Carotid revascularization and cerebral perfusion monitoring: clinical & experimental studies

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Carotid revascularization and cerebral perfusion monitoring:
clinical & experimental studies

Thesis Utrecht University, Faculty of medicine, with summary in Dutch
Proefschrift Universiteit Utrecht, faculteit Geneeskunde, met een samenvatting in het Nederlands

ISBN: 978-90-393-5997-6

Printed by: Gildeprint drukkerijen, Enschede

Carotid revascularization and cerebral perfusion monitoring: clinical & experimental studies

Carotisrevascularisatie en cerebrale perfusie monitoring:
klinische en experimentele studies
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 5 september 2013 des middags te 2.30 uur

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geboren op 18 mei 1985 te Gouda

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Dit proefschrift is mede tot stand gekomen door financiele steun van: Chipsoft B.V., Boehringer Ingelheim B.V., Vascutek, Krijnen Medical Innovations B.V. en Covidien B.V.

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Chapter 1

General introduction and outline of this thesis

Cerebral circulation

The brain is one of the best perfused organs of the human body and is supplied by four major arteries. The internal carotid arteries (ICAs) arising from the common carotid arteries principally supply the cerebrum, whereas the two vertebral arteries join distally to form the basilar artery and supply blood for the cerebrum, cerebellum and brain stem. At the base of the brain, the basilar artery, two internal carotid arteries, and communicating arteries form a collateral network named after Sir Thomas Willis, who described this circulus arteriosus cerebri in Cerebri Anatome (1664). The circle of Willis is formed anteriorly by the right and left anterior cerebral arteries, which are linked by the anterior communicating artery, and posteriorly by the posterior cerebral arteries and posterior communicating arteries linking the latter to the carotids. These arteries divide into progressively smaller arteries and arterioles that run along the surface until they penetrate the brain tissue to supply blood to the cerebral cortex. Because the capacity for anaerobic metabolism of the brain is very limited, maintenance of adequate cerebral blood flow (CBF), the amount of blood that the cerebral circulation carries, is highly important.[1] Under normal circumstances, CBF depends on the cerebral perfusion pressure (usually equal to the systemic arterial pressure) and the vascular resistance which is directly influenced by the diameter of the blood vessels. The ability to maintain stable CBF despite changes in cerebral perfusion pressure is called cerebral autoregulation, which induces vasoconstriction in case of increase of cerebral perfusion pressure and visa versa.[2] However, external factors, such as carotid artery disease, can cause an acute or chronic decrease in CBF.

Carotid artery disease

Carotid disease, which is usually caused by atherosclerotic narrowing of the ICAs, has been considered the underlying mechanism in approximately 20% of ischemic strokes. Broadly described, two mechanisms, namely, hemodynamic and embolic, are assumed to underlie most strokes in ICA disease.[3,4] In thromboembolic strokes, embolism of thrombotic material from an atherosclerotic plaque obstructs the arterial flow, and consequently, portions of the brain relying on the occluded vessel for oxygenated blood become deprived of oxygen, resulting in brain tissue ischemia and, eventually, infarction. Hemodynamic strokes are the result of carotid narrowing leading to a decrease in CBF, according to Hagen-Poiseuille, who described the relationship between flow rate and radius.[2,5] Under these circumstances, adequacy of collateral circulatory pathways is the primary determinant of cerebral perfusion and blood flow. In the absence of a sufficient collateral arterial flow, a significant ICA stenosis may lead to “watershed strokes,” which occur in parts of the brain that lie at the boundary between the zones of arterial distribution from different arteries. However, the pathophysiology of this distinction has resulted in controversy because watershed infarcts may occur in critical ICA disease, with substantial evidence for both the low-flow and the multi-embolic mechanism.[6,7] Moreover, the degree of carotid stenosis correlates poorly with the hemodynamic status of the ipsilateral cerebral circulation. Some patients may be diagnosed incidentally with asymptomatic carotid artery occlusion, whereas others present with devastating cerebral infarction. Other factors that have been associated with an increased risk of stroke

in patients with carotid artery disease include clinical and demographic characteristics of the patients and the absence of collateral circulation. Moreover, the autoregulatory mechanism may be affected in carotid artery disease caused by longstanding hypoperfusion.

Carotid artery revascularization

In the prevention of stroke in patients with carotid artery disease, carotid artery revascularization plays an important role. Carotid endarterectomy (CEA) was first introduced as a treatment to prevent stroke in the early 1950s, and the first definitive proof of the utility of CEA in preventing stroke compared with optimal medical treatment was performed four decades later. [8] Carotid artery stenting (CAS) was introduced as a treatment to prevent stroke in 1994 and offers a percutaneous alternative in selected patients, whereas CEA is still the standard revascularization therapy in symptomatic patients with >50% stenosis and in asymptomatic men aged <75 years with a stenosis between 70% and 99%.[9,10] CEA may be performed with general anesthesia or with local anesthesia, with or without cervical block. Some authors assume general anesthesia during CEA is more practical, more stable, less time-consuming, and more comfortable for patient and surgeon, whereas others advocate local anesthesia during CEA because of the possibility of awake monitoring (see below). A large randomized trial comparing regional versus general anesthesia could not prove a clear difference in the proportion of patients with stroke, myocardial infarction, or death within 30 days after surgery.[11] Therefore, the choice for a type of anesthesia is generally determined by the individual surgeon's and anaesthesiologist's preference and by patient characteristics and preference. CEA can be performed using a standard longitudinal incision or by the eversion technique. With the standard CEA technique, a longitudinal arteriotomy is performed below the level of the bifurcation and extended proximally and distally, after which the atheromatous plaque substance of the artery is removed. Subsequently, the artery is closed, preferably using a venous or prosthetic patch, because trials have shown benefit from patching regarding restenosis and the ipsilateral stroke rate.[12;13] The eversion technique was developed to reduce the restenosis rate at the distal ICA. When the eversion technique described by the DeBakey et al. in 1959 is used, the distal common carotid artery is transected horizontally, and the atheroma is removed by everting the bifurcation while the internal and external carotid arteries remained attached. However, a large randomized trial that compared standard CEA and the eversion technique did not favor either technique over the other in rates of death, stroke, or restenosis.[14] In all studies described in this thesis, the standard technique was applied.

Complications of CEA

The benefit from CEA in the prevention of stroke depends on the safety of this procedure.[15] CEA is therefore limited by the occurrence of perioperative strokes, which can be categorized according to time of onset. Intraoperative stroke is apparent at awakening from anesthesia, whereas postoperative stroke becomes apparent after a symptom-free interval.[16] Intraoperative strokes are mainly caused by embolism or hypoperfusion during cross-clamping. Cerebral embolism detected during CEA is an independent predictor of

perioperative stroke and can be categorized into gaseous or solid embolism. Hypoperfusion during cross-clamping occurs in approximately 15% of patients. Cerebral ischemia may be prevented in these patients by placement of an intraluminal shunt, which allows blood flow to be maintained during removal of the atheromatous plaque and thereby reduces the duration of interruption of blood flow to the brain. For patients undergoing CEA under general anesthesia, some surgeons routinely place a shunt; however, routine shunting may result in unnecessary shunt use in approximately 85% of patients because most patients do have a sufficient collateral cerebral perfusion during cross-clamping. Shunt use may also involve several important risks, including carotid artery dissection, shunt plaque embolisation, and inadequate shunt flow or shunt thrombosis.[17,18] Most surgeons therefore use cerebral perfusion monitoring to guide the need for selective shunt placement. Postoperative strokes are mainly due to embolism and cerebral hyperperfusion syndrome (CHS). CHS occurs in 1% to 3% of patients and usually becomes apparent in the first few days after surgery; however, CHS may manifest up to 4 weeks after surgery and is defined by a combination of neurologic symptoms and at least a doubling of preoperative CBF. The pathophysiology has not been clearly elucidated, but some have hypothesised that sudden augmentation of the blood flow can cause cerebral hyperperfusion in a brain with impaired autoregulation because of a previously hypoperfused state.[19-21] Early and adequate treatment of CHS is essential, because hemorrhagic strokes caused by CHS are associated with a mortality rate of up to 40%.

Cerebral perfusion monitoring

Perioperative perfusion monitoring has been introduced to reduce the perioperative stroke rate. A variety of CBF monitoring techniques are available, such as stable xenon-enhanced computed tomography, single-photon-emission computed tomography, and positron-emission tomography; these methods, however, are hampered by several clinical and practical drawbacks. Therefore, surrogate markers of CBF have been proposed and applied, each with a specific purpose. Computerized electroencephalography (EEG) and transcranial Doppler (TCD) sonography are the most well-known, investigated, and established brain monitoring modalities in CEA. There is a clear correlation between changes in CBF and changes in EEG and TCD.[22-25] EEG is an indirect qualitative measurement of CBF that is used for monitoring of brain function and as an indicator for selective shunting. TCD allows noninvasive, continuous measurement of the blood velocity in the large intracranial vessels through a temporal bone window. TCD-derived blood velocity can be used to indicate shunt use and identify patients at risk for the development of CHS. TCD can also be useful for the detection of embolism; nevertheless, a suitable temporal bone window is absent in approximately 15% of patients. Moreover, EEG and TCD both require dedicated clinical neurophysiological personnel for interpretation of the measurement. Near-infrared spectroscopy (NIRS), measuring relative frontal lobe oxygenation saturation (rSO_2) has also been proposed as an alternative for CBF monitoring. This technique, however, needs to be further explored before it can be widely applied as a cerebral monitoring technique during CEA. Improvement of surgical techniques and the introduction of intraoperative cerebral monitoring have already reduced the rate of intraoperative stroke; however, the postoperative

stroke rate has remained unchanged.[26]

Purpose and outline of this thesis

The general aim of the studies described in this thesis was to investigate the pathophysiology and prediction of perioperative complications of CEA and the role of cerebral monitoring in diagnosis and prevention of these complications. Perivascular nerves are believed to play a regulatory role in the cerebral circulation and the degree of fluctuations in CBF are thought to be associated with a particular nerve density.[27,28] The association between carotid artery occlusion and alterations in nerve density however has never been investigated. In **Chapter 2** therefore we evaluate the effect of bilateral carotid occlusion on cerebral hemodynamics and perivascular innervation in an animal model .

In **Chapter 3**, we analyze whether the status of the primary collateral pathways can predict the likelihood of shunt use. We set out to develop a clinical prediction rule to predict the likelihood for shunting during CEA based on preoperative assessment of collateral cerebral circulation and patient characteristics. To decrease the perioperative stroke rate, perioperative cerebral perfusion monitoring is essential.

The numerous monitoring modalities and their role in CEA in the prevention of perioperative complications are described in **Chapter 4**.

Chapter 5 provides an overview focusing on the role of TCD in prediction of CHS. Subsequently, in **Chapter 6**, we studied whether the diagnostic value for predicting CHS could be increased by an additional TCD measurement in the early postoperative phase after CEA as opposed to the current policy of only intraoperative monitoring. The value of NIRS, a promising alternative to the currently used monitoring techniques, and its relation to other monitoring techniques are described. First, in **Chapter 7**, is a systematic review that compares the value of NIRS related to existing cerebral monitoring techniques in the prediction of perioperative cerebral ischemia and the occurrence CHS in patients undergoing CEA. These issues were studied in a prospective investigation that is described in the next two chapters. **Chapter 8** evaluates the value of NIRS and TCD in relation to EEG changes for the detection of cerebral hypoperfusion necessitating shunt placement, and in **Chapter 9**, we describe whether NIRS and perioperative TCD are related to the onset CHS after CEA.

To prevent perioperative stroke, adequate CBF blood should be maintained throughout the procedure. Because CBF has become pressure-dependent in patients with ICA stenosis, decreases in blood pressure should be prevented. Different vasoactive agents that are commonly used for this purpose and their effect on cerebral hemodynamics are evaluated retrospectively and described in **Chapter 10**. However, to validate the results found in Chapter 10 and to determine the optimal agent to increase blood pressure during CEA, a prospective randomized control trial is warranted. The protocol describing the PEPPER study (Phenylephrine versus Ephedrine on Cerebral Perfusion during CEA) is presented in **Chapter 11**.

References

(1) Paulson OB. Blood-brain barrier, brain metabolism and cerebral blood flow. Eur Neuropsychopharmacol 2002; 12(6):495-501.
(2) Ursino M. Regulation of the circulation of the brain. In: Bevan RD, Bevan JA, editors. The human brain circulation: functional changes in disease. Totowa, New Jersey: Humana Press; 1994. 291-318.
(3) Rodda RA. The arterial patterns associated with internal carotid disease and cerebral infarcts. Stroke 1986; 17(1):69-75.
(4) Szabo K, Kern R, Gass A, Hirsch J, Hennerici M. Acute stroke patterns in patients with internal carotid artery disease: a diffusion-weighted magnetic resonance imaging study. Stroke 2001; 32(6):1323-1329.
(5) Hademenos GJ, Massoud TF. Biophysical mechanisms of stroke. Stroke 1997; 28(10):2067-2077.
(6) Kang DW, Chu K, Ko SB, Kwon SJ, Yoon BW, Roh JK. Lesion patterns and mechanism of ischemia in internal carotid artery disease: a diffusion-weighted imaging study. Arch Neurol 2002; 59(10):1577-1582.
(7) Momjian-Mayor I, Baron JC. The pathophysiology of watershed infarction in internal carotid artery disease: review of cerebral perfusion studies. Stroke 2005; 36(3):567-577.
(8) Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991; 325(7):445-453.
(9) Kakisis JD, Avgerinos ED, Antonopoulos CN, Giannakopoulos TG, Moulakakis K, Liapis CD. The European Society for Vascular Surgery guidelines for carotid intervention: an updated independent assessment and literature review. Eur J Vasc Endovasc Surg 2012; 44(3):238-243.
(10) Liapis CD, Bell PR, Mikhailidis D, Sivenius J, Nicolaides A, Fernandes e Fernandes et al. ESVS guidelines. Invasive treatment for carotid stenosis: indications, techniques. Eur J Vasc Endovasc Surg 2009; 37(4 Suppl):1-19.
(11) Lewis SC, Warlow CP, Bodenham AR, Colam B, Rothwell PM, Torgerson D et al. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. Lancet 2008; %20;372(9656):2132-2142.
(12) AbuRahma AF, Robinson PA, Saiedy S, Kahn JH, Boland JP. Prospective randomized trial of carotid endarterectomy with primary closure and patch angioplasty with saphenous vein, jugular vein, and polytetrafluoroethylene: long-term follow-up. J Vasc Surg 1998; 27(2):222-232.
(13) Rerkasem K, Rothwell PM. Patch angioplasty versus primary closure for carotid endarterectomy. Cochrane Database Syst Rev 2009;(4):CD000160.
(14) Cao P, Giordano G, De RP, Zannetti S, Chiesa R, Coppi G et al. A randomized study on eversion versus standard carotid endarterectomy: study design and preliminary results: the Everest Trial. J Vasc Surg 1998; 27(4):595-605.
(15) Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet 2010; %20;375(9719):985-997.
(16) Riles TS, Imparato AM, Jacobowitz GR, Lamparello PJ, Giangola G, Adelman MA et al. The cause of perioperative stroke after carotid endarterectomy. J Vasc Surg 1994; 19(2):206-214.
(17) Prioleau WH, Jr., Alken AF, Hairston P. Carotid endarterectomy: neurologic complications as related to surgical techniques. Ann Surg 1977; 185(6):678-683.
(18) Salvian AJ, Taylor DC, Hsiang YN, Hildebrand HD, Litherland HK, Humer MF et al. Selective shunting with EEG monitoring is safer than routine shunting for carotid endarterectomy. Cardiovasc Surg 1997; 5(5):481-485.
(19) Magee TR, Davies AH, Baird RN, Horrocks M. Transcranial Doppler measurement before and after carotid endarterectomy. J R Coll Surg Edinb 1992; 37(5):311-312.
(20) Sundt TM, Jr., Sharbrough FW, Piepgras DG, Kearns TP, Messick JM, Jr., O'Fallon WM. Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy: with results of surgery and hemodynamics of cerebral ischemia. Mayo Clin Proc 1981; 56(9):533-543.
(21) Waltz AG. Effect of blood pressure on blood flow in ischemic and in nonischemic cerebral cortex. The phenomena of autoregulation and luxury perfusion. Neurology 1968; 18(7):613-621.
(22) Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982; 57(6):769-774.
(23) McGrail KM. Intraoperative use of electroencephalography as an assessment of cerebral blood flow. Neurosurg Clin N Am 1996; 7(4):685-692.
(24) Poulin MJ, Robbins PA. Indexes of flow and cross-sectional area of the middle cerebral artery using doppler ultrasound during hypoxia and hypercapnia in humans. Stroke 1996; 27(12):2244-2250.

(25) Sharbrough FW, Messick JM, Jr., Sundt TM, Jr. Correlation of continuous electroencephalograms with cerebral blood flow measurements during carotid endarterectomy. Stroke 1973; 4(4):674-683.
(26) de Borst GJ, Moll FL, van de Pavoordt HD, Mauser HW, Kelder JC, Ackerstaf RG. Stroke from carotid endarterectomy: when and how to reduce perioperative stroke rate? Eur J Vasc Endovasc Surg 2001; 21(6):484-489.
(27) Bleys RL, Cowen T. Innervation of cerebral blood vessels: morphology, plasticity, age-related, and Alzheimer's disease-related neurodegeneration. Microsc Res Tech 2001; 53(2):106-118.
(28) van Denderen JC, van Wieringen GW, Hillen B, Bleys RL. Zinc sulphate-induced anosmia decreases the nerve fibre density in the anterior cerebral artery of the rat. Auton Neurosci 2001; 94(1-2):102-108

Chapter 2

Effect of bilateral carotid occlusion on cerebral hemodynamics and perivascular innervation

An animal experimental model

In preparation

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Abstract

Background
Cerebral blood flow (CBF) is maintained at a constant level by cerebrovascular pressure autoregulation mechanisms. Although the exact physiologic mechanism of cerebral autoregulation is unclear, neurogenic mechanisms are thought to play a regulatory role. Moreover, the degree of fluctuations in CBF is thought to be associated with a particular nerve density. The association between chronic cerebral hypoperfusion and alterations in cerebrovascular nerve density however has never been investigated. The aim of this study was to evaluate the effect of bilateral carotid occlusion on cerebral hemodynamics and perivascular innervation in an animal model.

Methods
Bilateral ligation (n=24) or bilateral sham-operation (n=24) of the two common carotid arteries was performed with a one-week interval. A subgroup of rats (ligated n=6 and sham-operated n=3) underwent MR imaging of the brain to evaluate whether morphological changes to the arterial system and/ or a reduced perfusion of the brain occurred and to determine whether the arteriolar system was still able to respond to a vasodilatory challenge. After termination four weeks after the second procedure the basal cerebral arteries were stained for the general neural marker protein gene product 9.5 (PGP 9.5), tyrosine hydroxylase (TH) to localize sympathetic nerves and vesicular acetylcholine transporter (VAChT) to localize parasympathetic nerves.

Results
Based on in vivo MR angiograms and post mortem macroscopical evaluation five rats were excluded. In all ligated rats a remarkable increase in tortuosity of the posterior communicating artery (Pcom) and first part of the posterior cerebral artery (P1) and the basilar artery was observed. Also an significantly increased median volume of the basilar artery and relative signal intensity in the basilar artery were measured. No significant differences between the ligated and sham-operated rats in cerebral perfusion or cerebrovascular reactivity were found. In the ligated animals the diameters of the first part of the anterior cerebral artery and carotid artery, P1 and Pcom segment were significantly larger compared to the diameters in the sham-operated rats. Also, the ligated animals showed a significant increase in nerve density in both the P1 and Pcom segment. TH staining showed a significant higher nerve density in the Pcom segment in the ligated group as compared to the sham-operated group. VAChT staining resulted in insufficient color contrast for performing computerized image analysis.

Conclusion
Although bilateral common carotid artery occlusion did not result in cerebral hyperperfusion, redistribution of blood flow resulted in significant changes in nerve density. This underlines the close morphological and functional relationships of working mechanisms in the basal cerebral arteries.

