural learning curve which the patients would hardly be expected to surpass. The use of compound cognitive score may be criticized for bringing about bias and redundancy or loss of information since no tests are domain-specific. Still, compounding may serve to bring out underlying trends, in addition to the obvious advantage of lesser need for multiple comparison and corrections. In the present study, the restricted sample size does not allow for robust corrections nor a breakdown into hemisphere-specific analysis.

The study on coagulation, fibrinolysis, and haemorheology has the most crucial limitations despite the largest sample size. Firstly, the selected study variables do not reflect the total haemostatic process but there are potential factors that have not been studied (e.g. platelet functions). Secondly, the timing of laboratory sample collection is hopelessly late, as the plasma markers of the intertwined dynamic processes of coagulation and fibrinolysis are part of a highly reactive and dynamic defense mechanism to protect the integrity of the vasculature, and they generally have short half-lives [529]. Thus, the acute phase before, during, and immediately after the onset of symptoms is not easily caught in a clinical study, and the risk of confounding elements accumulates when a single postictal assessment is to reflect the dynamic situation just before the acute stage as well as the time after the onset of symptoms. The time range since symptoms was from a few days to over 200 days in the ipsilaterally symptomatic, median at 41 days, and even longer in otherwise symptomatic patients; accordingly, the acute-phase reaction cannot be expected to be shown, and the subsequent phases such as endothelial regeneration could also induce variance. Thirdly, atherosclerosis is

a systemic process, as previously discussed, and drastic conclusions on a local process on the basis of blood samples may be misleading. Fourthly, a considerable number of patients were on warfarin, which has a confounding effect on part of the results. In addition, haemorheological conclusions are made indirectly on the basis of basic parameters without direct rheological measurements.

6.6 Summary of findings and their implications

The studies (II-III) yielded findings indicating that a high-grade CS may have implicit effects on the brain and its functions. Another main finding was that the haemodynamic aspect (I) and the microcirculation (IV) may influence the evolution of symptoms in these patients.

The main results in the brain diffusion and perfusion studies (I-II) were the ipsilateral findings of enhanced diffusion and the lower perfusion in the WM, as well as the corrective effect of CEA on them. Unlike the partially reversible diffusional elevation, the perfusion impairment differed between asymptomatic and symptomatic patients. The haemodynamic effect was reflected by the TCD modality as well. Both diffusion and perfusion results support the etiology of a chronic low-grade ischaemia, which has been the central hypothetical etiology to WM lesions [14].The preoperatively elevated ADC_{av} values were a novel finding suggesting an association between WM degeneration and CS. The perfusion data (II) are in line with previous studies on haemodynamics in carotid stenosis or occlusion, but they underscore the haemodynamic aspect in the symptomatic disease [77, 343, 502]. The results serve as a reminder not to overlook the haemodynamic state, either, which may have a contributory or synergistic role along with the unstable plaque seeding emboli [347, 351]. A closer haemodynamic evaluation could also help in selecting asymptomatic patients with CS for operative treatment.

The cognitive performance of patients with a high-grade CS (III) was found to be poorer than in healthy peers, on the basis of a multimodal approach and a versatile neuropsychological battery, in line with previous reports [416-418, 530]. The degree of impairment correlated with the severity of WM degeneration [531, 532]. However, the patients' postoperative cognitive improvement was equally good as that of controls in repeated testing, and even better in some domains in patients who initially had a deeper hypoperfusion, primarily in executive functions. The association of CEA and cognition appears twofold: despite a risk of transient cognitive decline, surgery of a high-grade CS in a dedicated unit seems to be a fairly safe means to protect the brain, and there is even a possibility of cognitive benefit in subgroups.

Prospective identification of individuals with the optimum benefit warrants further study with larger samples and multimodal designs, longer follow-up, and evaluation of the true impact of the observed cognitive dysfunction on the subjects' daily life and its quality. Much more data is needed also on the association of ADC levels and the progress of WM changes before the role of CEA as a potential means of WM protection can be established, and application of diffusion tensor imaging, possibly combined with other imaging modalities, would be more informative than the mere ADC approach.