Background

Cerebral hypoperfusion due to carotid occlusive stenosis or occlusion has been shown to play an important role in the occurrence of cerebral ischemia.[1] The hemodynamic effect of stenosis in the common carotid artery (CCA) on perfusion of the brain tissue depends mainly on the adequacy of collateral circulatory pathways.[2;3] Most important collaterals are formed by the circle of Willis, which connects the internal carotid arteries and the vertebrobasilar system. The functional role of the CoW in serving as a collateral to prevent cerebral hypoperfusion during carotid surgery and hyperperfusion after surgery is still unpredictable. The cerebral blood flow (CBF) is dependent on cerebral perfusion pressure, the diameter of cerebral blood vessels, the viscosity of the blood, as well as factors affecting these parameters.[5] Under normal circumstances the CBF is unaffected by changes in cerebral perfusion pressure (the difference between the mean arterial pressure and the mean cerebral venous pressure) because of autoregulatory mechanisms. The exact physiological mechanism has not yet been clarified, but the following mechanisms are thought to interact and contribute to the process of cerebral autoregulation: 1) metabolic or chemical mechanisms: vessel diameter and vascular resistance are affected by the concentration of vasoactive substances involved in tissue metabolism (e.g. O_2, CO_2, H^+), 2) myogenic mechanism: the capacity of vascular smooth muscle to constrict in response to a transmural pressure increase, and 3) neurogenic mechanism: cerebrovascular innervation may be involved in controlling cerebral hemodynamics. The nerve supply to the major cerebral arteries consists of sympathetic, parasympathetic, and sensory fibers and their regulatory role manifests itself by a topographical heterogeneity of nerve densities, corresponding to the potential fluctuations in flow to the concerning brain segment. Importantly, the nerve density has been shown to be dynamic with the capacity to adapt to altering functional demands.[6] For example, a decreased metabolic activity induced by anosmia resulted in a decreased nerve density in the anterior cerebral artery, the main arterial supplier of the rhinencephalon.[7] Furthermore, flow-related changes in both rats and humans due to aging and Alzheimer's disease respectively, have been correlated to a decline in nerve density in the anterior cerebral artery.[8,9]

We hypothesized that permanent bilateral CCA occlusion in rats, an established animal model to study the effect of chronic cerebral hypoperfusion-related changes, may result in a decreased perfusion of the brain and subsequent flow-related alterations in cerebral artery nerve density.[4] Therefore, the purpose of this study was to evaluate the effects of a staged bilateral CCA occlusion on cerebral hemodynamics and nerve density of the basal cerebral arteries in rats.

Materials and methods

Rat ligation model

Between October 2012 and November 2013, 48 Crl:CD (Sprague Dawley) rats (300-350 gram Charles River Laboratories, Wilmington, MA) were used in this study. We used a modified bilateral ligation procedure with a one-week interval between the first and the second CCA occlusion.[10] (Figure 1) After an acclimatization period of two weeks, rats were

pre-medicated with buprenorphine (0.05 mg/kg i.m.), anaesthetized with 4% isoflurane (induction) and 2% isoflurane (maintenance). After shaving and disinfection with iodine rats were placed on a heating pad. Rats were randomly assigned to first left-sided or first right-sided operation. A midline ventral incision was made and the unilateral CCA was separated from the cervical sympathetic and vagal nerves. In 24 rats, the unilateral CCA was subsequently ligated with 6-0 silk suture; in the other 24 rats the CCA was exposed, but not ligated (sham-operated). After hemostasis intra-cutaneous closure with Vicryl 4-0 was performed. One week after one-sided operation, the contralateral CCA was operated, resulting in 24 rats with bilateral ligation and 24 rats with a bilateral sham procedure. The animals were allowed to recover in the operation room and were housed in groups with 12/12 hours light/dark cycle. Both the sham-operated and ligated animals were processed for immunohistochemical studies at 28 days after the second surgical procedure.[7]

Figure 1. Timeline. T=0: preoperative), T=1: two weeks after bilateral ligation) and T=2: four weeks after bilateral ligation).

Magnetic Resonance Imaging (MRI)

A subgroup of rats (ligated n=6 and sham-operated n=3) underwent MR imaging of the brain in a 4.7 T animal MR system (Agilent, Palo Alto, CA, USA) at t=0 (before ligation), t=1 (two weeks after bilateral ligation) and t=2 (four weeks after bilateral ligation, just before sacrifice). See Figure 1. During MR scanning the rats were mechanically ventilated with 2% isoflurane in an air:O_2 (2:1) mixture. The animals were restrained in the scanner with earplugs and a tooth-holder. Body temperature was measured with a rectal probe and was kept at 37°C with a heating pad during the imaging procedure. A home-built Helmholtz volume coil (i.d. 90 mm) was used for signal excitation and a 35 mm inductively coupled surface coil was used for signal reception. To evaluate whether morphological changes to the arterial system in the rat brain occurred, two flow-compensated 3D time-of-flight MR angiograms of the basal cerebral arteries were acquired (repetition time (TR)/echo time (TE) 20/2 ms, flip angle 40°, field-of-view (FOV) 20 x 25.2 x 15.2 mm^3, data matrix size 100 x 126 x 76 points, 4 averages). The second angiogram was acquired at 7.5 mm posterior to the first one. Additionally, perfusion MRI with arterial spin labeling (ASL) using Flow-Sensitive Alternating Inversion Recovery (FAIR)[11,12] and a 2-shot gradient-echo EPI acquisition (TR/TE 10000/4.8 ms, delay between images in the inversion curve 150 ms, flip angle 10°, FOV 32 x 32 mm^2, data matrix 64 x 64, slice thickness 2 mm, selective inversion slab: 10 mm, 16 averages) was performed to determine whether the ligation caused reduced perfusion of the brain. Cerebrovascular reactivity testing using carbogen inhalation and blood oxygenation level-dependent (BOLD) MRI acquisition was

used to determine whether the arteriolar system was still able to respond to a vasodilatory challenge. The BOLD acquisition protocol consisted of a 2D single shot spin-echo EPI acquisition (TR/TE 2000/27 ms, FOV 32 x 32 mm^2, data matrix size 64 x 64 points, 24 coronal slices of 0.5 mm thickness) repeated 600 times. During the first 150 acquisitions the rat was ventilated with an air:O_2 (2:1) mixture, followed by 150 acquisitions with 100% O_2. The third set of 150 acquisitions was performed during ventilation with carbogen (5% CO_2, 95% O_2), and this was followed by 150 acquisitions during ventilation with the air:O_2 mixture again.

Tissue preparation

Four weeks after the second operation the rats were terminated by perfusion fixation with a Watson Marlow SCI 323 peristaltic pump (Watson-Marlow Pumps Group, Falmouth, Cornwall, UK). Under anesthesia (sodium pentobarbital 0.1 ml/100 gram body weight i.p.) a cannula was inserted into the ascending aorta and the rats were successively perfused with 300 ml 0.9% NaCl containing 5000 IE heparin, 500 ml 4% paraformaldehyde in 0.1M phosphate buffer (pH 7.4, at 4°C) and 500ml 15% sucrose in 0.1M phosphate buffer (pH 7.4).[7] Subsequently, the brains including the basal cerebral arteries were removed and stored in 15% sucrose in 0.1M phosphate buffer (pH 7.4).

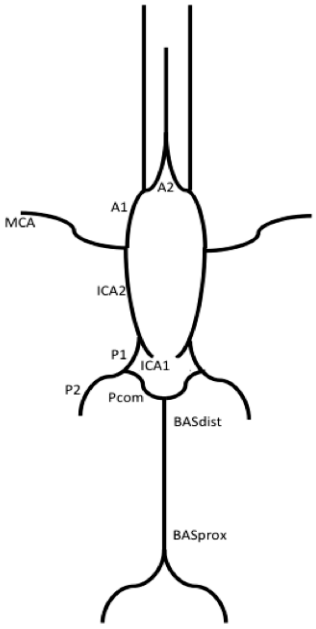

Figure 2. Schematic overview of basal cerebral arteries and segments of the circle of Willis.
A1: first part of the anterior cerebral artery
A2: second part of the anterior cerebral artery
ICA1: first part of the internal carotid artery
ICA2: second part of the internal carotid artery
MCA: middle cerebral artery
P1: first part of the posterior cerebral artery
P2: second part of the posterior cerebral artery
Pcom: posterior communicating artery
BASprox: proximal part of the basilar artery
BASdist: distal part of the basilar artery.

Immunohistochemistry

After termination all subjects were macroscopically evaluated for succeeded ligation. If the ligation was questionable based on either in vivo MR angiograms or post mortem macroscopical evaluation these rats were excluded from further analysis. The basal cerebral arteries were dissected in segments (Figure 2) and mounted on Sylgard (Dow Corning, Midland, MI USA) with entomology needles. Subsequently, the ligated group (n=24) and sham-operated group (n=24) were divided into three subgroups (each n=8), which underwent various immunohistochemical procedures to localize the general neural marker protein gene product 9.5 (PGP 9.5), the parasympathetic nerves containing vesicular acetylcholine transporter (VAChT), or the sympathetic nerves containing tyrosine hydroxylase (TH). The segments selected for PGP 9.5 staining were washed three times in Hepes buffer containing 0.1% Triton X-100 for 10 minutes followed by incubation of 5% normal swine serum (Jackson immunoresearch, West Grove, PA, USA) in Hepes buffer containing 0.1% Triton X-100 for 90 minutes. Subsequently, they were incubated in Rabbit anti-PGP 9.5 (Millipore, Temecula, CA, USA) diluted 1:400 in Hepes buffer containing 0.1% Triton X-100, 0.1% DL lysine and 1% normal swine serum for 48 hours at 4°C. After two days the segments were washed three times in PBS for 10 minutes and the segments were incubated in fluorescein isothiocyanate (FITC)- conjugated swine anti-Rabbit serum (Dako, Denmark) diluted in 1:40 in PBS containing 1% normal swine serum, 0.1% Triton X-100 and 0.1% DL-lysine for 90 minutes. Thereafter, the segments were washed three times in PBS for 10 minutes and stained for 10 minutes in 0.05% pontamine sky blue (Gurr, Poole, UK) to reduce background autofluorescence and washed in PBS three times for five minutes.[13] Lastly, the segments were stretched on glass slides and mounted with Vectashield (Vector Laboratories, Inc., Burlingame, CA) mounting medium. A second series of segments selected for VAChT staining were washed three times in Hepes buffer containing 0.1% Triton X-100 for 10 minutes followed by incubation of 5% normal goat serum (Jackson immunoresearch, West Grove, PA, USA) in Hepes buffer containing 0.1% Trion X-100 for 90 minutes. The segments were subsequently incubated overnight at room temperature in Rabbit anti-VAChT (Abcam, Cambridge, MA, USA) diluted 1:1500 in Hepes buffer containing 0.1% Triton X-100, 0.1% DL lysine, 1% normal goat serum and 5% Bovine Serum Albumin (Across Organics, Fair Lawn, New Jersey, USA) After washing three times in PBS for 10 minutes the segments were incubated in Streptavidin FITC (Dako, Denmark) diluted in 1:1000 in PBS containing 0.1% Triton X-100 and 0.1% DL-lysine for 90 minutes. Thereafter, the segments were washed three times in PBS for 10 minutes and stained for 10 minutes in 0.05% pontamine sky blue and washed in PBS three times for five minutes. Lastly, the segments were stretched on glass slides and mounted with Vectashield mounting medium. A third series of segments selected for TH staining were washed three times in Hepes buffer containing 0.1% Triton X-100 for 10 minutes followed by incubation of 5% normal swine serum (Jackson immunoresearch, West Grove, PA, USA) in Hepes buffer containing 0.1% Trion X-100 for 90 minutes and subsequently incubated overnight at room temperature in Rabbit anti-TH (Pel-Freez biological, Rogers, AR, USA) diluted 1:400 in Hepes buffer containing 0.1% Triton X-100, 0.1% DL lysine and 1% normal swine serum. The next day the segments were washed three times in PBS for 10 minutes and incubated in FITC-conjugated swine anti-Rabbit serum diluted in 1:40 in PBS containing 1% normal swine serum, 0.1% Triton X-100 and 0,1% DL-lysine for 90 minutes. Thereafter, the segments were washed three times in PBS for 10 minutes and stained for 10 minutes

in 0.05% pontamine sky blue and washed in PBS three times for five minutes. Lastly, the segments were stretched on glass slides and mounted with Vectashield mounting medium.

Image processing and analysis

For quantification of PGP 9.5, VAChT and TH reactivity at the adventitial-medial border in the segments of the basal cerebral arteries (Figure 2) microscope slides were reviewed using an Axiophot fluorescence microscope (Carl Zeiss, Oberkochen, Germany) and images were obtained at 20X using a Leica digital camera (DFC 420C, Leica Camera, AG, Germany) and Leica application Suite acquisition software. Images were imported in the public domain software for image analysis, ImageJ, and subjected to an established method of image analysis.[14] Blinded to ligation status, the diameters of the basal cerebral arteries were measured and in each image, the area percentage (percentage of specific fluorescence in the measuring frame) was scored in three random chosen fields, which were subsequently averaged and used for further analysis. The two MRA images were combined into one image for visual inspection, where the anterior part of the posterior image was removed in favor of the anterior image. The images were also normalized to compensate for the signal decay as a result of the use of a surface coil. In each individual MRA image the area containing the basilar artery was manually selected. The number of voxels with a signal intensity above a threshold of 0.2 times the maximum signal intensity in the selected area was counted as belonging to the basilar artery. Multiplication with the voxel dimensions thus provides apparent artery volumes. Apparent CBF values were obtained by manually selecting the brain in the last images of the non-slice-selective inversion series. The signal intensity of this region of interest (ROI) was summed for each image in each inversion series. The signal difference between the signal intensity of the non-slice-selective inversion series was subtracted from the slice-selective image series, thus producing a signal difference curve, that can be fitted to a modified equation as described by Kober et al. (2008):[12]

$$\Delta S = C_{inv} S_0 \frac{CBF}{\lambda} \left(\frac{e^{-TI \cdot R_1^{app}} - e^{-TI \cdot R_1^{A}}}{R_1^{A} - R_1^{app}} \right)$$

Where C_{inv} is a constant depending on the inversion efficiency and the Look-Locker saturation, which was estimated to be 2 (perfect inversion and no saturation). S_0 is the signal intensity of the brain without any weighting. l is the blood partition coefficient which was estimated to be 0.9 ml/g. TI is the inversion time. R_1^{A} and R_1^{app} are the relaxation time of blood (estimated to be 2.5 s) and apparent relaxation time of the tissue (in the slice-selective inversion case), respectively. R_1^{app} was obtained from the measured inversion relaxation curve. Time-dependent signal intensities as a result of the BOLD effect during a carbogen challenge were obtained by manually outlining the rat's brain in the images and averaging the signal intensity of all voxels in the brain. This signal was normalized by dividing it with the mean signal intensity obtained during the air/O_2 ventilation period

at the start. Changes in signal intensity were observed relative to this signal intensity.

Statistical analysis

This study had a statistical power of 90% to identify a difference of 3.0 area-percent nerve density, given a two-sided value of 0.05 and a standard deviation of 1.7.[7] Based on these calculations eight rats were required in each group for each staining. Continuous variables are presented as median (IQR: interquartile range). Due to the limited sample size, non- parametric tests were used. Nerve densities between groups were compared using the Mann-Whitney *U* test, whereas the Friedman test was used for comparison of multiple groups with repeated measures. All analyses were performed using commercially available statistical software (SPSS 20.0, SPSS Inc, Chicago, Il). A two-sides p-value <0.05 was considered significant.

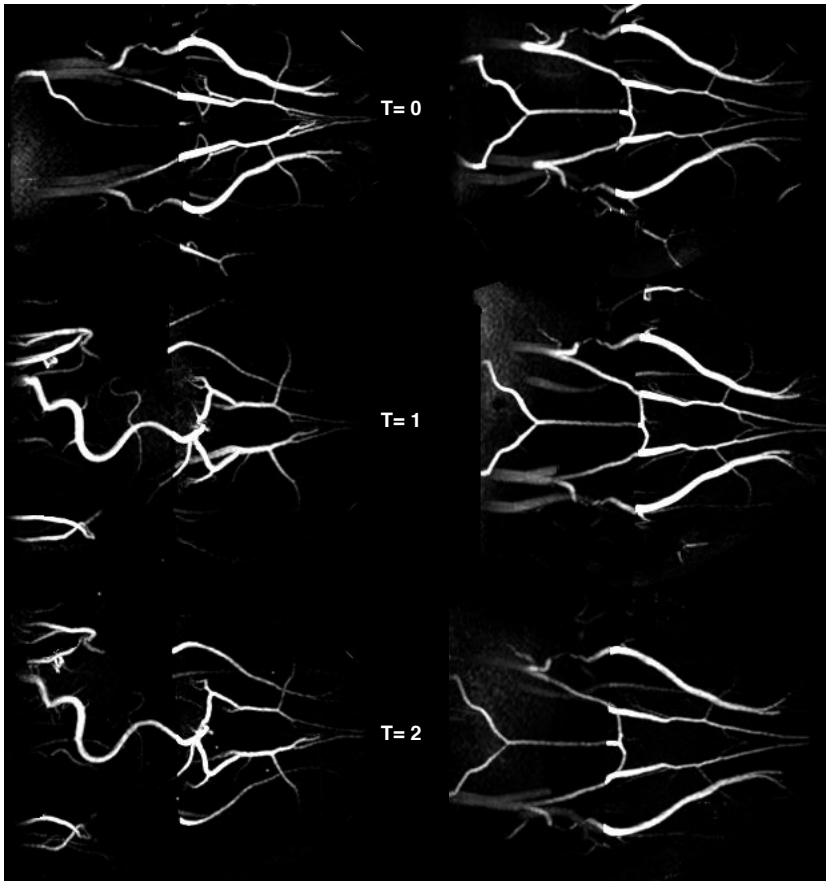

Figure 3. MR images of one ligated rat (left) and one sham-operated rat (right) group at T=0 (preoperative), T=1 (two weeks after bilateral ligation) and T=2 (four weeks after bilateral ligation).

Results

Ligation procedure and macroscopical analysis
All rats survived the whole study period. Two rats developed a subcutaneous hematoma following surgery, which was relieved during the second procedure. In six rats unilateral ptosis was observed postoperatively, which persisted till termination. Based on in vivo MR angiograms and post mortem macroscopical evaluation uncertainty existed on achieved occlusion in five rats which were subsequently excluded for further analysis.

MRI
A subgroup of ligated (n=6) and sham operated (n=3) rats underwent MR scanning three times. Four of the ligated rats showed bilateral CCA occlusion at t=1 and t=2, while two of the rats only showed a unilateral occlusion of the CCA. In all ligated rats a remarkable increase in tortuosity of the posterior communicating artery (Pcom segment) and first part of the posterior cerebral artery (P1 segment) and the basilar artery was observed at t=1 and t=2, compared to t=0 (before operation). See Figure 3. In the ligated rats a significantly increased median volume of the basilar artery (p= 0.05) and relative signal intensity in the basilar artery (p= 0.04) were measured (Table 1a). In the sham-operated rats, the CCAs were patent at t=0, t=1 and t=2, and no tortuosity of the basilar artery was observed. The median volumes and relative median signal intensity of the basilar artery did not change (both p=0.72).

Basilar artery volumes (μl)		**T=0**	**T=1**	**T=2**	**p-value**
Ligated	Median (IQR)	16 (14- 18)	29 (26- 47)	34 (25- 42)	0.05*
Sham	Median (IQR)	20 (19- 21)	22 (18- 29)	21 (18- 28)	0.72
Relative signal intensity (%)					
Ligated	Median (IQR)	0.0031 (0.0018- 0.0045)	0.011 (0.0097- 0.0122)	0.0095 (0.0074- 0.0107)	0.04*
Sham	Median (IQR)	0.0040 (0.0036- 0.0068)	0.0048 (0.0016- 0.0051)	0.0072 (0.0043- 0.0079)	0.72
CBF (ml/100g)					
Ligated	Median% (IQR)	303 (283-334)	278 (211- 287)	268 (218- 313)	0.26
Sham	Median% (IQR)	299 (232-580)	312 (236- 393)	269 (224- 317)	0.37

Table 1. Median values and interquartile range (IQR) volumes (μl) and relative signal intensity (%) of the basilar artery (A) and apparent cerebral blood flow values (CBF, B: ml/100g/min) in the ligated and sham-operated rats at T=0 (preoperative), T=1 (two weeks after bilateral ligation) and T=2 (four weeks after bilateral ligation). Statistically significant differences are indicated by an asterisk (*).

	ICA1	ICA2	MCA	ACA1	ACA2	P1	P2	P-com	Bas-prox	Bas- dist
Sham- operated	22,8 (22,1-24,6)	20,3 (19,1- 23,1)	10,6 (9,5- 11,5)	28.9 (24,3- 29,3)	27,4 (23,3- 29,4)	6,6 (5,4- 7,4)	5,6 (4,7- 6,3)	3,2 (2,4- 4,3)	3,7 (3,1- 7,6)	3,9 (3,5- 5,6)
N	8	10	10	10	8	8	10	8	5	7
Ligated	19,6 (19,3-26,2)	18,9 (17,8- 21,4)	8,8 (5,4- 10,5)	24,3 (23,5-25,6)	25,9 (21,3- 27,1)	10,1 (8,7- 10,5)	6,3 (5,2- 7,9)	6,4 (5,8- 6,5)	8,5 (4,1-12,5)	5,7 (4,3- 6,5)
N	3	5	5	6	5	6	7	5	3	4
p-value	0,41	0,27	0,11	0,08	0,38	0,003*	0,08	0,003*	0,18	0,09

Table 2A. Median values and interquartile range (IQR) area percentage of protein gene product 9.5 (PGP 9.5)-immunoreactive nerve fibers in various segments of the basal cerebral arteries from ligated and sham-operated animals. Statistically significant differences are indicated by an asterisk (*). For abbreviations see Figure 2 legend. N= number of rats.

	ICA1	ICA2	MCA	ACA1	ACA2	P1	P2	P-com	Bas-prox	Bas- dist
Sham- operated	16,6 (15,3-19,8)	14,7 (12,3- 16,3)	7,8 (6,3- 10,0)	23,8 (19,0- 29,0)	20,7 (15,7- 28,0)	4,9 (3,7- 7,6)	3,9	3,2 (2,4- 4,3)	3,7 (3,1- 7,6)	3,9 (3,5- 5,6)
N	10	10	10	10	8	9	10	6	10	7
Ligated	16,3	4,7	8,8 (5,4- 10,5)	24,3 (23,5-25,6)	25,9 (21,3- 27,1)	10,1 (8,7- 10,5)	6,3 (5,2- 7,9)	6,4 (5,8- 6,5)	8,5 (4,1-12,5)	5,7 (4,3- 6,5)
N	7	7	7	8	6	7	7	4	5	5
p-value	0,50	0,92	0,33	0,05	0,70	0,63	0,85	0,02*	0,22	0,17

Table 2B. Median values and interquartile range (IQR) area percentage of tyrosine hydroxylase (TH)-immunoreactive nerve fibers in various segments of the basal cerebral arteries from ligated and sham-operated animals. Statistically significant differences are indicated by an asterisk (*). For abbreviations see Figure 2 legend. N= number of rats.

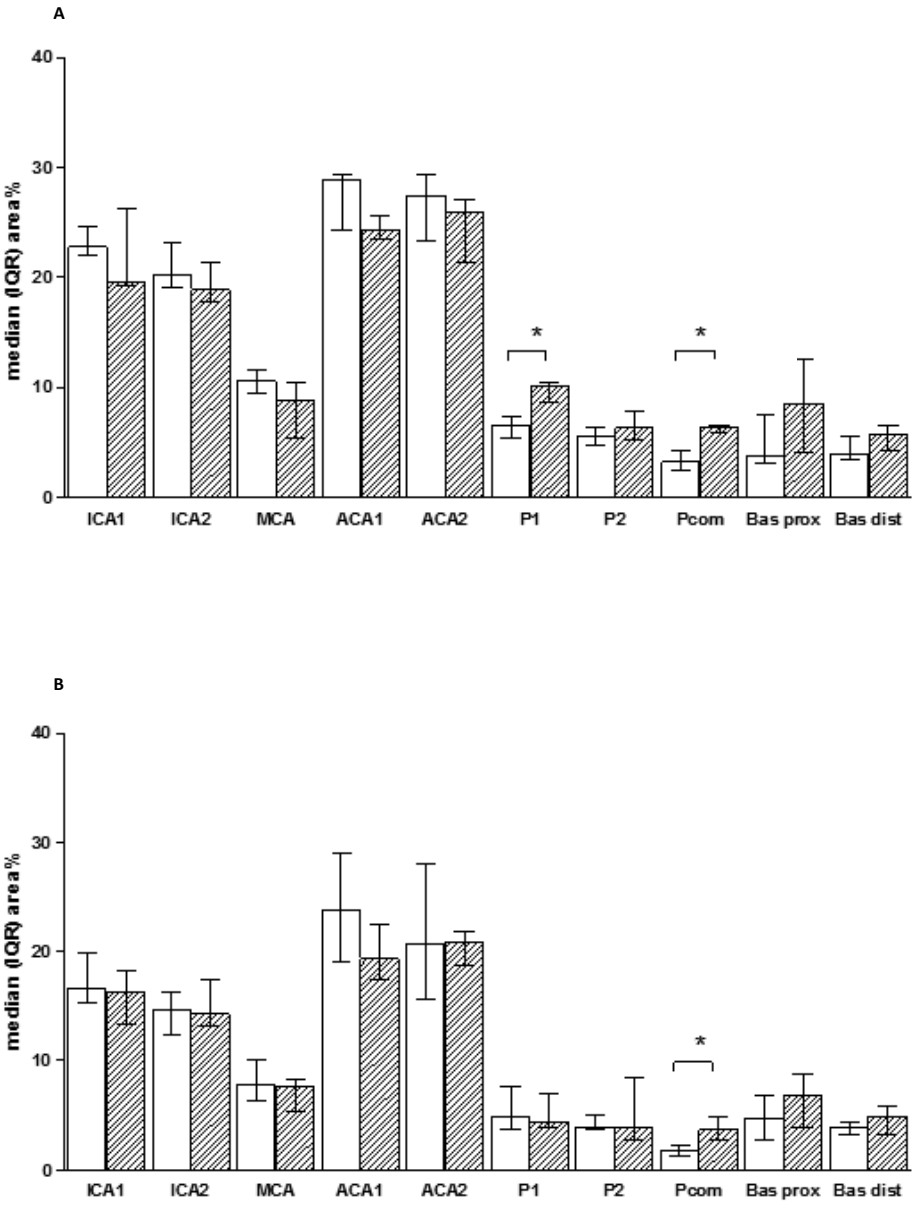

Figure 5. Median values and interquartile range (IQR) area percentage of PGP 9.5-immunoreactive nerve fibers (A) and TH-immunoreactive nerve fibers (B) in various segments of the basal cerebral arteries from sham-operated (white) and ligated animals (striped). Statistically significant differences are indicated by an asterisk (*). For abbreviations see Figure 2 legend.

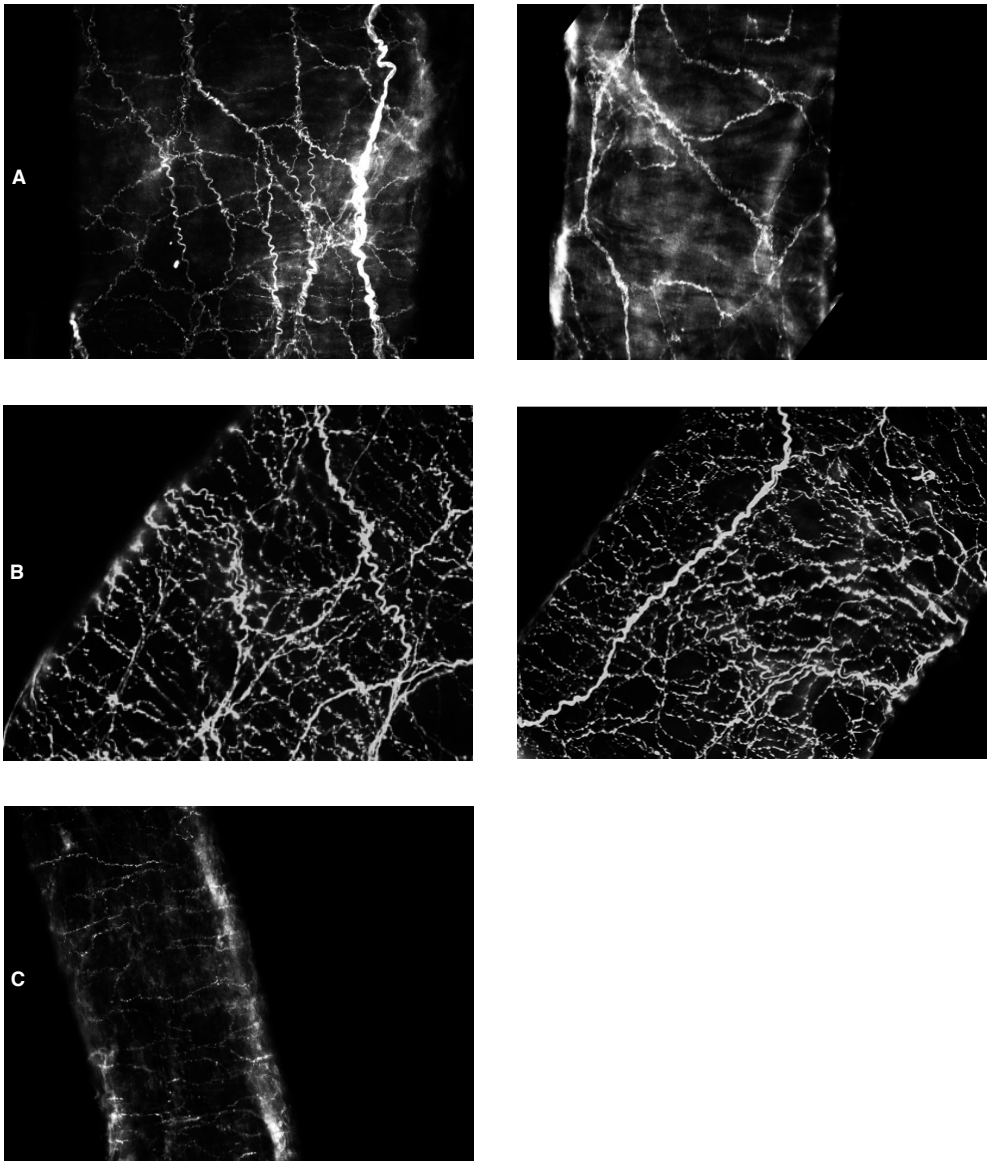

Figure 4.
A. Whole mount preparations of perivascular nerves stained for TH, A1 segment of a ligated (left) and a sham-operated rat (right). B. Whole mount preparations of perivascular nerves stained for PGP 9.5, Pcom segment of a ligated (left) and a sham-operated rat (right). C. Whole mount preparation of perivascular nerves stained for VAChT, B, P1 segment of a ligated rat. For abbreviations see Figure 2 legend.

Carbogen challenge
In all rats an increase in signal intensity was observed at t=0, t=1 and t=2 for both the switch from air to oxygen and for the switch from oxygen to carbogen, without significant difference between sham-operated and ligated rats.

Perfusion measurements
No significant differences in apparent CBF between the ligated and sham-operated rats were found (Table 1). The differences fell within the natural range of deviations.

Immunohistochemistry analysis
The diameters of the first part of the anterior cerebral artery (median 1.00 mm, IQR: 0.88- 1.08, versus median 0.82 mm, IQR: 0.77-0,93, respectively, p= 0.03), first part of the carotid artery (median 1.21 mm, IQR: 1.09- 1.27 versus median 1.06 mm, IQR: 0.96-1.17, respectively, p= 0.03), P1 segment (median 0.99 mm, IQR: 0.82- 1.14 versus median 0.81 mm, IQR: 0.75-0.85, respectively, p= 0.05) and Pcom segment (median 0.99 mm, IQR: 0.82- 1.14 versus median 0.60 mm, IQR: 0.48-0.69, respectively, p< 0.001) in the ligated rats were significantly larger compared to the diameters in the sham-operated rats.

PGP 9.5 immunoreactivity
In all studied segments PGP 9.5 immunoreactivity was seen in the deep nerve plexus at the adventitial medial border. The PGP 9.5 nerve density was greatest in the anterior segments of the basal cerebral arteries (Figure 4A). The ligated animals showed a significant increase in nerve density compared to the sham-operated animals, in both the P1 segment, median area 10.1% (IQR:8.7- 10.5) versus 6.6% (IQR: 5.5-7.4) respectively, p= 0.003 and the Pcom segment, median area 6.4% (IQR: 5.8-6.5) versus 3.2% (IQR: 2.4- 4.3) respectively, p=0.003 (Table 2A, Figure 5). When rats with ptosis were excluded, the nerve density in the P1 segment and Pcom segment were still significantly different between the ligated and sham-operated rats (both p=0.006, data not shown).

TH immunoreactivity
In all studied segments TH immunoreactivity was observed in the deep nerve plexus at the adventitial medial border (Figure 4B). The topographical distribution between the ligated and sham-operated group did not differ. The highest nerve density was found in the anterior segment of the circle of Willis. Posteriorly, the nerve density in the Pcom segment was significantly higher in the ligated group as compared to the sham-operated group, it was median 3.7% (IQR: 2.8-4.8) versus 1.7% (IQR: 1.3- 2.2, p= 0.02), respectively (Table 2B, Figure 5). When rats with ptosis were excluded, there was still a significant difference in sympathetic nerve density in the P1 segment (p= 0.02, data not shown).

VAChT immunoreactivity
Unfortunately, VAChT staining generally resulted in unsatisfactory color contrast, making it impossible to perform computerized image analysis of VAChT reactivity (Figure 4C). Visual impression of the presence of VAChT containing nerves revealed that VAChT was present in the circular oriented terminal plexus at the adventitial medial border in all investigated segments.

Discussion

The major findings of this study are the remarkable changes in morphology and nerve density of the posteriorly located basal cerebral arteries that developed after bilateral CCA ligation in rats. Probably the procedure induced a major redistribution of blood supply to the head accompanied by increased flow fluctuations through the vertebral and basilar arteries, resulting in increased basilar artery and Pcom tortuosity, as well as enlargement and concurrent increase in the nerve supply of the Pcom and P1 segments. However, in the applied animal model no significant changes in cerebral perfusion or cerebrovascular reactivity were measured during follow-up. These findings suggest that the brain's undiseased vascular system has a large adaptation range to compensate the bilateral CCA ligation. Previously, bilateral CCA occlusion in rodents has been performed to study the effects of chronic hypoperfusion on cognitive dysfunction, neurogenerative processes, ischemic white matter injury and ischemic eye disease.[4] The fact that bilateral CCA occlusion did not result in significant chronic cerebral hypoperfusion in the current study may be explained by the surgical procedure chosen. In our experience (unpublished data), confirmed by others,[10] contemporaneously bilateral CCA ligation was followed by progressive neurologic deterioration in the first 48 hours postoperatively with a survival rate of <10-40%. Therefore we used a modified surgical procedure with a one week interval between the ipsilateral and contralateral ligation to avoid a too abrupt reduction of CBF. As a consequence the survival rate was 100% the highest compared to previous reports.[15] It has been shown previously that gradual occlusion of a vessel results in a less deleterious effect on the tissue elements of the distal territory in comparison to an abrupt occlusion,[16] while changes in cognitive impairment are comparable to the conventional model. It is imaginable that immediately after the performance of the second ligation, CBF was reduced but that it was normalized after two weeks, when we measured. Chronic CBF recovery after bilateral CCA ligation in rats has been observed previously, however CBF remained slightly but significantly lowered up to at least four weeks after bilateral CCA ligation as compared to controls.[17] The current observation that the nerve density in the posteriorly located basal cerebral arteries increases with an increase in blood flow, is in line with previous findings that the regional nerve density correlates with local blood flow[18] and has the capacity to adapt to altering functional demands.[6] It seems that changes in flow and pressure trigger the adaptation of cerebrovascular innervation until a new optimal innervation pattern is reached. As the sympathetic nerves are capable of producing alteration in cerebral perfusion,[18,19] we hypothesize that in order to keep the CBF within normal range, neurotrophic factors are released in response to local changes in flow and pressure, resulting in an increase in sympathetic nerve density. This finding supports the hypothesis that the sympathetic nerves play a functional role in regulation of CBF and are therefore part of the autoregulation mechanism. It is unclear whether the changes in nerve density as observed in the current study are temporary or permanent. It may be interesting to study whether these changes are reversible and disappear after restoration of blood flow in the carotid artery. From the clinical point of view this would be of importance to understand the relevance of chronic carotid occlusion on autoregulatory mechanisms when operating on the contralateral carotid artery with implications on the need for intraoperative shunting, as well as the risk for postoperative hyperperfusion.

The results of this study should be interpreted in the context of its design. Because of technical reasons animal studies are required to investigate the influence of redistribution of blood flow on cerebrovascular innervation. Moreover, experimental animal studies can utilize pure models as cerebrovascular innervation can be influenced by several other factors such as degenerative processes, ageing, silent cerebral embolism, and diabetes mellitus.[20] A different topographical distribution of the nerve density in the vascular system between humans and rats has been described. In humans the posterior segment of the cerebral circulation has been described as most densely innervated as compared to the anterior segment, whereas in rats the highest nerve density was found in the anterior cerebral artery.[6,21] As this contrast might be due to a higher metabolic need of the vascular territory of this segment in comparison to other vascular territories of the brain, such as arteries supplying the visual cortex in humans and rhinencephalic structures respectively, we do not believe this difference has influenced our results. We acknowledge that in man carotid artery disease is an indicator of generalized atherosclerosis and that in many patients with symptomatic carotid artery disease also intracranial carotid artery disease exists,[22] while in healthy rats other alterations of vessels are absent. In addition, progressive generalized atherosclerosis may limit compensatory mechanisms in man, ultimately resulting in watershed infarction. Some discussion on the MRAs is necessary. The TOF method is dependent on the amount and speed of the flow going through the arteries. The initial flow through the rat's basilar artery may have been too low for robust visualization with MRA with the chosen settings. After bilateral CCA occlusion the flow presumably increases, which improves the reliability of detection of the basilar artery. Consequently, the measurements of the diameter of the vessel should be interpreted with caution. In six rats ptosis was observed, however as no significant difference between rats with and without ptosis was found, we do not believe the ptosis was a symptom of a complete interruption of the sympathetic nervous system and we did not exclude these rats from our analysis.

In conclusion, our findings provide support for the hypothesis that bilateral CCA occlusion results in alterations in cerebral hemodynamics and nerve density and underline close morphological and functional relationships of working mechanisms in the basal cerebral arteries.

Acknowledgements

We thanks Mr. J.W. de Groot for assistance with immunohistochemistry and Dr. T.A.P. Roeling for technical help with image analysis.

References

(1) Klijn CJ, Kappelle LJ, Tulleken CA, van GJ. Symptomatic carotid artery occlusion. A reappraisal of hemodynamic factors. Stroke 1997; 28(10):2084-2093.

(2) Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. Ann Neurol 1991; 29(3):231-240.

(3) Sillesen H, Schroeder T. Haemodynamic evaluation of carotid artery disease. Clin Phys Physiol Meas 1989; 10 Suppl A:15-22.:15-22.

(4) Farkas E, Luiten PG, Bari F. Permanent, bilateral common carotid artery occlusion in the rat: a model for chronic cerebral hypoperfusion-related neurodegenerative diseases. Brain Res Rev 2007; 54(1):162-180.

(5) Ursino M. Regulation of the circulation of the brain. In: Bevan RD, Bevan JA, editors. The human brain circulation: functional changes in disease. Totowa, New Jersey: Humana Press; 1994. 291-318.

(6) Bleys RL, Cowen T. Innervation of cerebral blood vessels: morphology, plasticity, age-related, and Alzheimer's disease-related neurodegeneration. Microsc Res Tech 2001; 53(2):106-118.

(7) van Denderen JC, van Wieringen GW, Hillen B, Bleys RL. Zinc sulphate-induced anosmia decreases the nerve fibre density in the anterior cerebral artery of the rat. Auton Neurosci 2001; 94(1-2):102-108.

(8) Martin AJ, Friston KJ, Colebatch JG, Frackowiak RS. Decreases in regional cerebral blood flow with normal aging. J Cereb Blood Flow Metab 1991; 11(4):684-689.

(9) Salehi A, Lucassen PJ, Pool CW, Gonatas NK, Ravid R, Swaab DF. Decreased neuronal activity in the nucleus basalis of Meynert in Alzheimer's disease as suggested by the size of the Golgi apparatus. Neuroscience 1994; 59(4):871-880.

(10) Cechetti F, Worm PV, Pereira LO, Siqueira IR, Netto A. The modified 2VO ischemia protocol causes cognitive impairment similar to that induced by the standard method, but with a better survival rate. Braz J Med Biol Res 2010; 43(12):1178-1183.

(11) Gunther M, Bock M, Schad LR. Arterial spin labeling in combination with a look-locker sampling strategy: inflow turbo-sampling EPI-FAIR (ITS-FAIR). Magn Reson Med 2001; 46(5):974-984.