Both fibrinolytic mechanisms and haemorheology may be associated with the evolution of CS into the symptomatic stage (IV). Elevated levels of tPA antigen may be an indicator of carotid plaque instability and associated thrombogenic potential, and higher viscosity of blood, an established risk factor for stroke, may contribute to symptoms in severe CS. A longitudinal follow-up study of the mediators, a more comprehensive overview of the haemostatic process, direct measurements of viscosity, and a more specific look at the flow conditions, in a closer temporal proximity to the acute stage, would probably provide more accurate information on the interplay of coagulation, fibrinolysis, and haemorheology.

On the basis of these results, future carotid trials could be encouraged to take advantage of more functional and dynamic methods for an improved evaluation and risk assessment in carotid disease, instead of the mere categorical observation of stenosis degree. With the evolution of angioplasty and stenting, the cognitive aspect and multimodality should be incorporated into the design of carotid trials, particularly as the recent systematic reviews have concluded that a greater number of brain lesions are detected after carotid stenting than after CEA [463, 476]. Apart from this difference with potential cognitive sequelae, the putative effects of altered perfusion and diffusion would probably be analogical after stenting and CEA, but remain to be verified by further study.

7. CONCLUSIONS

1. Cerebral haemodynamics in symptomatic patients with a high-grade carotid stenosis is less well adapted and more often results in haemodynamic deficit than in asymptomatic patients. Accordingly, the haemodynamics of symptomatic patients benefit more from removal of stenosis as indicated by improvement in perfusion, pulsatility, and reactivity.

2. A high-grade CS is associated with elevated ADC_{av} values in the WM and watershed regions of the ipsilateral hemisphere in comparison to the contralateral hemisphere and to healthy control population. The interhemispheric difference is promptly abolished by CEA, but the ADC_{av} levels remain higher than in healthy controls also in the chronic stage. This implies the existence of both reversible and irreversible component in the effect a high-grade CS has on the WM, and it may indicate an association to the WM degeneration.

3. Carotid occlusive disease is associated with a lower level of cognitive functioning irrespective of vascular events. After carotid surgery, despite a trend towards transient cognitive decline, the patients improve within months as expected by learning effect in repeated testing. Cognitive improvement is greater in patients with deeper preoperative cerebral hypoperfusion, and the improvement is most evident in the domain of executive functions.

4. Symptomatic patients with a high-grade stenosis differ in terms of coagulation activity and fibrinolysis, as well as basic haemorheology**.** Mediators of fibrinolysis and unfavourable haemorheology may contribute to progress of an asymptomatic carotid disease into a symptomatic one in patients with a high-grade CS.

ACKNOWLEDGMENTS

This study emerged as a by-product of the Helsinki Carotid Endarterectomy Study (HeCES), sparked off by professor Markku Kaste in the second half of 1990's. My indebtedness to him for his encouragement and benevolence is beyond measure and words. He is the key person who has introduced many of us to the spheres of stroke and helped us realize the impact of cerebrovascular disease and the power of untiring work to combat stroke worldwide. As being the chair of the department as well as the professor at the time, he also made the project possible on the practical level in many ways. The other ground figure and tutor of this work has been docent Turgut Tatlisumak, whose help has been absolutely vital from the beginning. Heartfelt thanks to Turgut for being the tough, righteous, and at the same, the very supporting person with a good sense of humour, and thanks for sharing the same office for many years and for many good laughs at worldly phenomena. The tutors - despite all their inherent vigour - have shown great patience with the gradual evolution of this thesis as an aside of the clinical work and other adventures of the undersigned. I also thank the present head of the clinic, docent Markus Färkkilä, for the opportunity to combine the clinical routine with research and finish up the work, and the custos and the professor of the department Timo Erkinjuntti for his most encouraging and supportive attitude.