(12) Kober F, Duhamel G, Cozzone PJ. Experimental comparison of four FAIR arterial spin labeling techniques for quantification of mouse cerebral blood flow at 4.7 T. NMR Biomed 2008; 21(8):781-792.

(13) Cowen T, Haven AJ, Burnstock G. Pontamine sky blue: a counterstain for background autofluorescence in fluorescence and immunofluorescence histochemistry. Histochemistry 1985; 82(3):205-208.

(14) Cowen T, Thrasivoulou C. Cerebrovascular nerves in old rats show reduced accumulation of 5-hydroxytryptamine and loss of nerve fibres. Brain Res 1990; 513(2):237-243.

(15) Tsuchiya M, Sako K, Yura S, Yonemasu Y. Cerebral blood flow and histopathological changes following permanent bilateral carotid artery ligation in Wistar rats. Exp Brain Res 1992; 89(1):87-92.

(16) Kaliszewski C, Fernandez LA, Wicke JD. Differences in mortality rate between abrupt and progressive carotid ligation in the gerbil: role of endogenous angiotensin II. J Cereb Blood Flow Metab 1988; 8(2):149-154.

(17) Otori T, Katsumata T, Muramatsu H, Kashiwagi F, Katayama Y, Terashi A. Long-term measurement of cerebral blood flow and metabolism in a rat chronic hypoperfusion model. Clin Exp Pharmacol Physiol 2003; 30(4):266-272.

(18) Edvinsson L, Hamel E. Perivascular Nerves in Brain Vessels. In: Edvinsson L, Krause DN, editors. Cerebral Blood Flow and Metabolism. Lippincott Williams & Wilkins; 2002. 43-67.

(19) Sercombe R, Aubineau P, Edvinsson L, Mamo H, Owman CH, Pinard E et al. Neurogenic influence on local cerebral blood flow. Effect of catecholamines or sympathetic stimulation as correlated with the sympathetic innervation. Neurology 1975; 25(10):954-963.

(20) Sarti C, Pantoni L, Bartolini L, Inzitari D. Cognitive impairment and chronic cerebral hypoperfusion: what can be learned from experimental models. J Neurol Sci 2002; 203-204:263-266.

(21) Bleys RL, Cowen T, Groen GJ, Hillen B, Ibrahim NB. Perivascular nerves of the human basal cerebral arteries: I. Topographical distribution. J Cereb Blood Flow Metab 1996; 16(5):1034-1047.

(22) Kappelle LJ, Eliasziw M, Fox AJ, Sharpe BL, Barnett HJ. Importance of intracranial atherosclerotic disease in patients with symptomatic stenosis of the internal carotid artery. The North American Symptomatic Carotid Endarterectomy Trail. Stroke 1999; 30(2):282-286.

Chapter 3

Incompleteness of the circle of Willis is related to the need for shunting during carotid endarterectomy

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Abstract

Background
The occurrence of cerebral ischemia during carotid endarterectomy (CEA) can be prevented by (selective) placement of an intraluminal shunt during cross-clamping. We set out to develop a rule to predict the likelihood for shunting during CEA based on preoperative assessment of collateral cerebral circulation and patient characteristics

Methods
Patients who underwent CEA between January 2004 and November 2010 were included. Patients without preoperative magnetic resonance or computed tomography angiography were excluded. Primary endpoint was intraluminal shunt placement based on electroencephalography changes. Age, sex, cardiovascular risk factors, degree of ipsilateral and contralateral carotid en vertebral artery stenosis and the presence of variations in segments of the circle of Willis were studied as potential predictors for shunt use. A prediction model was derived from a multivariable regression model using discrimination, calibration, bootstrapping approaches and transformed into a clinical prediction model.

Results
In the study 431 patients were included, of which 65 patients (15%) received an intraluminal shunt. Factors related to the use of shunt in multivariate analysis were ipsilateral high degree carotid stenosis (90-99%; Odds ratio [OR]: 0.23, 95%CI:0.09-0.57), contralateral carotid occlusion (OR 3.13, 95%CI:1.55-6.29) and a not-visible anterior (OR 3.73, 95%CI:1.90-7.32) or ipsilateral posterior segment of the circle of Willis (OR 2.59, 95% CI:1.38- 4.87) respectively. The c-statistic of this model was 0.74 (95% CI 0.67- 0.80). Among patients with an estimated chance that a shunt would be needed of lower than 10%, (49% of the population) the likelihood of shunting was 6%. In those in whom this chance was estimated higher than 30% (14% of the population) the likelihood was 40%.

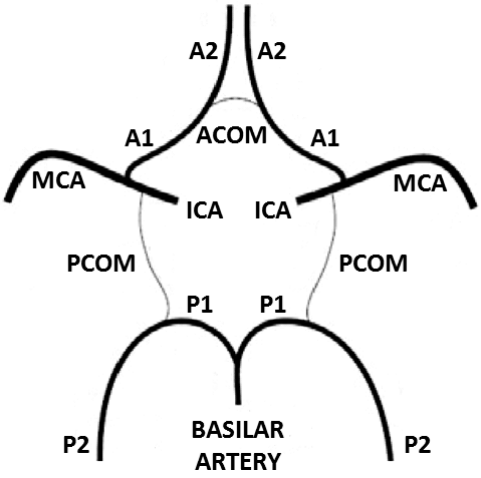
Conclusion
Among patients scheduled for CEA, assessment of cerebropetal arteries and of the configuration of the circle of Willis can help to identify patients with low and high likelihood of the need of shunt use during surgery.

Background

During carotid endarterectomy (CEA), cross clamping (CC) may induce intraoperative cerebral ischemia. This can be grossly prevented or diminished by placement of an intraluminal shunt during CC. Furthermore, a sufficient collateral circulation is important to maintain adequate blood supply to the brain in case of interruption of one of the principle blood suppliers by CC. The Circle of Willis (CoW) plays an important role in the collateral circulation, both by the anterior communicating artery (A-com), which connects the right and left anterior cerebral arteries (A1 segments) and by the posterior cerebral arteries (P1 segments) and posterior communicating arteries (P-com), which link the carotids with the basilar artery (Figure 1).
Considerable variability exists in the configuration of the different arteries of the CoW, which can be large, hypoplastic or even absent. Based on post-mortem studies anomalies of the CoW are present in approximately 50-80% of individuals.[1,2] Previous studies have demonstrated that both computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are sensitive and minimal invasive modalities that can be used to examine the configuration of the CoW.[3,4] Besides the status of the CoW, the risk of cerebral ischemia requiring shunt placement is determined by several other factors, including clinical characteristics and the degree of stenosis in the contralateral carotid artery and the bilateral vertebral artery. We set out to develop a clinical prediction rule to assess the likelihood of the need for shunting during CEA based on routine clinical information and preoperative assessment of the collateral cerebral circulation.

Methods

Patients
Patients who underwent CEA between January 2004 and August 2010 in University Medical Center Utrecht, The Netherlands were eligible for this cohort study. Indications for CEA were symptomatic or asymptomatic carotid stenosis >70% as discussed in a multidisciplinary team. The severity of the carotid artery stenosis was assessed by carotid colour Doppler-assisted duplex ultrasound and confirmed by MRA or CTA and categorized on a four-point scale: <50%, 50-70%, 70-99% stenosis or occlusion. Patients who did not undergo preoperative MR or CT angiography were excluded. We performed a subgroup analysis of these excluded patients confirming that no important information was lost for the purpose of this study.All patients were operated under general anaesthesia and intraoperative monitoring included both electroencephalography (EEG; Inc., Treviso, Italy) and transcranial Doppler (TCD; DWL Multidop X4, Sipplingen, Germany). An intraluminal Javid shunt was placed selectively based on the occurrence of new delta or theta activity on the EEG, during a period of at least two minutes of test-clamping, as described in detail previously.[5] After surgery, patients remained for six hours at the recovery ward for continuous invasive radial artery blood pressure monitoring. All patients underwent neurological examination before and after surgery.



Artery	Status				
A-com	Not visible	Visible			
A1 Right/ Left	Not visible	hypoplastic	normal		
P-Com Right/ Left	Not visible	<P1	=P1	>P1	Not visible P1

Figure 1. Diagram of the Circle of Willis and score model
Anterior segment. A-com: anterior communicating artery. Not-visible: if flow was not visualized between the left and right A1 segment. Present: if flow was visualized between the left and right A1 segments. A1 (right/ left): proximal segment of the anterior cerebral artery (ACA). Normal: at least 0.8 mm in diameter. Hypoplastic: less than 0.8 mm in diameter. Not-visible: if one of the component vessel segments was not- visible. Posterior segment. P-com (right/left): posterior communicating arteries. P1: Proximal part of the posterior cerebral artery (PCA). Not-visible: not seen. <P1: smaller than P1 ('normal' circle). =P1: of the same size as P1 (transitional configuration). >P1: larger than P1 (partial fetal variant). Not-visible P1: P1 was not seen (full fetal variant).

Outcome parameter and potential predictors

The primary outcome parameter was the need of a intraluminal shunt.[5] Age, sex, cardiovascular risk factors, degree of ipsilateral and contralateral carotid stenosis, status of the vertebral arteries (VA) and morphology of the CoW based on contrast-enhanced CTA or contrast-enhanced MRA images were considered as potential predictors. The CoW morphology for each individual patient was assessed by two experienced radiologists (JH/ PJvL), unaware of clinical outcome, patient characteristics and whether or not a shunt was used. The anterior CoW, segments were considered as 1) normal (at least 0.8 mm in diameter), 2) hypoplastic (diameters measuring <0.8 mm) or 3) not-visible.6 [Figure 1] For the posterior circle of Willis the classification was based on the comparison of the relative size of P1 segment of the posterior cerebral artery with the connected P-com. Subsequently, per individual patient the not-visible segments were grouped into: Anterior CoW (A-com, ipsilateral A1 and contralateral A1), ipsilateral posterior CoW (not visible ipsilateral P1 or Pcom) and contralateral posterior CoW (not visible contralateral P1 or Pcom).

Statistical analysis

After the selection of all potential predictors, identification of missing values was performed. Since the percentage of missing values was below 5%, we did not impute missing values. Continuous variables were presented as mean± SD and categorical variables as absolute number combined with percentage. Baseline variables between shunt and non-shunt groups were compared using the chi-square test or Student t test when appropriate.

The relation between potential predictors and shunt use was examined by multivariable logistic regression models using a backward stepwise approach with the p-value for removal set at 0.20.7;8 Prediction models derived with multivariable regression analysis are known for overestimated regression coefficients, which results in too extreme predictions when applied in new patients.8;9 Therefore, we internally validated our model with bootstrapping techniques where in each bootstrap sample the entire modelling process was repeated. This resulted in a shrinkage factor for the regression coefficients. The bootstrap procedure was also used to estimate a value of the AUC that was corrected for overoptimism to provide an estimate of discriminative ability that is expected in future similar patients. To study the performance of the final prediction model, we assessed its discrimination and calibration. Discrimination is the ability of the model to distinguish between patients that did and did not receive a shunt, and was quantified with the area under the receiver operating characteristic curve (AUC). An AUC ranges from 0.5 (no discrimination; same as flipping a coin) to 1.0 (perfect discrimination). Calibration refers to the agreement between the predicted probabilities and observed frequencies of hypertension. This was tested with the Hosmer-Lemeshow statistic where a significant test result implies insufficient calibration. To facilitate practical application of the model based on all patient data, the regression coefficients of the predictors in the model were converted into points on a score chart (by dividing the coefficients of all variables by the lowest coefficient observed). The total points (sum scores) were linked to the likelihood of receiving a shunt during surgery. Finally, various cut-off values were introduced in the predicted probabilities, categorizing patients as having a low risk, moderate risk and high risk to receiving a shunt. Data were analysed using SPSS for Windows (SPSS 20.0, SPSS Inc, Chicago, Il).

Results

Patient characteristics

Of all 582 patients who underwent CEA in the study period, 431 patients were included (Table 1). The majority of patients (n= 381, 88%) were symptomatic. In 65 patients (15%) an intraluminal shunt was used. An ipsilateral high degree stenosis of the ICA of 90-99% was less often present in patients who required placement of an intraluminal shunt than in patients who could be operated without shunting (14% versus 58%; p<0.01), whereas a contralateral occlusion was more often seen in the shunt group (28% vs. 14%; p= 0.01). The excluded patients did not significantly differ from the study population regarding clinical outcome.

Circle of Willis on MRA/ CTA

In 289 patients (67%) MRA was performed and in 142 patients (33%) CTA. The number of patients that underwent MRA instead of CTA did not differ between shunted and non-shunted

patients (71% vs. 66%; p= 0.49) In 394 patients (91%) any deviation from the normal anatomy of the CoW was seen (Figure 2; Table 2). A normal A-com was found in most patients (88%), as well as a normal ipsilateral (82%) and contralateral A1 segment (87%). Posteriorly, the most observed abnormality was a not-visible P-coms (47% and 45% for the ipsilateral and contralateral P-com respectively).

Candidate predictors	All (n=431)	Shunt (n= 65)	Non-Shunt (n= 366)	p-value	Missing values
Age, y	69 (±9)	69±8	69±9	0.51	0 (0%)
Gender, male	289 (67%)	46 (71%)	243 (66%)	0.49	0 (0%)
Risk factors					
Diabetes Mellitus	96 (22%)	13 (20%)	82 (22%)	0.78	1 (0.2%)
Hypertension	376 (87%)	56 (86%)	323 (88%)	0.68	1 (0.2%)
Current smoking	144 (33%)	22 (34%)	118 (32%)	0.87	0 (0%)
Body mass index, kg/m^2	26.5 (±3.8)	25.8 (±3.6)	26.6 (±3.8)	0.21	5 (1.2%)
CEA-related factors					
Clinical presentation (symptomatic)	381 (88%)	56 (86%)	327 (89%)	0.44	0 (0%)
Ipsilateral carotid stenosis 90- 99%	129 (30%)	9 (14%)	119 (33%)	<0.01*	0 (0%)
Contralateral occlusion	70 (16%)	18 (28%)	52 (14%)	0.01*	0 (0%)
Reversal flow/ occlusion/ gracile ipsilateral vertebral artery	48 (11%)	8 (13%)	40 (11%)	0.73	10 (2.3%)
Reversal flow/ occlusion/ gracile contralateral vertebral artery	45 (11%)	5 (8%)	40 (11%)	0.487	19 (4.4%)
Circle of Willis morphology					
Not visible anterior segment (any)	78 (18%)	21 (32%)	55 (15%)	<0.01	2 (0.5%)
Not visible posterior segment ipsilateral (any)	216 (50%)	49 (75%)	192 (53%)	0.001	1 (0.2%)
Not visible posterior segment contralateral (any)	207 (48%)	32 (49%)	190 (52%)	0.75	1 (0.2%)

Table 1. Candidate predictors of shunt use during carotid endarterectomy.
Values are shown as mean (± standard deviation) or number of patients (%). Statistically significant differences are indicated by an asterisk (*).

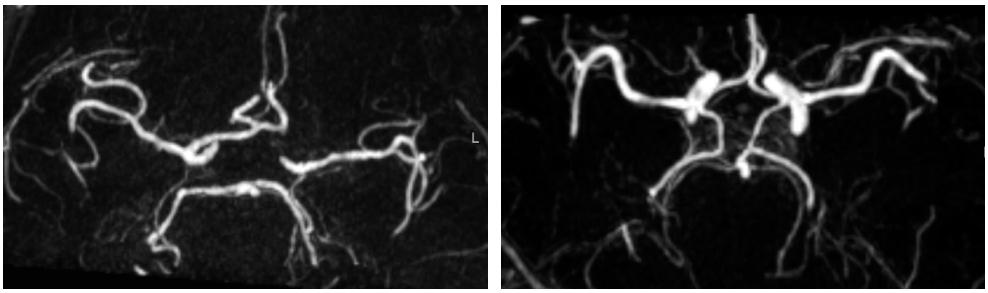


Figure 2. Contrast enchanced MRA maximum intenstiy projection images of the circle of Willis.

Circle of Willis segment	All (n=431)	Shunt (n= 65)	Non-shunt (n= 366)	p-value
Absent anterior segment (any)	77 (18%)	21 (32%)	55 (15%)	<0.01*
Absent A-com	49 (11%)	12 (18%)	37 (10%)	0.05*
Ipsilateral A1 segment				
normal	351 (81%)	58 (89%)	293 (80%)	0.08
hypoplastic	61 (14%)	1 (2%)	60 (16%)	<0.01*
not visible	16 (4%)	5 (8%)	11 (3%)	0.07
Contralateral A1 segment				
normal	371 (86%)	52 (80%)	319 (87%)	0.12
hypoplastic	44 (10%)	8 (12%)	36 (10%)	0.54
not visible	14 (3%)	4 (6%)	10 (3%)	0.15
Absent ipsilateral posterior segment (any)	241 (56%)	49 (75%)	192 (53%)	0.001*
P- com not-visible	201 (47%)	38 (59%)	163 (45%)	0.04*
P-com < P1	121 (28%)	9 (14%)	112 (31%)	<0.01*
P-com = P1	37 (9%)	3 (5%)	34 (9%)	0.22
P- com >P1	27 (6%)	4 (6%)	23 (6%)	0.97
P1 not visible	40 (9%)	11 (17%)	29 (8%)	0.02*
Absent contralateral post segment	222 (52%)	32 (49%)	190 (52%)	0.75
P- com not-visible	194 (45%)	25 (39%)	169 (46%)	0.25
P-com < P1	115 (27%)	17 (26%)	98 (27%)	0.92
P-com = P1	47 (11%)	6 (9%)	41 (11%)	0.64
P- com >P1	44 (10%)	9 (14%)	35 (10%)	0.29
P1 not visible	28 (6%)	7 (11%)	21 (6%)	0.13

Table 2. Candidate predictors of shunt use during carotid endarterectomy. Statistically significant differences are indicated by an asterisk (*).

Model development and performance

Carotid stenosis 90-99% (Odds ratio [OR]: 0.23, 95%CI: 0.09-0.57), contralateral carotid occlusion (OR 3.13, 95%CI:1.55-6.29) and any not-visible anterior (OR 3.73, 95%CI:1.90-7.32) or ipsilateral posterior segment of the circle of Willis (OR 2.59, 95% CI:1.38- 4.87) were independently related to the need of shunt use during CEA. None of the clinical variables were related to the likelihood of shunting [Table 1]. The calibration of the model was good, confirmed by a non-significant Hosmer-Lemeshow test (P= 0.867). The model discriminated well between patient who did receive and who did not receive a shunt, with an AUC after correction for optimism of 0.74 (95%CI: 0.67- 0.80). Subsequently, the bootstrapped betas of the predictors in the final model were used for constructing a risk score for shunt use during CEA [Table 3]. Patients were categorized according to their model- derived likelihood of shunt use into low risk (<10%, n= 210), medium risk (10-30%, n= 160) or high risk (>30%, n= 58). The observed incidence of shunt use in the low risk, medium risk and high-risk groups was 6%, 18% and 40% [Table 4].

Variable	Bootstrapped beta's	95% CI	Points*
Ipsilateral carotid stenosis 90- 99%	-1.247	-2.400- -0.537	-1.5
Contralateral occlusion	1.053	0.334- 1.764	1.5
Not visible anterior segment (any)	1.179	0.488- 1.860	1.5
Not visible ipsilateral posterior segment ipsilateral (any)	0.764	0.229- 1.478	1
		Total points	2.5

Table 3. Independent predictors identified by multivariate analysis.
The risk score for an individuale patient was determined by assigning points for each factor and summing. The resulting risk score was then use in Table 4 to estimate the shunt risk. *Calculated by dividing the beta coefficient by 0.764 and rounding to the nearest half. CI: confidence interval.

Risk score	Score category	Predicted shunt risk (mean±SD)	Observed incidence of shunt (95% CI)	Patients within score category (%)
<1	Low (<10%)	6.69 ± 2.65	5.7% (n=12)	210 (49,1%)
1- 2	Medium (10-30%)	17.60 ± 2.40	18.1% (n=29)	160 (37,3%)
≥ 2	High (>30%)	39.07 ± 6.33	39.7% (n= 23)	58 (13,6%)

Table 4. Predicted and observed incidence of shunt use during cross-clamping divided into three risk categories. Risk score: sum of points, SD: standard deviation, CI: confidence interval.

Discussion

The present study suggests that preoperative imaging of the cerebropetal arteries and the basal arteries of the CoW, but not clinical characteristics can help to identify preoperatively which patients are at increased risk for cerebral ischemia during CC and thus need a shunt during CEA surgery. Our main finding is that three abnormalities in the cerebral circulation predict a higher risk of shunt use: an occluded contralateral carotid artery, any not- visible segments of the anterior part of the CoW and any not-visible segments of the ipsilateral posterior part of the CoW. The relation between these factors and shunt use may be explained by the lack of a sufficient collateral circulation. A preocclusive (near-total) stenosis of the ipsilateral carotid artery predicts lower risk of shunt use, probably because adequate collateral circulation has been developed already to sustain adequate cerebral blood flow. The association between CoW abnormalities and failing collateral circulation in case of diminished supply through the ICA has been described previously.[10] Based on unselected post-mortem studies variation of the CoW exists in approximately 50-80% and several configurations of the CoW have been extensively described.[1;2] Moreover, a higher incidence in abnormalities has been found in patients with an ICA stenosis or occlusion (64%) as compared to control subjects (45%).[11] Furthermore, the observation that the need for a shunt use is high in patients with failure of both the anterior and the posterior segments, is in line with previous studies.[12;13] However, we could not confirm that only in patients without contralateral ICA occlusion shunt placement is predicted by MRA measured incompleteness of the CoW.[14] Moreover, in our cohort 89 percent of all patients with an intact A1 segment required shunt insertion, whereas either an intact anterior or the posterior pathway on the ipsilateral or contralateral site on digital subtraction angiography (DSA) has been associated with stable intraoperative EEG recordings. These contrasting results might be explained by the limited number of events in the study described by Schwartz et al.[12] Although the number of shunts in the current study is still relatively small, the number of events is higher than in previous studies evaluating the value of imaging the CoW prior to carotid endarterectomy.[14,15] In agreement with previous reports, our study indicated that clinical patient characteristics are not related to the likelihood of receiving a shunt.[16]

Our model enables identification of a group of patients that have a low likelihood of receiving a shunt. In our group of patients fifteen percent received a shunt and with our model discrimination can be improved to a likelihood of about 6% for the risk of 10 percent or lower and about 40% for the group with a risk of 30% or higher.

Our results might be hampered by the methods used to visualize the anatomy of the CoW. Digital subtraction angiography (DSA), which is the best method, is not commonly performed anymore due to the inherent risk of this invasive technique. Both CTA[4;17;18] and MRA[3;19;20] have previously been shown reliable tools for the assessment of the CoW. Nevertheless, some segments of the CoW may have been present, but not detected because the signal intensity may be below the threshold. Moreover, from post-mortem studies it appears that a complete CoW is present in most individuals, an absent P-com was only found in 5% of the cases.[21] Their contribution to the blood flow however, depends on the vessel diameter, which vary among individuals. Even a complete CoW may therefore be functionally insufficient as a collateral pathway during cross-clamping. Unfortunately we had to exclude several patients, however as the results between these two cohorts were similar we think this has not influenced

our results. Missing data concerning the status of the secondary collateral pathways such as the ophthalmic arteries and leptomeningeal collaterals, may have affected our results as these vessels are able to compensate in case of a failing primary collateral network (CoW).[21] The presence of flow in the leptomeningeal vessels is linked to a better outcome after stroke, but the association with CEA is unknown.[22;23]

In conclusion, with the current study we have identified independent predictors and we have developed a prediction model for the likelihood of shunt use during CEA that is based on the configuration of the CoW. This may be useful in clinical decision-making regarding surgical strategy. However, despite internally validating the model by means of bootstrapping methods, external validation in different CEA populations is warranted.

References

(1) Alpers BJ, Berry RG, Paddison RM. Anatomical studies of the circle of Willis in normal brain. AMA Arch Neurol Psychiatry 1959; 81(4):409-418.
(2) Riggs HEI, Rupp C. Variation in form of circle of Willis. The relation of the variations to collateral circulation: anatomic analysis. Arch Neurol 1963; 8:8-14.:8-14.
(3) Hendrikse J, Klijn CJ, van Huffelen AC, Kappelle LJ, van der GJ. Diagnosing cerebral collateral flow patterns: accuracy of non-invasive testing. Cerebrovasc Dis 2008; 25(5):430-437.
(4) Waaijer A, van Leeuwen MS, van der Worp HB, Verhagen HJ, Mali WP, Velthuis BK. Anatomic variations in the circle of Willis in patients with symptomatic carotid artery stenosis assessed with multidetector row CT angiography. Cerebrovasc Dis 2007; 23(4):267-274.
(5) Visser GH, Wieneke GH, van Huffelen AC. Carotid endarterectomy monitoring: patterns of spectral EEG changes due to carotid artery clamping. Clin Neurophysiol 1999; 110(2):286-294.
(6) Krabbe-Hartkamp MJ, van der GJ, de Leeuw FE, de Groot JC, Algra A, Hillen B et al. Circle of Willis: morphologic variation on three-dimensional time-of-flight MR angiograms. Radiology 1998; 207(1):103-111.
(7) Harrell FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis. New York, NY: Springer-Verlag; 2001.
(8) Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996; 15(4):361-387.
(9) Altman DG, Royston P. What do we mean by validating a prognostic model? Stat Med 2000; 19(4):453-473.
(10) Schneider PA, Ringelstein EB, Rossman ME, Dilley RB, Sobel DF, Otis SM et al. Importance of cerebral collateral pathways during carotid endarterectomy. Stroke 1988; 19(11):1328-1334.
(11) Hartkamp MJ, van der GJ, van Everdingen KJ, Hillen B, Mali WP. Circle of Willis collateral flow investigated by magnetic resonance angiography. Stroke 1999; 30(12):2671-2678.
(12) Schwartz RB, Jones KM, LeClercq GT, Ahn SS, Chabot R, Whittemore A et al. The value of cerebral angiography in predicting cerebral ischemia during carotid endarterectomy. AJR Am J Roentgenol 1992; 159(5):1057-1061.
(13) DePippo PS, Ascher E, Scheinman M, Yorkovich W, Hingorani A. The value and limitations of magnetic resonance angiography of the circle of Willis in patients undergoing carotid endarterectomy. Cardiovasc Surg 1999; 7(1):27-32.
(14) Lee JH, Choi CG, Kim DK, Kim GE, Lee HK, Suh DC. Relationship between circle of Willis morphology on 3D time-of-flight MR angiograms and transient ischemia during vascular clamping of the internal carotid artery during carotid endarterectomy. AJNR Am J Neuroradiol 2004; 25(4):558-564.
(15) Montisci R, Sanfilippo R, Bura R, Branca C, Piga M, Saba L. Status of the circle of Willis and intolerance to carotid cross-clamping during carotid endarterectomy. Eur J Vasc Endovasc Surg. 2013; 45(2):107-12.
(16) Tan TW, Garcia-Toca M, Marcaccio EJ, Jr., Carney WI, Jr., Machan JT, Slaiby JM. Predictors of shunt during carotid endarterectomy with routine electroencephalography monitoring. J Vasc Surg 2009; 49(6):1374-1378.
(17) Wintermark M, Uske A, Chalaron M, Regli L, Maeder P, Meuli R et al. Multislice computerized tomography angiography in the evaluation of intracranial aneurysms: a comparison with intraarterial digital subtraction angiography. J Neurosurg 2003; 98(4):828-836.
(18) Velthuis BK, van Leeuwen MS, Witkamp TD, Ramos LM, Berkelbach van der Sprenkel JW, Rinkel GJ. Surgical anatomy of the cerebral arteries in patients with subarachnoid hemorrhage: comparison of computerized tomography angiography and digital subtraction angiography. J Neurosurg 2001; 95(2):206-212.
(19) Schomer DF, Marks MP, Steinberg GK, Johnstone IM, Boothroyd DB, Ross MR et al. The anatomy of the posterior communicating artery as a risk factor for ischemic cerebral infarction. N Engl J Med 1994; 330(22):1565-1570.
(20) Patrux B, Laissy JP, Jouini S, Kawiecki W, Coty P, Thiebot J. Magnetic resonance angiography (MRA) of the circle of Willis: a prospective comparison with conventional angiography in 54 subjects. Neuroradiology 1994; 36(3):193-197.
(21) Hillen B. The variability of the circle of Willis: univariate and bivariate analysis. Acta Morphol Neerl Scand 1986; 24(2):87-101.
(22) Liebeskind DS. Collateral circulation. Stroke 2003; 34(9):2279-2284.
(23) McVerry F, Liebeskind DS, Muir KW. Systematic review of methods for assessing leptomeningeal collateral flow. AJNR Am J Neuroradiol 2012; 33(3):576-582.

Chapter 4

The potential benefit and the role of cerebral monitoring in CEA

Published in:

Current opinion in Anesthesiology, 2011;24(6):693-7

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Abstract

Purpose of review
The benefit of carotid endarterectomy (CEA) in patients with symptomatic severe carotid stenosis is highly dependent on the perioperative stroke rate. Cerebral monitoring plays an important role in reducing the perioperative stroke rate as it allows detection of the main causes of perioperative stroke, being embolism, intraoperative hypoperfusion and postoperative hyperperfusion syndrome. However, some physicians doubt about the benefit of cerebral monitoring and consider it costly and time consuming. The aim of this review is to provide an overview of the available cerebral monitoring modalities and their role in CEA.

Recent findings
Electroencephalography, transcranial Doppler, stump pressure and sensory-evoked potentials, are known and used for years. Near-infrared spectroscopy is a relatively new valuable technique, as it is noninvasive, easy to apply and applicable in all CEA patients, but remains to be validated.

Summary
In our opinion, cerebral monitoring during CEA is essential because it provides direct information regarding new neurological deficits, which might otherwise be missed. Intraoperative cerebral monitoring provides immediate feedback to the treating physician allowing prompt correction in tissue handling. Several monitoring modalities are available for cerebral monitoring in CEA, but no single test is comprehensive. Therefore, a combination of several monitoring modalities with each specific strength not only during but also after CEA is recommended to cover all needs and reduce the perioperative stroke rate.

Introduction

Carotid endarterectomy (CEA) is the recommended treatment for patients with a symptomatic high degree stenosis of the internal carotid artery (ICA).[1] However, the benefit of this surgery in the prevention of stroke depends on the safety of this procedure, and is therefore, limited by the occurrence of perioperative adverse neurological events. To reduce the perioperative stroke rate, it is essential to understand the underlying pathophysiological mechanisms. The first step is to categorize perioperative adverse events into intraoperative and postoperative stroke. Intraoperative stroke is apparent at awakening from anesthesia and is mainly caused by embolism or hypoperfusion during cross-clamping, whereas postoperative stroke becomes apparent after a symptom-free interval and is mainly due to thromboembolism and cerebral hyperperfusion syndrome (CHS). Intraoperative monitoring can guide the surgeon to adjust his technique or to shunt selectively. Improvement of surgical techniques and the introduction of intraoperative cerebral monitoring including computerized electro-encephalography (EEG) and transcranial Doppler (TCD) have already reduced the rate of intraoperative stroke, but have not altered the rate of postoperative stroke.[2]

In order to reduce the postoperative stroke rate, TCD monitoring is a promising monitoring technique, as it has been demonstrated to be useful for the detection of embolism and postoperative identification of patients at risk for the development of CHS.[3,4] Despite this proven relationship, some physicians still doubt the benefit of cerebral monitoring and consider it costly and time-consuming. Most proponents of routine use of an intraluminal assume that it reduces the risk on perioperative strokes and it provides extra time. However, routine shunting has several disadvantages including possible plaque embolisation, carotid artery dissection and inadequate shunt flow or shunt thrombosis. Therefore, others advocate selective use of shunting based on cerebral monitoring parameters, or no shunting at all.[5] Nonetheless, irrespective of whether routine shunting is used or not, cerebral monitoring is essential, as it may be the only tool that provides information to the surgeon on actual shunt function. In doing so, it may be life saving for those who are at risk of perioperative stroke because of shunt malfunction. Moreover, cerebral monitoring offers interaction between the clinical neurophysiologist and the treating physician providing the option to act on observed changes in either TCD or EEG measures and is, therefore, a helpful tool for teaching and evaluation of technical skills in vascular surgery.

Besides the optimal technique of cerebral monitoring, the optimal type of anesthesia during CEA remains controversial. Some authors assume general anesthesia during CEA is more practical, provides more stable anesthesia especially for cardiac compromised patients, is less time-consuming and possibly more comfortable for both patient and surgeon. Others advocate local anesthesia during CEA because of claimed advantages such as allowing continuous and objective testing of the conscious level in the awake patient. A large randomized trial comparing regional versus general anesthesia could not prove a clear difference in the proportion of patients with stroke, myocardial infarction or death within 30 days after surgery between both.[6]

Regardless of the choice of anesthesia, cerebral monitoring during CEA is essential because it provides direct information about cerebral condition and new neurological deficits, which might otherwise be missed and might require acute intervention; for example, changing the surgical technique in case of TCD-measured embolisation during the dissection phase. The

aim of this review is to provide an overview of the available cerebral monitoring modalities and their role in CEA.

Monitoring techniques

Several cerebral monitoring modalities are available for early identification of neurological deficits in the intraoperative phase of carotid surgery. Because direct measurement of cerebral blood flow (CBF) is logistically difficult and unlikely to be practiced widely as a routine method of CEA monitoring, alternative monitoring techniques have been proposed and applied, each with a specific purpose.

EEG and sensory-evoked potentials (SSEP) are used for monitoring of brain function; TCD and stump pressure provides information on the hemodynamic status and near-infrared spectroscopy (NIRS) of the frontal lobe oxygenation of the brain. The latter has been suggested as a surrogate marker for EEG and TCD monitoring. This technique, however, needs to be further explored before its value in cerebral monitoring during CEA can be established.[7] EEG and TCD are the most well known, investigated and established brain monitoring modalities in CEA and should be considered as complimentary monitoring techniques, not as alternatives. A correlation between changes in CBF and changes in both EEG and TCD has been well established in the 70s and 80s of the 20th Century. Furthermore, recently Moritz et al.[8] showed that the accuracy of EEG and TCD in detecting cerebral ischemia evaluated by the appearance of clinical signs of cerebral ischemia in patients who underwent carotid surgery under local anesthesia, are transferable to patients under general anesthesia. EEG represents the spontaneous electrical activity of the cerebral cortex. It is applicable in all patients and a sensitive and continuous method comparing electrical activity in the treated versus contralateral hemisphere.[9] However, preoperative preparation can be time-consuming and requires experienced and dedicated personnel. Furthermore, anesthetics exert effects on cerebral metabolism and may result in alteration of EEG recordings. The use of bispectral index (BIS), a processed EEG parameter mostly used to indicate the depth of the anesthetic also has been suggested as an indicator to detect cerebral ischemia due to cross-clamping. Because BIS has to be calculated using an algorithm, there is a delay of 30–60 s. Recent evaluation of this method in awake CEA patients resulted in a low positive predictive value.[10]

SSEP parameters record critical detoriations in CBF by stimulating peripheral afferent nerves, with the help of scalp electrodes. According to the most recent literature, the use of SSEP is controversial, as SSEP is sensitive for detecting cerebral ischemia but associated with false-negative results. Moreover, threshold values detecting critical reduction in CBF are disputable; SSEP is susceptible to anesthetics and time-consuming.[11]

TCD allows a noninvasive continuous measurement of the blood flow velocity in the large intracranial vessels in patients with a suitable temporal bone window. Usually the proximal segment of the ipsilateral middle cerebral artery (MCA) is measured accompanied with the contralateral anterior cerebral artery. Except for MCA blood flow velocity monitoring, TCD can be applied for intraoperative and postoperative detection of microembolic signals (MES) during CEA and prediction of postoperative CHS. Furthermore, TCD can assist EEG in the prediction of shunt requirement. TCD is generally easy to apply and repeated measurements

can be performed in either the preoperative, or postoperative phase to continue monitoring of the hemodynamic status over time. However, TCD had technical limitations because it is operator-dependent and 10–15% of all patients do not have an adequate temporal window, which is essential for adequate monitoring.[3,12]

For a long time, it was believed that stump pressure measurements could provide information about the hemodynamic brain status by measuring the carotid backpressure. However, stump pressure has neither been proven as a standardized nor a reliable method for detecting cerebral ischemia during cross-clamping.[13]

	Monitoring technique	Measurement	Advantages	Disadvantages	Ref.
Hypoperfusion	EEG	Asymmetry Changes compared to preoperative data	Applicable in all patients Sensitive Continuous	Expensive Requires experienced personnel Influenced by anesthesia	9
	SSEP	Modification	Sensitive	Influenced by anesthetics and blood pressure	11
	SP	SP (mmHg) decrease	Inexpensive Easy to obtain	High degree of inter-variability	13
	NIRS	rSO_2 (%) decrease	Inexpensive Applicable in all patients Easy to apply	Limited evidence	7
	TCD	V_{mca} (cm/s) decrease	Inexpensive	Absent temporal window in 10-15% of patients Interpreter dependency Operator dependency	3;12
Embolism	TCD	Micro-embolic signals	Adjustment of surgical technique Long term monitoring Repeatability Portability	Absent temporal window in 10-15% of patients Interpreter dependency Operator dependency	3,14
CHS	NIRS	rSO_2 (%) increase	Inexpensive Applicable in all patients Easy to apply	Limited evidence	7
	TCD	V_{mca} (cm/s) increase	Inexpensive Long term monitoring Repeatability Portability	Absent temporal window in 10-15% of patients Interpreter dependency Operator dependency	16

Table 1. Summary of clinical indications and advantages and disadvantages of different cerebral monitoring techniques in carotid endarterectomy. CHS: Cerebral Hyperperfusion Syndrome. EEG: Electroencephalography. SSEP: Sensory-evoked potentials. SP: Stump pressure. TCD:Transcranial Doppler. NIRS: Near-infrared spectroscopy.

All the techniques described above are known and used for years. In recent years only the development of NIRS as cerebral perfusion monitoring, is worth mentioning. NIRS provides online information about the frontal lobe cerebral perfusion (rSO2). In order to save time and reduce costs, NIRS is a promising technique because it is noninvasive, easy to apply and applicable in all patients. However, NIRS has not been validated yet for use in CEA patients and evidence for clear threshold to detect hypoperfusion of the brain is limited.[7]

Clinical indications

The choice for the optimal cerebral monitoring technique depends on the indication, as each monitoring technique has its own strengths and weaknesses. Clinical indications and appropriate techniques are summarized in Table 1.[3,7,9,11-14] Hypoperfusion of the brain during surgery is mainly caused by the temporary interruption of blood flow during the procedure, whereas the carotid artery is clamped. If the collateral blood flow through the contralateral carotid and vertebral arteries is insufficient, placement of an intraluminal shunt is required. Based on intraoperative monitoring in sedated patients, this occurs in approximately 15% of procedures.[5,9] However, due to several disadvantages as described before, routine insertion of an intraluminal shunt during CEA is controversial.[7]

EEG is the most widely used technique for detection of intraoperative cerebral ischemia. Changes in neuronal perfusion and oxygen supply lead to changes in EEG recording and is a reliable detector of cerebral ischemia. Besides asymmetry, comparison of data obtained during clamping with preclamping data should also be considered because unilateral clamping may induce bilateral changes.[9] Nevertheless, EEG monitoring requires a test-clamping period and is, therefore, time-consuming.

MES are an independent predictor of transient ischemic attack and stroke risk and can be categorized into gaseous or solid embolism. The former can be introduced by arterial dissection, whereas the latter can end up in the bloodstream by either breaking off of a thrombus formed on an ulcerated surface of a ruptured atherosclerotic plaque or when flow distal to the plaque is slowed. It is important to realize, that TCD is the only available intraoperative monitoring modality capable of detecting embolism. Because MES are larger, of different material and with different acoustic impedance than the surrounding blood cells, they can be seen and heard as high-intensity transient signals.[3,14] Intraoperatively, the highest numbers of MES are found during declamping and shunting. However, during surgery, only MES detected during dissection and especially during wound closure are associated with operative stroke and stroke-related death. In addition, a high frequency of MES in the immediate postoperative period is also a strong risk predictor of postoperative stroke.[3] Furthermore, TCD detection of MES can potentially be used as a surrogate marker to evaluate the effectiveness of antiplatelet therapy given in order to prevent postoperative thrombosis of the endarterectomized arterial segment.[15] Besides the technical problems as described above, TCD embolism detection can be tedious and time-consuming. Therefore, automatic embolus detection systems claiming both a high sensitivity and specificity are in development.

The other important cause of postoperative stroke occurring after a symptom-free interval is CHS, which appears in 1–3% of patients in the first few days up to four weeks after surgery.