The fruitful HeCES collaboration has involved eminent founder figures in addition to Markku Kaste such as professors Perttu Lindsberg and Petri Kovanen, and it has been a privilege to learn from them during these years. Docent Riitta Lassila has been the sovereign ideologist of the hematological sidetrack of HeCES, and docent Oili Salonen has been the gentle and diligent authority on the neuroradiological field. I am grateful for their vision and generous help. My young and talented colleague Johanna Helenius has had an indispensable role for this work, taking care of the neuroradiological post-processing, a major part of the hard and tiring 'gluteal' work, along with bringing about a fresh breeze of a charming and inquisitive mind. The skillful surgical and ultrasonological contribution of Eija Saimanen formed the operative basis of HeCES study; collaboration with Eija was most rewarding, and everything used to proceed smoothly. Docent Marja Hietanen has been providing the highest expertise on cognitive functions, and she has been a quietly supportive and friendly figure throughout the work, for which I wish to express my gratitude. I also thank Irene Tikkala for a great many neuropsychological examinations of patients, often at unconventional times of the week, and many thanks are also due to Pia Mäenpää for a very good and consistent collaboration for the same end. I thank my colleague Kirsi Malmberg-Céder for working with us and taking part in the HeCES collaboration before setting out and leaving us missing her cheerful company. I gratefully acknowledge the expertise of Jussi Perkiö and Veli-Pekka Poutanen, who have generously helped with all matters pertaining to MRI. I have greatly appreciated the expertise of professor Seppo Sarna, who has readily and patiently emailed back many answers to my questions on several intricacies of statistics. An integral part of HeCES has also been the consistent and skillful work of the study nurses of our research unit, 'the Cellar', especially Riitta Kärkkäinen, Riitta Lönnqvist, and Saija Eirola; sincere thanks could not be better

deserved than theirs. The HeCES collaboration has since the early phases involved several younger colleagues, especially Krista Nuotio, Petra Ijäs, Jani Saksi, Pia Isoviita, Riitta Sonninen, and previously also Erno Lehtonen-Smeds and Mikko Mäyränpää. They have been a great bunch to work with. Along with the HeCES collaboration, I am also greatly indebted to professor Risto O. Roine for his integral role and contribution to the development of the neurovascular and neurocardiological traditions in Helsinki. After HeCES, the very good carotid collaboration has continued with professor Mauri Lepäntalo and his vascular surgeons, especially Pirkka, Anders, and Mikael.

I owe my gratitude to professor Matti Hillbom and docent Niku Oksala for their constructive and detailed criticism and expert views on the manuscript, as well as for showing great flexibility and understanding with the timetables.

I am deeply indebted to all the patients and control subjects who willingly participated in the studies and went through copious examinations for the sake of science, as well as to the personnel on the surgical and neurological wards that greeted the extra curricula of the study patients with a positive attitude.

Many colleagues and friends have made the daily work and existence interesting, colourful, poignant, and pleasurable. I thank Mikko, Olli, Pena, Satu, Kirsi, Nina, Mika, Daniel, Tiina, Elena, Katja, Jukka, Seppo, Eero, Kari-Pekka, Mervi, Sari, Mari, Tarja, Ville, Laaxis, Hanna, Auli, and many others in the clinic - not to forget the young hopes led by Atte, and the rest of the stroke team - for all of their contributions to the daily work, interesting discussions, and the keen preoccupation with the brain. Very special thanks to Marjaana, Martti, and Merja for their friendship, personal warmth, and collegiality. Special thanks also to Leena Hänninen for continuous and multitudinous help through years, as well as to Anu Eräkanto for prompt resolution of some practical problems. Thanks to my old pal and artist Jukka Nissinen for a brief introduction to computer graphics.

Finally, I want to express my deepest gratitude not only to Kirsi Marjaana but also to my beloved children Tuomas, Sara, Samuel, Sonja, and Heta, for being there, and my parents Irja and Paavo for their unfailing support through all times.

Ultimately, my love and gratitude to Helena for being with me.

This study was financially supported by grants from the Helsinki University Central Hospital (EVO), the Maire Taponen Foundation, the Neurology Foundation, the Medical Foundation of Finland, and the Orion Research Foundation.

Helsinki, October 29, 2009

Lauri Soinne

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