It is defined by a combination of neurological symptoms and at least a doubling of preoperative CBF, which is correlated to a doubling of the mean blood velocity (V_{mca}) measured in the ipsilateral MCA with TCD. The pathophysiology has not been clearly defined, but it is hypothesized that sudden augmentation of the blood flow through a brain with disturbed autoregulation because of a previously hypoperfused state can cause cerebral hyperperfusion. Early and adequate treatment of CHS is essential, as hemorrhagic strokes caused by CHS are associated with mortality up to 40%. Therefore, intraoperative estimation of risk for developing CHS is widely used. An increase in V_{mca} of more than 100% three min after declamping the ICA compared to the preclamping V_{mca} is commonly used as a predictor for the occurrence of CHS. However, applying this intraoperatively performed measurement, not all patients at risk for CHS are identified, whereas others may be treated unnecessarily. In an unpublished study, we reported that the positive predictive factor of TCD in the prediction of CHS can be increased by adding a postoperative TCD measurement on the recovery ward within 2 h after CEA. A comparison of this postoperatively performed measurement with the intraoperative measurement showed an increase in both positive and negative values for CHS prediction.

However, TCD has technical disadvantages. As an alternative cerebral monitoring entity, NIRS can be used. Especially for the subgroup in which TCD cannot be applied, NIRS might be helpful in identifying a threshold for postoperative risk for CHS, but as stated above more research is needed.

Conclusion

Cerebral monitoring plays an important role in reducing the perioperative stroke rate as it allows detection of the main causes of perioperative stroke, being embolism, intraoperative hypoperfusion and postoperative hyperperfusion syndrome. Furthermore, intraoperative cerebral monitoring provides the ability to assess function of the shunt after insertion and immediate feedback to the treating physician allowing prompt correction in tissue handling. Many techniques are available for cerebral monitoring during CEA and these techniques should be considered as complementary and not as alternatives, as all current modalities have their specific indication and own strength and weaknesses. Most modalities address only one of the underlying mechanisms of perioperative stroke. Therefore, the simultaneous application of more than one monitoring technique is recommended. The combination of detection of intraoperative brain hypoperfusion during cross-clamping along with detection of embolism and prediction of hyperperfusion of the brain postoperatively currently covers all needs, and thereby, enables physicians to further reduce the perioperative stroke rate in CEA.

References

(1) Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomized controlled trial. Lancet 2010; 375(9719):985-997.

(2) de Borst GJ, Moll FL, van de Pavoordt HD, Mauser HW, Kelder JC, Ackerstaf RG. Stroke from carotid endarterectomy: when and how to reduce perioperative stroke rate? Eur J Vasc Endovasc Surg 2001; 21(6):484-489.

(3) King A, Markus HS. Doppler embolic signals in cerebrovascular disease and prediction of stroke risk: a systematic review and meta-analysis. Stroke 2009; 40(12):3711-3717.

(4) Alexandrov AV, Sloan MA, Tegeler CH, Newell DN, Lumsden A, Garami Z et al. Practice Standards for Transcranial Doppler (TCD) Ultrasound. Part II. Clinical Indications and Expected Outcomes. J Neuroimaging 2010.

(5) Rerkasem K, Rothwell PM. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). Cochrane Database Syst Rev 2009;(4):CD000190.

(6) Lewis SC, Warlow CP, Bodenham AR, Colam B, Rothwell PM, Torgerson D et al. General anesthesia versus local anesthesia for carotid surgery (GALA): a multicentre, randomized controlled trial. Lancet 2008; 372(9656):2132-2142.

(7) Pennekamp CW, Bots ML, Kappelle LJ, Moll FL, de Borst GJ. The value of near-infrared spectroscopy measured cerebral oximetry during carotid endarterectomy in perioperative stroke prevention. A review. Eur J Vasc Endovasc Surg 2009; 38(5):539-545.

(8) Moritz S, Schmidt C, Bucher M, Wiesenack C, Zimmermann M, Schebesch KM et al. Neuromonitoring in carotid surgery: are the results obtained in awake patients transferable to patients under sevoflurane/fentanyl anesthesia? J Neurosurg Anesthesiol 2010; 22(4):288-295.

(9) Ballotta E, Saladini M, Gruppo M, Mazzalai F, Da GG, Baracchini C. Predictors of electroencephalographic changes needing shunting during carotid endarterectomy. Ann Vasc Surg 2010; 24(8):1045-1052.

(10) Estruch-Perez MJ, usina-Aguilar A, Barbera-Alacreu M, Sanchez-Morillo J, Solaz-Roldan C, Morales-Suarez-Varela MM. Bispectral index changes in carotid surgery. Ann Vasc Surg 2010; 24(3):393-399.

(11) Fielmuth S, Uhlig T. The role of somatosensory evoked potentials in detecting cerebral ischaemia during carotid endarterectomy. Eur J Anaesthesiol 2008; 25(8):648-656.

(12) Ali AM, Green D, Zayed H, Halawa M, El-Sakka K, Rashid HI. Cerebral monitoring in patients undergoing carotid endarterectomy using a triple assessment technique. Interact Cardiovasc Thorac Surg 2011; 12(3):454-457.

(13) Manwaring ML, Durham CA, McNally MM, Agle SC, Parker FM, Stoner MC. Correlation of cerebral oximetry with internal carotid artery stump pressures in carotid endarterectomy. Vasc Endovascular Surg 2010; 44(4):252-256.

(14) Markus HS, King A, Shipley M, Topakian R, Cullinane M, Reihill S et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. Lancet Neurol 2010; 9(7):663-671.

(15) Wong KS, Chen C, Fu J, Chang HM, Suwanwela NC, Huang YN et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomized, open-label, blinded-endpoint trial. Lancet Neurol 2010; 9(5):489-497.

(16) Pennekamp CW, Tromp SC, Ackerstaff RG, Bots ML, Immink RV, Spiering W et al. Prediction of cerebral hyperperfusion after carotid endarterectomy with transcranial Doppler. Eur J Vasc Endovasc Surg 2012; 43(4):371-376.

Chapter 5

The role of transcranial Doppler in cerebral hyperperfusion syndrome

Published in: The Journal of Cardiovascular Surgery (Torino), 2012;53(6):765-71

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Abstract

The benefit of carotid revascularization is hampered by occurrence of periprocedural cerebrovascular complications. Cerebral Hyperperfusion Syndrome (CHS) is a potentially life threatening complication occurring in approximately 3% of all patients following either carotid endarterectomy (CEA) or carotid angioplasty with stenting (CAS). CHS generally is defined as a transcranial Doppler (TCD) derived increase of >100% over baseline. To reduce related morbidity and mortality early identification of patients at risk is essential. As such, TCD offers a technique for cerebral blood flow measurement that is nowadays the only applied and useful clinical monitoring tool for CHS prediction. Several studies have assessed the diagnostic value of TCD in the prediction of CHS and found promising results. However, results were based on a small number of cases and different definitions have been used to diagnose CHS. Moreover, the role of TCD in the onset of CHS has been studied most extensively following CEA, and it is unclear whether the findings of these studies can be generalized to patients undergoing CAS. Therefore we conclude that further studies in larger cohorts are required to assess the changes in cerebral hemodynamic in patients undergoing either CAS or CEA.

Carotid revascularization

High grade stenosis of the internal carotid artery (ICA) is an important cause of ischemic stroke.[1] Carotid revascularization has been shown to be an effective treatment in the prevention of recurrent stroke in these patients. Revascularization can be performed by carotid endarterectomy (CEA) or carotid angioplasty with stenting (CAS). Following the results of several randomized trials, CEA is still the gold standard therapy and recommended in symptomatic patients with >50% stenosis and in asymptomatic men below 75 years with a stenosis of 70 to 99 percent.[2] However, the benefit of treatment in terms of long term stroke prevention is still hampered by occurrence of procedural related stroke and death.[3] According to treatment guidelines, the above recommendation therefore also requires a periprocedural stroke or death risk of <6% for symptomatic and <3% for asymptomatic patients. Only when the operative risk can be maintained low, any benefit in terms of long-term stroke prevention can be warranted. Differentiation between strokes with an intraoperative onset as opposed to strokes with a postoperative onset occurring after a symptom-free interval can help in understanding the underlying mechanism. Moreover, mechanisms responsible for stroke and death associated with CEA may involve a different process compared with those of CAS. Intraoperative strokes may be caused by embolisation, thromboembolism or cerebral hypoperfusion.[4-6] On the other hand, postprocedural strokes are mainly caused by thromboembolism, local thrombosis, postoperative hypertension or the related cerebral hyperperfusion syndrome (CHS). Introduction of intra-operative monitoring during CEA has already lowered the intraoperative complication rate and the use protection filters devices during CAS are promising.[4] However, the rate of postoperative strokes was not altered.

Cerebral hyperperfusion syndrome

CHS is a serious postoperative complication of carotid revascularization. Following removal of the carotid plaque and subsequent restoral of flow, a major increase in cerebral blood flow (CBF; the blood supply to the brain in a given time) can occur, that is well above the metabolic demands of the brain tissue. Quantitatively, hyperperfusion has been defined as a 100% or greater increase in CBF compared with preoperative values as measured by transcranial Doppler sonography (TCD). Hyperperfusion occurs in approximately ten percent of all patients, most often within the first few days.[7;8] The majority of these patients remain asymptomatic. However in approximately a quarter of patients with increases in CBF of >100% increase over baseline development of clinical symptoms of hyperperfusion including throbbing ipsilateral, frontotemporal or periorbital headache, eye and face pain, vomiting, confusion, macular edema, and visual disturbances, focal motor seizures with frequent secondary generalization, focal neurological deficits, and intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH) may result in the clinical picture of CHS (table 1).[8;9] The incidence of CHS following CEA and CAS is reported as almost equal and ranges from 0.5-3%. A subset, approximately 0.6% of all patients subsequently develops ICH, the most catastrophic event secondary to CHS.[7;8;10-12] No differences in clinical features between those who developed CHS after CEA and CAS are suggested except for an earlier onset of CHS after CAS.[13;14]

The pathophysiology of CHS is unclear and many interlinked factors are thought to play a role.[8] A rapid restoration of normal cerebral perfusion pressure after CEA may result in an increase in CBF secondary to impaired autoregulation that occurs in the context of longstanding severe chronic cerebral ischemia. This mechanistic approach to hyperperfusion is similar to the normal perfusion pressure breakthrough theory described by Spetzler et al, who studied patients undergoing surgery for brain arteriovenous malformations.[15] Many preoperative factors have been proposed to be associated with the postoperative onset of CHS, however besides a diminished cerebrovascular reserve capacity as a result of autoregulatory vasodilatation to maintain cerebral blood flow in patients with chronic hypoperfusion, no risk factors have been identified.[8;16]

Cerebral hyperperfusion syndrome
1. Increase in V_{MCA} and
2. Symptoms of cerebral hyperperfusion
Throbbing ipsilateral, frontotemporal or periorbital headache
Eye and face pain
Vomiting
Confusion
Macular edema
Focal neurological deficits
Visual disturbances
Focal motor seizures with frequent secondary generalization
Intracerebral hemorrhage (ICH)
Subarachnoid hemorrhage (SAH)

Table 1. Criteria for clinical diagnosis of cerebral hyperperfusion syndrome

Investigatory techniques in CHS prediction and diagnosis

To reduce CHS-related morbidity and mortality, early identification is essential. Associations between CBF measurements and CHS following CEA have been described and association was found between doubling of the CBF and the occurrence of ICH.[9] In order to prevent CHS, frequent evaluations of CBF after carotid revascularization are required. A variety of techniques have been employed for measurement of CBF. However, as most techniques are expensive, require radiation exposure and are not available for bed-side monitoring, they may not to be the appropriate modalities to use repeatedly after revascularization.[9;17] Changes in blood velocity (V) measured in the middle cerebral artery (MCA) using TCD have been

shown to have a direct relationship with changes in CBF. Moreover, TCD is non-invasive, relatively cheap, may easily be performed at bedside with portable machines and is useful for continuous monitoring. Therefore this surrogate technique for CBF measurement is nowadays the only useful clinical monitoring tool.[16] TCD ultrasound examination monitoring allows a noninvasive continuous measurement of the V in the large intracranial vessels. Using a 2-MHz pulsed Doppler-transducer the V within the intracranial vessels is measured, usually the proximal segment of the middle cerebral artery (V_{MCA}), through a thinning of the skull at the temporal bone, the so-called temporal window. Using spectral analysis, the peak systolic (V_{peak}) and diastolic velocity (V_{diast}), the mean velocity (V_{mean}) and the Gosling pulsatility index (P/I) of the blood within the interrogated vessel can be measured. Whereas the P/I is defined by: P/I= (V_{peak}- V_{diast})/ V_{mean} and is a reflection of vascular resistance.[18] However, as the V is dependent of the diameter of the vessel and the diameter can vary, this technique can only be used for determination of relative changes in flow.

Although TCD has major advantages this technique has substantial limitations. An absent temporal bone window in 10-15% of patients undergoing carotid revascularization makes TCD measurement in these patients impossible. Moreover, the measurements are operator dependent and could easily be disturbed. Shifting of the actual location can cause a change in the angle between the Doppler probe and the insonated vessel and changes in the measured values consequently. In addition, in the event that there is occlusion or hemodynamically limiting stenosis in the ipsilateral MCA, TCD monitoring would not be useful for this purpose. Nevertheless previous studies has found that changes in V_{MCA} reliably correlate with changes in CBF.[16;19;20] Therefore, changes in TCD can be used to evaluate the changes in hemodynamics, especially in the perioperative phase as postoperative TCD derived doubling of preoperative (baseline) V_{MCA} can be used to indicate patients at risk to develop CHS. A number of studies have discussed this issue and are described below. It is of notice that most of these studies describe the role of TCD in the onset of CHS following CEA, while studies on TCD and development of CHS after CAS are relatively scarce.[21-23]

Identification of patients at risk for CHS following CEA with transcranial Doppler

Identification of patients at risk to develop CHS is important to reduce CHS-related morbidity and mortality. In these patients strict blood pressure control is recommended, as in patients with an impaired autoregulation the CBF depends primarily on systemic blood pressure and symptoms have been shown to disappear with reduction in systemic blood pressure.[24;25] Preoperatively, TCD and acetazolamide provocation tests have been suggested to demonstrate a diminished reserve capacity.[26] Also, preoperative loss of reserve capacity could be associated with the development of CHS following CEA.[27] Out of 36 patients the reserve capacity was reduced in three (8%). After surgery, only these three patients complained of unilateral headache and showed a significant difference in V_{MCA} increase compared to patients without headache, but V_{MCA} was not increased >100%. In these patients blood pressure was controlled strictly and none of the patients progressed to more severe CHS.

Intraoperative TCD measurements have also been proposed to be associated with the onset of CHS. Therefore, several studies have evaluated the changes in V_{MCA} during CEA, which results are summarized in Table 2. In a relatively large cohort on 688 patients the role of TCD monitoring for identifying patients at risk of hyperperfusion was investigated.[12] Sixty-two

patients (9%) showed hyperperfusion (>100% increase of V_{peak} or P/I compared to intraoperative preclamp values), of which seven patients (1%) also developed clinical symptoms. In patients with hyperperfusion, intra-operatively both V_{peak} and P/I increased with 146% (95% CI: 122-170) and 68% (95% CI: 47-89) as opposed to 16% (95% CI: 8-24) and 16% (95% CI 9-23) respectively for the non-hyperperfusion patients. However, changes in V_{peak} were not specified for patients who developed additional symptoms. In another study, intraoperative TCD monitoring was performed in 60 patients.[28] Six patients (10%) developed hyperperfusion, of which two patients (3%) developed additional symptoms. Only in one of these CHS patients a reliable TCD measurement was performed, which showed immediately after declamping 100% V_{peak} increase of preclamping value. Fourteen CHS patients were included in a study in which CHS was defined as 'acute neurological deterioration in the immediate postoperative period that was attributable to impaired autoregulation of CBF after exclusion of other identifiable causes'.[29] Patients with CHS were found to have a higher ipsilateral V_{MCA} compared to patients who did not develop CHS. However, the definition applied requires any form of measurement of cerebral hemodynamics and as preoperative TCD values for CHS patients were not given, relative increases in V_{MCA} in the postoperative phase as compared to baseline could not be determined. To evaluate whether TCD can be used to identify patients at risk for ICH 233 patients were studied.[30] Seventeen patients (7%) developed CHS, of which four (2%) suffered ICH. Patients in the ICH group were compared to non-ICH patients and using a combination of increase in V_{peak} of 175% and increase in P/I of 100% as indices of ICH a positive predictive value, negative predictive value, sensitivity and specificity of 100%. 99%, 80% and 100%, respectively were found. Others focused on postoperative TCD measurements associated with CHS to omit the transient reactive hyperemia phenomenon directly after declamping, which often occurs and results in transient increases in V_{MCA}. Therefore TCD measurements were evaluated in 14 patients of which two patients (14%) developed CHS after CEA.[31] In both patients an increase in V_{MCA} was seen in the recovery room, and further increases were seen on the next day combined with neurological complaints. Subsequently the symptoms resolved and the V_{MCA} returned to normal. However, only preoperative values of one of the patients were mentioned and increases could not be determined. To describe the changes in cerebral hemodynamics during and after CEA, postoperative changes in V_{peak} were evaluated in 45 patients, which were preoperatively divided into two groups, one with suspected postoperative neurologic complications and one without.[17] Postoperative increases in bilateral V_{peak} as compared to preoperative V_{peak} were found often to occur, also in patients without postoperative neurological complications. In 14 patients (31%) a postoperative V_{peak} increase of >100% compared to preoperative V_{peak} was seen and two patients (4%) subsequently developed CHS. However, TCD values of patients were not specified. In a previous study we assessed whether the value of TCD in the prediction of the development of CHS could be improved by adding a postoperative TCD measurement on the recovery ward within two hours after CEA.[32] A postoperative increase in V_{mean} as compared to preoperative values predicted the onset of CHS more accurately than an intraoperative V_{mean} increase. An additional postoperative TCD measurement increased the positive predictive value three times (from 13% to 41%) and the negative predictive value from 95% to 99%. Another study focused on patients with postoperative episodes of ipsilateral headache and hypertension and included 95 patients.[25] Eighteen patients (19%) developed headache after surgery and showed an increase in V_{mean}

of 77% as compared to preoperative values. Subsequent reduction in mean arterial pressure (from 101 [80-128] to 88 [60-103] mmHg; median and range) not only normalized the V_{mean}, but also resolved the neurological symptoms. However, as V_{mean} was increased 77% the strict criteria for CHS were not fulfilled. On the other hand, these reports clearly show the benefit of early blood pressure reduction in symptomatic patients with a diagnosed increase in V_{mean} after intervention.

Using Transcranial color-coded real-time sonography (TCCS) with contrast agents instead of conventional TCD, absolute values of V_{peak}, V_{diast} and V_{mean} could be measured. The accuracy of TCCS with contrast agents to detect CHS following CEA was evaluated in 95 patients.[33] In all patients propofol was continued to maintain sedation until the morning after CEA. Subsequently, 12 patients (13%) developed 'a focal seizure, temporary deterioration of consciousness level with remarkably abnormal speech and conduct for >six hours after stopping propofol sedation, development of focal neurological signs or ICH on computed tomography'. An increase in V_{peak} >50% compared to preoperative V_{peak} was observed in all 12 patients within first four postsurgical days and was significantly higher than in control patients. However as neither doubling in preoperative TCD nor doubling in preoperative CBF was a criterion for the diagnosis CHS, the patients in this study did not fulfill the criteria for CHS.

Transcranial Doppler and CHS following CAS

A few studies have evaluated the association of TCD measurements and the onset of CHS following CAS; however, the study populations described are small. In a series of 86 patients two patients (2%) developed CHS following carotid angioplasty.[23] Of these patients one developed a subarachnoidal hemorrhage and died within 20 hours. The other patient developed ICH within three days after the procedure and showed increases in V_{mean} and P/I of 114-200% and 266% respectively. In retrospective analysis of 64 patients who underwent CAS, nine patients (14%) developed post-CAS deteriorating neurological symptoms with headache.[21] The immediate post-CAS V_{mean} versus pre-CAS V_{mean} in these patients as compared to patients without symptoms however, did not significantly differ. Changes in V_{peak} following CAS were assessed in 92 patients of which two patients (2%) developed CHS.[22] One of the patients developed ICH in the ipsilateral hemisphere with an increase in V_{mean} of 170% at time of onset (12 hours post-CAS) as compared to preoperative values. The other patient developed ICH in the contralateral hemisphere and showed increases in V_{mean} of 143% (ipsilateral) and 640% (contralateral).

Differences between CHS following CEA and following CAS

Two studies compared the incidence and clinical features of CHS following CEA and CAS and found an almost equal incidence of CHS in both groups.[13;14] CHS following CAS occurred significantly earlier than after CEA, that is mostly after the first days post-CEA and within the first twelve hours post-CAS. Another difference was the development of subarachnoid hemorrhages in the CAS group, while patients who suffered a hemorrhage following CEA, only developed hemorrhages within the cerebral parenchyma. Furthermore, factors related to the development of hemorrhages after either CHS or CAS could not be identified. The differential long-term effects of CEA and CAS on blood pressure have been studied in 766 en 819 patients undergoing CAS and CEA respectively.[34] Decreases in blood pressure were

Study	Total nr. of patients	Nr. of patients	Definition
Conventional transcranial Doppler sonography			
Maltezos et al.[29]	100	14 (14%)	Acute neurological deterioration in the immediate postoperative period that was attributable to impaired autoregulation of CBF after exclusion of other identifiable causes.
Jørgenson et al.[25]	95	18 (19%)	Focal neurological symptoms of hyperperfusion.
Ogasawara et al.[28]	60	2 (13%))	CBF increase >100% compared to preoperative values.
Jansen et al.[30]	233	17 (7%) ICH: 5 (2%)	Transient unilateral headache ICH
Powers et al.[31]	14	2 (14%)	Not defined
Zachrisson et al.[17]	45	2 (4%)	>100% increase in V_{peak} and neurological symptoms
Dalman et al.[12]	688	7 (1%)	>100% increase in PSV or P/I
Pennekamp et al.[32]	184	10 (5%)	>100% increase in V_{mean} and Neurological complaints
Transcranial color-coded real-time sonography with contrast agents			
Fujimoto et al.[33]	105	12 (11%)	Focal seizure, temporary detoriation of consciousness level with remarkably abnormal speech and conduct for >6 hours after stopping propofol sedation, development of focal neurological signs or ICH on computed tomography

Time of TCD measurement	Reference	TCD measurement
Fist postoperative day	Non- CHS patients	V_{peak} 132 (SD± 10 cm/s) versus 109 (SD± 9) cm/s.
Onset of symptoms	Preoperative	V_{mean} 77% increase (95% CI: 130-332)
Immediately after declamping/ End of the procedure/	preclamping preclamping	V_{peak} 190% increase V_{peak} 260% increase
1 minute before test-clamping/	1 minute after test-clamping	ICH-group: PSV: 134% (95% CI: 28- 240) P/I: 71% (95% CI: 30-112) Non-ICH group: PSV: 25% (95% CI: 20-30%) P/I: 15% (95% CI: 11-18%)
1st day postoperatively	Preoperative	240%
1st, 2nd and 3rd postoperative day	Preoperative	V_{peak} > 100%
1 min before CC/	3 min after CC	Hyperperfusion PSV 146% (95% CI: 122-170) P/I: 68% (95% CI: 47-89)
1 min before clamping- 2nd hour postoperative	3 minutes after declamping Preoperative	Intraoperative: 23% increase (IQR: 5-85) Postoperative: 107% increase (IQR: 99- 115)
First postoperative day	Preoperative	V_{mean} 90 (SD± 29) cm/s versus 49 (SD± 13) cm/s.

Table 2. Overview of studies on transcranial Doppler and cerebral hyperperfusion syndrome.
CHS: cerebral hyperperfusion syndrome. CEA: carotid endarterectomy. PTA: percutaneous transluminal angioplasty. CAS: carotid artery stenting. V_{peak}: peak systolic velocity. V_{mean}: mean velocity. P/I = Gosling pulsatility index

found in the first post-procedural days following both CEA and CAS. The decrease after CAS was larger, however this difference was disappeared one month after treatment. Possibly this difference was associated with a decreased number of CHS patients in the CAS group, as CHS has been associated with hypertension, however, such data was not mentioned.

Conclusion

The hemodynamic changes following carotid revascularization are complex and vary between patients. Several studies have attempted to assess these changes in order to identify patients at risk for CHS. However, the numbers of cases discussed are small and it is not possible to make direct comparisons between the data as different definitions have been used to identify subjects with CHS. Moreover, most of these studies have been performed in patients who underwent CEA; therefore it is unclear whether the findings of these studies can be generalized to patients undergoing CAS. Therefore further studies in larger cohorts are required to assess the changes in cerebral hemodynamic in patients undergoing either CAS or CEA.

References

(1) Petty GW, Brown RD, Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of incidence and risk factors. Stroke 1999; 30(12):2513-2516.

(2) Liapis CD, Bell PR, Mikhailidis D, Sivenius J, Nicolaides A, Fernandes e Fernandes et al. ESVS guidelines. Invasive treatment for carotid stenosis: indications, techniques. Eur J Vasc Endovasc Surg 2009; 37(4 Suppl):1-19.

(3) Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomized controlled trial. Lancet 2010; 375(9719):985-997.

(4) de Borst GJ, Moll FL, van de Pavoordt HD, Mauser HW, Kelder JC, Ackerstaf RG. Stroke from carotid endarterectomy: when and how to reduce perioperative stroke rate? Eur J Vasc Endovasc Surg 2001; 21(6):484-489.

(5) Riles TS, Imparato AM, Jacobowitz GR, Lamparello PJ, Giangola G, Adelman MA et al. The cause of perioperative stroke after carotid endarterectomy. J Vasc Surg 1994; 19(2):206-214.

(6) Theron JG, Payelle GG, Coskun O, Huet HF, Guimaraens L. Carotid artery stenosis: treatment with protected balloon angioplasty and stent placement. Radiology 1996; 201(3):627-636.

(7) Sundt TM, Jr., Sharbrough FW, Piepgras DG, Kearns TP, Messick JM, Jr., O'Fallon WM. Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy: with results of surgery and hemodynamics of cerebral ischemia. Mayo Clin Proc 1981; 56(9):533-543.

(8) van Mook WN, Rennenberg RJ, Schurink GW, van Oostenbrugge RJ, Mess WH, Hofman PA et al. Cerebral hyperperfusion syndrome. Lancet Neurol 2005; 4(12):877-888.

(9) Piepgras DG, Morgan MK, Sundt TM, Jr., Yanagihara T, Mussman LM. Intracerebral hemorrhage after carotid endarterectomy. J Neurosurg 1988; 68(4):532-536.

(10) Ascher E, Markevich N, Schutzer RW, Kallakuri S, Jacob T, Hingorani AP. Cerebral hyperperfusion syndrome after carotid endarterectomy: predictive factors and hemodynamic changes. J Vasc Surg 2003; 37(4):769-777.

(11) Brantley HP, Kiessling JL, Milteer HB, Jr., Mendelsohn FO. Hyperperfusion syndrome following carotid artery stenting: the largest single-operator series to date. J Invasive Cardiol 2009; 21(1):27-30.

(12) Dalman JE, Beenakkers IC, Moll FL, Leusink JA, Ackerstaff RG. Transcranial Doppler monitoring during carotid endarterectomy helps to identify patients at risk of postoperative hyperperfusion. Eur J Vasc Endovasc Surg 1999; 18(3):222-227.

(13) Matsumoto S, Nakahara I, Higashi T, Iwamuro Y, Watanabe Y, Takahashi K et al. Near-infrared spectroscopy in carotid artery stenting predicts cerebral hyperperfusion syndrome. Neurology 2009; 72(17):1512-1518.

(14) Ogasawara K, Sakai N, Kuroiwa T, Hosoda K, Iihara K, Toyoda K et al. Intracranial hemorrhage associated with cerebral hyperperfusion syndrome following carotid endarterectomy and carotid artery stenting: retrospective review of 4494 patients. J Neurosurg 2007; 107(6):1130-1136.

(15) Spetzler RF, Wilson CB, Weinstein P, Mehdorn M, Townsend J, Telles D. Normal perfusion pressure breakthrough theory. Clin Neurosurg 1978; 25:651-672.

(16) Bishop CC, Powell S, Rutt D, Browse NL. Transcranial Doppler measurement of middle cerebral artery blood flow velocity: a validation study. Stroke 1986; 17(5):913-915.

(17) Zachrisson H, Blomstrand C, Holm J, Mattsson E, Volkmann R. Changes in middle cerebral artery blood flow after carotid endarterectomy as monitored by transcranial Doppler. J Vasc Surg 2002; 36(2):285-290.

(18) Gosling RG, King DH. Arterial assessment by Doppler-shift ultrasound. Proc R Soc Med 1974; 67(6 Pt 1):447-449.

(19) Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982; 57(6):769-774.

(20) Poulin MJ, Robbins PA. Indexes of flow and cross-sectional area of the middle cerebral artery using doppler ultrasound during hypoxia and hypercapnia in humans. Stroke 1996; 27(12):2244-2250.

(21) Iwata T, Mori T, Tajiri H, Nakazaki M. Predictors of hyperperfusion syndrome before and immediately after carotid artery stenting in single-photon emission computed tomography and transcranial color-coded real-time sonography studies. Neurosurgery 2011; 68(3):649-656.

(22) Kablak-Ziembicka A, Przewlocki T, Pieniazek P, Musialek P, Motyl R, Moczulski Z et al. Assessment of flow changes in the circle of Willis after stenting for severe internal carotid artery stenosis. J Endovasc Ther 2006; 13(2):205-213.

(23) Schoser BG, Heesen C, Eckert B, Thie A. Cerebral hyperperfusion injury after percutaneous

transluminal angioplasty of extracranial arteries. J Neurol 1997; 244(2):101-104.
(24) Derdeyn CP, Videen TO, Yundt KD, Fritsch SM, Carpenter DA, Grubb RL et al. Variability of cerebral blood volume and oxygen extraction: stages of cerebral haemodynamic impairment revisited. Brain 2002; 125(Pt 3):595-607.
(25) Jorgensen LG, Schroeder TV. Defective cerebrovascular autoregulation after carotid endarterectomy. Eur J Vasc Surg 1993; 7(4):370-379.
(26) Vagal AS, Leach JL, Fernandez-Ulloa M, Zuccarello M. The acetazolamide challenge: techniques and applications in the evaluation of chronic cerebral ischemia. AJNR Am J Neuroradiol 2009; 30(5):876-884.
(27) Sbarigia E, Speziale F, Giannoni MF, Colonna M, Panico MA, Fiorani P. Post-carotid endarterectomy hyperperfusion syndrome: preliminary observations for identifying at risk patients by transcranial Doppler sonography and the acetazolamide test. Eur J Vasc Surg 1993; 7(3):252-256.
(28) Ogasawara K, Inoue T, Kobayashi M, Endo H, Yoshida K, Fukuda T et al. Cerebral hyperperfusion following carotid endarterectomy: diagnostic utility of intraoperative transcranial Doppler ultrasonography compared with single-photon emission computed tomography study. AJNR Am J Neuroradiol 2005; 26(2):252-257.
(29) Maltezos CK, Papanas N, Papas TT, Georgiadis GS, Dragoumanis CK, Marakis J et al. Changes in blood flow of anterior and middle cerebral arteries following carotid endarterectomy: a transcranial Doppler study. Vasc Endovascular Surg 2007; 41(5):389-396.
(30) Jansen C, Sprengers AM, Moll FL, Vermeulen FE, Hamerlijnck RP, van GJ et al. Prediction of intracerebral haemorrhage after carotid endarterectomy by clinical criteria and intraoperative transcranial Doppler monitoring. Eur J Vasc Surg 1994; 8(3):303-308.
(31) Powers AD, Smith RR. Hyperperfusion syndrome after carotid endarterectomy: a transcranial Doppler evaluation. Neurosurgery 1990; 26(1):56-59.
(32) Pennekamp CW, Tromp SC, Ackerstaff RG, Bots ML, Immink RV, Spiering W et al. Prediction of cerebral hyperperfusion after carotid endarterectomy with transcranial Doppler. Eur J Vasc Endovasc Surg 2012; 43(4):371-376.
(33) Fujimoto S, Toyoda K, Inoue T, Hirai Y, Uwatoko T, Kishikawa K et al. Diagnostic impact of transcranial color-coded real-time sonography with echo contrast agents for hyperperfusion syndrome after carotid endarterectomy. Stroke 2004; 35(8):1852-1856.
(34) Altinbas A, Algra A, Brown MM, Featherstone RL, Kappelle LJ, de Borst GJ et al. Effects of carotid endarterectomy or stenting on blood pressure in the International Carotid Stenting Study (ICSS). Stroke 2011; 42(12):3491-3496.

Chapter 6

Prediction of cerebral hyperperfusion after carotid endarterectomy with transcranial Doppler

Published in: European Journal of Vascular and Endovascular Surgery. 2012 Apr;43(4):371-6

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Abstract

Background
The aim of this study was to determine the diagnostic value for predicting cerebral hyperperfusion syndrome (CHS) by adding a transcranial Doppler (TCD) measurement in the early postoperative phase after carotid endarterectomy (CEA).

Methods
Patients who underwent carotid endarterectomy between January 2004 and August 2010 and in whom both intra- and postoperative TCD monitoring were performed were included. In 184 CEA patients the mean velocity (V_{mean}) preoperatively (V_1), pre-clamping (V_2), post-declamping (V_3) and postoperatively (V_4) was measured using TCD. The intraoperative V_{mean} increase $((V_3 - V_2)/V_2)$ was compared to the postoperative increase $((V_4 - V_1)/V_1)$ in relation to CHS. CHS was diagnosed if the patient developed neurological complaints in the presence of a preoperative V_{mean} increase >100%.

Results
Sixteen patients (9%) had an intraoperative V_{mean} increase >100% and 22 patients (12%) a postoperative V_{mean} increase of >100%. In 10 patients (5%) CHS was diagnosed; two of those had an intraoperative V_{mean} increase of >100% and nine postoperative V_{mean} increase >100%. This results in a positive predictive value of 13% for the intraoperative and 41% for the postoperative measurement.

Conclusion
Besides the commonly used intraoperative TCD monitoring additional TCD measurement in the early postoperative phase is useful to more accurately predict CHS after CEA.

Introduction

Carotid endarterectomy (CEA) is the standard treatment for patients with high-grade symptomatic stenosis of the internal carotid artery (ICA). Operative treatment has also been demonstrated to be superior to medical treatment in patients younger than 75 years with an asymptomatic high-grade stenosis of the ICA. Unfortunately, the benefits of this procedure are hampered by serious procedure-related complications resulting in perioperative death or stroke in up to 5% of patients.[1,2] Perioperative strokes can be categorized by time of onset. Ischemic strokes that occur during the operation and become apparent upon recovery from anesthesia are thought to be caused by hypoperfusion during clamping or by thrombo-embolism.[3] Postoperative strokes develop after a symptom-free interval and are mainly caused by local thrombosis, thrombo-embolism or cerebral hyperperfusion syndrome (CHS).[3] Introduction of intraoperative cerebral monitoring using computerized electroencephalography (EEG) and transcranial Doppler (TCD) has significantly decreased the intraoperative stroke rate.[4,5,6] However, complications in the postoperative phase cannot be prevented by this approach.[7]

CHS can occur during the first few days up to 4 weeks after CEA in 1–3% of patients.[8] It is hypothesized that in a previously hypoperfused area with a disturbed autoregulation a sudden increase of blood flow may lead to cerebral hyperperfusion.[9] CHS can cause a spectrum of symptoms including headache, vomiting, neurological deficit or seizures.[10] Patients may have only mild and transient symptoms, but if not recognized and treated adequately in time (i.e., strict blood pressure control), hemorrhagic stroke and subsequent death may occur in up to 40% of patients.[11]

The generally accepted definition of postoperative cerebral hyperperfusion in the context of CEA is defined as an increase in cerebral blood flow (CBF) of >100% over baseline.[12] This occurs in approximately 10% of CEA patients[13] and has been associated with a 10-fold higher risk for postoperative intra-cerebral hemorrhage in patients operated under general anaesthesia.[12,14] Changes in CBF are correlated with changes in the mean blood velocity (V_{mean}) in the ipsilateral middle cerebral artery (MCA) as measured with TCD.[15,16] Currently, during CEA under general anesthesia, an increase in V_{mean} of >100% 3 min after declamping the ICA, compared to the pre-clamping V_{mean} is the most commonly used predictor of CHS.[11,17-19] However, intraoperative TCD monitoring is associated with both false negative and false positive results.[11,20] Therefore, a more precise method is needed to predict which patients are at risk for CHS.

This study aimed to assess the predictive power of intraoperative TCD monitoring regarding the development of CHS, by introducing an additional TCD measurement in the first two postoperative hours.

Materials and Methods

Patients

Data were derived from two Dutch Vascular referral centers. Patients operated between February 2009 and August 2010 in the University Medical Center Utrecht (UMCU) were prospectively and patients who underwent CEA between January 2004 and August 2010 in

St. Antonius Hospital, Nieuwegein, were retrospectively included. All patients who underwent CEA for a high degree ICA stenosis and in whom both intra- and postoperative TCD monitoring were performed were included.

Carotid endarterectomy

In both centers, surgery was performed under general anesthesia and all patients received the same anesthetic regimen. Anesthesia was induced with propofol, sufentanil and rocuronium, and maintained with isoflurane. After tracheal intubation, mechanical ventilation was adjusted to maintain normocapnia. CEA was performed by an experienced vascular surgeon or by a vascular trainee under supervision in a standardized way. An intra-luminal shunt was used selectively in case of EEG asymmetry or a decrease of >60% of V_{mean} measured by TCD.[21] Postoperatively, patients stayed for at least 6 h on the recovery ward for continuous blood pressure (BP) monitoring.

Definition of study end points

CHS (primary end point) was diagnosed if the patient developed headache, confusion, seizures, intracranial hemorrhage or focal neurological deficits in the presence of postoperative cerebral hyperperfusion (defined as >100% increase of the preoperative V_{mean}) after a symptom-free interval. The diagnosis of CHS was made by an independent neurologist.[8] Postoperative hypertension (PH) (secondary end point) was defined either as an absolute high BP threshold (BP >160 mmHg systolic) or as a relative high BP (20% above the preoperative BP).[22] Moreover, PH was also scored if, in patients identified as being at risk for CHS based on the intraoperative V_{mean} increase, BP was raised above the adjusted restriction (see below).[22]

Measurements

The preoperative BP was measured (non-invasively) during the preoperative TCD measurement. If these data were not available, the BP obtained during preoperative assessment was used. In the perioperative period, BP was measured using an intra-arterial catheter in the radial or brachial artery. Systolic BP was kept above 140 mmHg during cross-clamping.

For the TCD registration, a pulsed Doppler transducer (Pioneer TC4040, EME, Überlingen, Germany), gated at a focal depth of 45–60 mm, was placed over the temporal bone to insonate the main stem of the ipsilateral MCA, with the TCD transducer being fixed with a head frame and V_{mean} was recorded continuously. The values used for further analysis were gathered in real time on indicated data points as described below.

Post-CEA anti-hypertensive treatment protocol

All patients with PH, that is, BP >160 mmHg systolic (absolute), >20% above the preoperative BP, or BP risen above the individual restriction in patients with an intraoperative V_{mean} increase >100%, underwent strict individualized BP control during the early postoperative period. Anti-hypertensive treatment consisted of intravenous labetalol (first choice) or clonidine (second choice). If BP was not controlled appropriately after 6 h on the recovery ward, the patient was transferred to the medium care unit (MCU) for continuous BP monitoring and treatment until BP reached the appropriate limits. If BP was

within the required limits, intravenous anti-hypertensive treatment was tapered as soon as possible and an oral beta-blocker (labetalol or metoprolol) was started. If PH occurred on the nursing ward, oral beta-blockers (labetalol or metoprolol) were given firstly. However, if the BP was not sufficiently controlled or even increased, whether or not in combination with neurological symptomatology, (re)transfer to the MCU was established.

Timeframes

Four timeframes were indicated, which are schematically shown in Figure 1. For the preoperative V_{mean} (V_1), a TCD measurement of the MCA ipsilateral to the treated carotid artery was performed within one week prior to operation. During operation, the pre-clamping V_{mean} (V_2) was registered 30 s prior to carotid cross-clamping. The post-declamping V_{mean} (V_3) was determined three min after declamping. An additional postoperative V_{mean} (V_4) was measured within the first hour after arrival on the recovery ward. All patients received their last TCD measurement within the first two hours after surgery. This V_4 measurement was performed in all patients in the UMCU, but mainly in case of hypertension or an increased V_3 in the St. Antonius hospital.

The intraoperative increase of V_{mean} was defined and calculated as follows:

$(V_3–V_2)/V_2\times100\%.(V_3– V_2)/ V_2\times100\%$

For calculating the postoperative increase of V_{mean} the following formula was used:

$(V_4– V_1)/ V_1\times100\%.(V_4– V_1)/ V_1\times100\%$

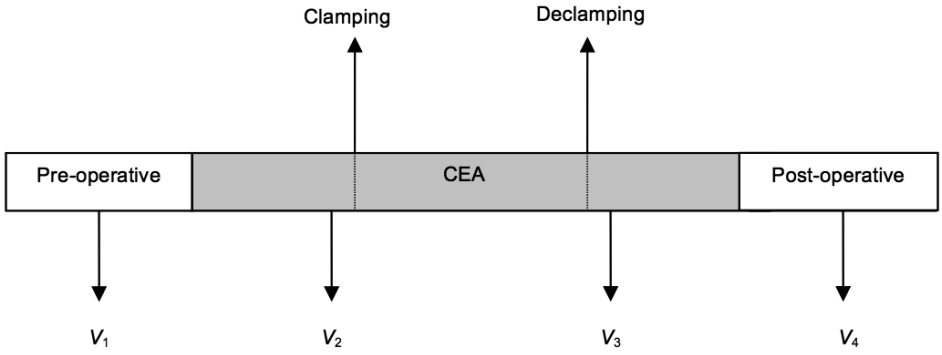

Figure 1. Timeline TCD measurements around CEA.
V1: Pre-operative mean blood velocity (V_{mean}) prior to CEA
V2: Pre-clamping V_{mean} measured at most one minute before carotid clamping.
V3: Post-declamping V_{mean} measured three minutes after carotid declamping.
V4: Post-operative V_{mean} measured within the first two hours on the recovery ward.

Statistical analysis

Patients were classified according to the relative increase in V_{mean} (i.e., less or more than 100% increase) at predefined two timeframes (intraoperatively and postoperatively) in relation to CHS occurrence (Figure 1).

The positive predictive value (PPV) and negative predictive value (NPV) of both intra-operative and postoperative increase of V_{mean} were calculated. Differences in BP between the intraoperative and postoperative measurements and between CHS and non-CHS groups were compared using the Chi-square test for categorical variables and Student's t-test or Mann–Whitney U test for continuous variables, as appropriate. These statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 15.0 software. A confidence level of less than 5% ($p < 0.05$) was considered significant.

Patient characteristics	**Combined N= 112**	**UMCU N= 112**	**St.Antonius N= 72**	**p-value**
Age (yrs)	68.8 (± 9.9)	69.1 (± 9.8)	68.4 (± 10.1)	0.68
Gender (male)	141 (77%)	88 (79%)	53 (74%)	0.438
Risk factors				
Diabetes	36 (20%)	26 (23%)	10 (17%)	0.330
Hypertension	135 (73%)	85 (76%)	50 (69%)	0.334
Hypercholesterolemia	164 (89%)	102 (91%)	62 (86%)	0.436
Coronary artery disease	50 (27%)	36 (32%)	14 (20%)	0.091
Smoking	61 (33%)	43 (38%)	18 (25%)	0.077
Alcohol use	124 (67%)	85 (76%)	39 (54%)	0.005
Site (right)	83 (45%)	47 (42%)	36 (50%)	0.285
Symptomatic	159 (87%)	97 (87%)	62 (86%)	0,924
Degree of stenosis (ipsilateral)				
>70%	174 (95%)	106 (95%)	68 (94%)	0.901
≥ 50%	10 (5%)	6 (5%)	4 (5%)	
Degree of contralateral stenosis				
Occlusion	27 (15%)	15 (13%)	12 (17%)	0.257
Stenosis >70%	17 (9%)	12 (11%)	5 (7%)	
Stenosis 50-70%	30 (16%)	18 (16%)	12 (17%)	
Stenosis <50%	94 (51%)	61 (55%)	33 (46%)	
Unknown	16 (9%)	10 (%)	6 (14%)	
Shunt use	33 (18%)	11 (10%)	22 (31%)	<0.001
Post-operative hypertension	34 (19%)	15 (13%)	19 (26%)	0.027
Cerebral hyperperfusion syndrome	10 (5%)	5 (5%)	5 (7%)	0.469

Table 1. Patient characteristics. Values are shown as mean (±SD) or number of patients (%).

Results

Patient characteristics

In the St. Antonius Hospital Nieuwegein 560 patients underwent CEA during the time of the study. Of these 560, 72 (13%) received both intra- and postoperative TCD monitoring and were included for the present analysis (Table 1). In the UMCU, a postoperative TCD measurement was performed in 112 of 211 patients (53%) who underwent CEA within the time frame February 2009–August 2010. Therefore, out of 771 patients a total of 184 patients were included in this study. In both hospitals, patients were excluded for the study because of logistic reasons. The majority of patients were symptomatic (159 patients, 87%). Thirty-three patients (18%) required the use of an intra-luminal shunt because of either EEG asymmetry or a decrease of >60% of V_{mean} measured by TCD. After stratification according to hospital, the majority of patients' characteristic parameters were comparable. Three variables significantly differed between the St. Antonius and the UMCU: alcohol usage (54% vs. 76%, p = 0.005), PH (26% vs. 13%, p = 0.027) and shunt use (31% vs. 10%, p < 0.001).

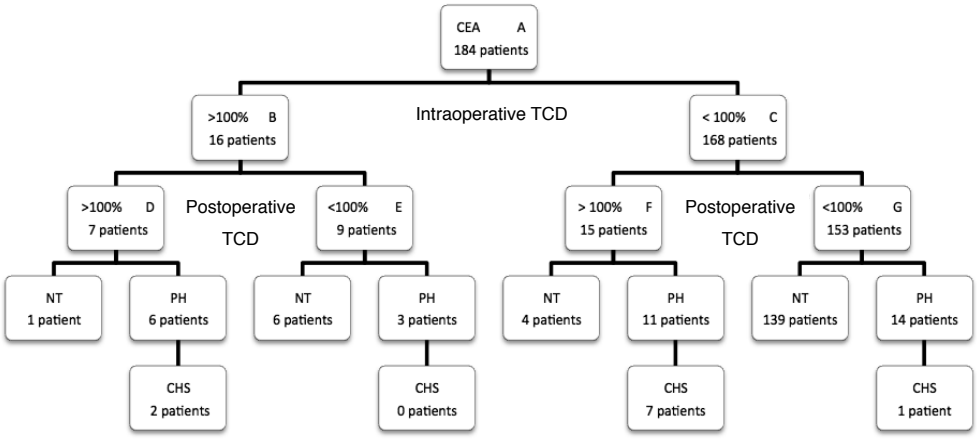

Figure 2. Flowchart
Intraoperative TCD: V_{mean} increase 3 minutes after declamping as compared to the pre-clamping values. Postoperative TCD: V_{mean} increase on the recovery room in the first two hours post-operatively compared to pre-operative values. NT: Normotensive. PH: Post-operative hypertension. CHS: Cerebral hyperperfusion syndrome.

Combined data		CHS+	CHS-	PPV(%)	NPV(%)
Intraoperative increase	> 100% (B)	2 (1%)	14 (8%)	13	95
	< 100% (C)	8 (5%)	160 (86%)		
Postoperative increase	> 100% (D+F)	9 (5%)	13 (7%)	41	99
	< 100% (E+G)	1 (1%)	161 (87%)		
Intraoperative increase	Postoperative increase				
> 100%	> 100% (D)	2 (1%)	5 (3%)	29	95
> 100%	< 100% (E)	0 (0%)	9 (5%)	0	94
< 100%	> 100% (F)	7 (4%)	8 (4%)	47	98
< 100%	< 100% (G)	1 (1%)	152(82%)	1	71
	Total (%)	10 (6%)	174(94%)		

St. Antonius Hospital (retrospectively included)		CHS+	CHS-	PPV(%)	NPV(%)
Intraoperative increase	> 100% (B)	2 (3%)	10 (14%)	17	95
	< 100% (C)	3 (4%)	57 (79%)		
Postoperative increase	> 100% (D+F)	5 (7%)	8 (11%)	38	100
	< 100% (E+G)	0	59 (82%)		
Intraoperative increase	Postoperative increase				
> 100%	> 100% (D)	2 (3%)	4 (6%)	33	95
> 100%	< 100% (E)	0	6 (8%)	0	92
< 100%	> 100% (F)	3 (4%)	4 (6%)	43	97
< 100%	< 100% (G)	0	53 (73%)	0	74
	Total (%)	5 (7%)	67 (93%)		

UMCU (prospectively included)		CHS+	CHS-	PPV(%)	NPV(%)
Intraoperative increase	> 100% (B)	0	4 (4%)	0	95
	< 100% (C)	5 (4%)	103 (92%)		
Postoperative increase	> 100% (D+F)	4 (4%)	5 (4%)	44	99
	< 100% (E+G)	1 (1%)	102 (91%)		
Intraoperative increase	Postoperative increase				
> 100%	> 100% (D)	0	1 (1%)	0	95
> 100%	< 100% (E)	0	3 (2%)	0	95
< 100%	> 100% (F)	4 (4%)	4 (4%)	50	99
< 100%	< 100% (G)	1 (1%)	99 (88%)	1	67
	Total (%)	5 (4%)	107 (96%)		

Table 2. Cross tables
Predictive values of TCD measurements for the occurrence of CHS at different timeframes (capitals refer to Figure 2). CHS+: number of patients who developed CHS (%). CHS-: number of patients who did not develop CHS (%). PPV: positive predictive value (%). NPV: negative predictive value (%).

TCD measurements

Sixteen patients (9%) had an intraoperative V_{mean} increase >100% (Figure 2; B). Postoperatively, a V_{mean} increase >100% was found in an additional 15 patients (8%) (Figure 2 D and F). In seven patients (4%) both the intraoperative and the postoperative measurement showed a V_{mean} increase >100% (Figure 2 D). During all TCD measurements the systolic BP was significantly lower after declamping compared to the pre-clamping systolic BP, the mean decrease was 11.3 mmHg (95% confidence interval (C.I.) 7.3–15). Postoperatively, the systolic BP was 4.0 mmHg lower (95% C.I. –12.6 to –20.6) compared to the preoperative systolic BP.

Clinical outcome

Of all 184 patients, one (0.5%) patient had an intraoperative stroke. Postoperatively, 34 patients (19%) developed PH and 10 patients (5%) suffered from CHS. All 10 patients with CHS had hypertension during the postoperative phase. Nine fully recovered, but one patient refused further treatment and died because of intracranial hemorrhage. The overall 30-day rate of death/stroke was 1%.

TCD measurements and clinical outcome

Of 16 patients with an intraoperative increase of V_{mean} >100% (Figure 2 B), nine developed PH and, of these, two patients developed CHS. On the other hand, in 168 patients who had an intraoperative increase less than 100% (Figure 2 C), 25 patients developed PH and eight of them suffered from CHS. This results in a PPV of 56% (9/16) and a NPV of 85% (143/166) in the prediction of PH and a PPV of 13% (2/16) and NPV of 95% (160/168) in the prediction of CHS (Table 2 and Table 3). With respect to the postoperative TCD measurements 17 of the 22 patients with a doubling of postoperative V_{mean} (Figure 2 D and F) developed PH and in nine of them CHS occurred.

		PH+	PH-	PPV(%)	NPV(%)
Intraoperative increase	> 100% (B)	9 (5%)	7 (4%)	56	85
	< 100% (C)	25 (13%)	143 (78%)		
Postoperative increase	> 100% (D+F)	17 (9%)	5 (3%)	77	90
	< 100% (E+G)	17 (9%)	145 (79%)		
Intraoperative increase	Postoperative increase				
> 100%	> 100% (D)	6 (3%)	1 (1%)	86	84
> 100%	< 100% (E)	3 (2%)	6 (3%)	33	82
< 100%	> 100% (F)	11 (6%)	4 (2%)	73	86
< 100%	< 100% (G)	14 (7%)	139 (76%)	9	35
	Total (%)	34 (18%)	150 (82%)		

Table 3. Cross tables
Predictive values of TCD measurements for the occurrence of post-operative hypertension (PH) at different timeframes (capitals refer to Figure 2). PH+: number of patients who developed PH (%). PH-: number of patients who did not develop PH (%). PPV: positive predictive value (%). NPV: negative predictive value (%).

In the subgroup of 162 patients with postoperative increase of less than 100% (Figure 2 E and G), 17 patients developed PH and one patient CHS. This results in a PPV of 77% (17/22) and a NPV of 90% (145/162) for PH and a PPV 41% (9/22) and a NPV of 99% (161/162) for the development of CHS (Table 2 and Table 3). Of all 31 patients, who had an intraoperative and/or postoperative V_{mean} increase of more than 100% (Figure 2 B and F), 20 developed PH and nine CHS. Only one patient with CHS did not have postoperative V_{mean} doubling. Of the 153 patients without an increase >100% at any time point (Figure 2 G), 14 patients developed PH and one patient developed CHS. This results in a PPV of 65% (20/31) and NPV of 91% (139/153) for the prediction of postoperative hypertension and a PPV of 29% (9/31) and NPV of 99% (152/153) for the development of CHS.

CHS versus non-CHS

The median (interquartile range) intraoperative V_{mean} increase was 10% (0–31) in the non-CHS group (n = 174) and 23% (5–85) in CHS patients (n = 10; p = 0.122). The differences in median postoperative V_{mean} increase was 18% (1–47) in the non-CHS and 107% (99–115) in the CHS group respectively (p < 0.005) (Figure 3). PH occurred in all 10 patients who developed CHS (100%) and in only 24 patients out of 174 (14%) in the non-CHS group (p < 0.005). There was no significant difference in intraoperative BP changes between the CHS and non-CHS group neither during the intraoperative measurements (p = 0.234) nor during the postoperative measurements (p = 0.463).

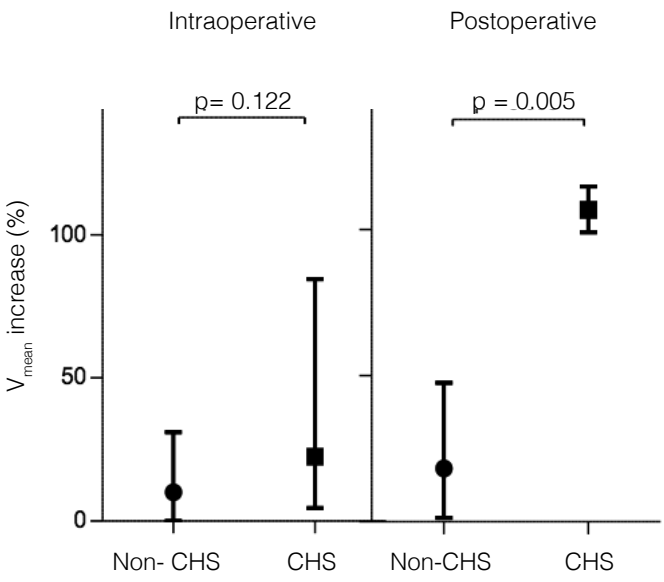

Figure 3. V_{mean} increase for CHS and non-CHS patients.
Intraoperative and postoperative V_{mean} increase in patients who developed CHS (n= 10) and patients who did not (n= 174). Values are median with interquartile range.

Discussion

An increase in V_{mean} measured postoperatively predicts the development of CHS better than the commonly used increase in V_{mean} measured 3 min after declamping versus pre-clamping value. The PPV of the postoperative measurement in the prediction of CHS is more than three times higher than of the intraoperative measurement (41% and 13%, respectively). Thus, for 28% of the patients who developed CHS in our cohort, this complication would have been predicted in an early stage if a postoperative TCD measurement had been performed. Moreover, the absence of doubling of the V_{mean} at the postoperative measurement excluded the development of CHS almost completely. Therefore, with postoperative measurement fewer patients will be treated unnecessarily by strict intravenous anti-hypertensive medication.

The association between changes in cerebral artery flow after CEA and the development of CHS has been extensively described.[23] In 1988 Piepgras et al. showed that doubling of the CBF measured by intra-carotid injection of xenon-133, was associated with the occurrence of intra-cerebral haemorrhage.[14] Nowadays, TCD, which is relatively inexpensive and does not require radiation exposure is widely applied for monitoring in CEA.

A critical issue is to what extent blood velocity reflects on actual volume flow. In the unlikely case that blood flow is not laminar, the blood velocity changes out of proportion with volume flow. Second, changes in velocity are parallel with volume flow only when both the angle of insonation and the diameter of the vessel remain constant. The large cerebral arteries are conductance rather than resistance vessels and changes in systemic arterial blood pressure within the physiological range appear to have a negligible effect on the diameter of the insonated artery.[24,25] Third, validation studies found that changes in mean middle cerebral artery blood velocity follow cerebral 133Xe clearance.[26,27] Technical limitations of TCD include the lack of sufficient bone window in 10–15% of patients. Furthermore, TCD monitoring, like many other diagnostic techniques, is operator-dependent and requires training and experience to perform and interpret results correctly. Nevertheless, as the measurements were performed by experienced personnel, the reproducibility of TCD measurement is high. According to literature, TCD determination of V_{mean} are reproducible with a difference of less than 3% with $R = 0.95$.

Ogasawara et al. showed that the accuracy of intraoperative TCD monitoring is less reliable in predicting CHS than TCD at the end of the procedure.[20] However, they defined postoperative TCD as ‘at the end of the procedure at the operating room’, while the patient was still influenced by anesthetic medication. As anesthetics may reduce cerebral blood flow, these values could not be reliably compared with preoperative TCD values. As far as we know, analysis or studies comparing the accuracy of postoperatively with intraoperatively measured TCD values in the prediction of CHS have never been performed. Therefore, besides determination of the cerebrovascular reserve capacity with 123I-IMP SPECT[13] or TCD[28] after acetazolamide administration, preoperative selection of patients at risk to develop CHS is not yet possible, since well-known patient factors supposedly predisposing for CHS have not been clarified, or have been analyzed for a single risk factor only.[8]

In our study, only 10 of patients developed CHS. The low incidence of CHS hampers the interpretation of our results. This small number did not allow multivariate statistical analysis

(logistic regression). However, the incidence in our group (5%) of patients is relatively high compared to other series. This might be explained by the fact that in our referral hospitals a selected group of patients with relatively severe haemodynamic compromise are treated. To determine the influence of the retrospective inclusion of the St. Antonius Hospital patient cohort, analyses on outcome were stratified according to hospital. The first variable that significantly differed between both hospitals was alcohol use, which we believe is coincidence and does not affect the risk for CHS. Furthermore, postoperative hypertension and the use of an intraoperative shunt was more frequently present in the St. Antonius patients. This can be explained by the fact that postoperative TCD was preferentially performed in patients with PH or an intraoperative V_{mean} increase of >100%. Also the use of intraoperative shunting was believed to potentially increase the risk of CHS and, as a consequence, this was reflected by the difference in shunt use between the St. Antonius and UMCU (31% vs. 10%, $p < 0.001$, respectively, Table 1).

As patients were followed up by a postoperative TCD measurement, but being treated (for BP control) based on the intraoperative TCD measurement, this approach might have led to an underestimation of the predictive value of intraoperative measurements in the UMCU. Nevertheless, the difference in incidence of CHS between the prospectively and retrospectively included data was small and non-significant (5% vs. 7%, respectively; Table 1) and the predictive values were almost identical in both hospitals. Importantly, in both hospitals the majority of CHS patients being identified by postoperative TCD but being missed by intraoperative TCD were significant in both hospitals (Table 2). Thus, the assumption that postoperative measurement improves identification of patients at risk for CHS was confirmed in each hospital separately in equal measures. These findings further underline the lack of significant preoperative and intraoperative prediction models for CHS development by technical aspects of the procedure. We assume that the changes in V_{mean} could not be explained by the differences in BP among the several TCD measurements, since the changes in BP were inversely correlated to the changes in V_{mean} (increase) for the intraoperative measurements and no significant change in MAP was found between the pre- and postoperative TCD measurements.

In conclusion, besides the commonly used intraoperative TCD monitoring, additional TCD measurement in the early postoperative phase is useful to predict CHS in patients who underwent CEA under general anesthesia. However, this observation needs to be validated for patients undergoing CEA under local anesthesia. Furthermore, most patients who develop CHS do so following prior PH development. Therefore, anti-hypertensive treatment for all patients having PH should be administered appropriately since they are at risk to develop CHS subsequently. By measuring V_{mean} in the postoperative instead of only in the intraoperative phase, both the positive and negative predictive values of TCD for development of CHS after CEA can be improved. Therefore, we recommend a baseline measurement before the administration of anesthetics and a postoperative measurement within 2 hours after surgery.

Conflict of interest

W.F. Buhre receives honoraria from Edwards Life sciences hemodynamic monitoring.

References

(1) Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomized controlled trial. Lancet 2010; 375(9719):985-997.

(2) Holliday A, Mansfield A, Marrow J, Pete C, Pete R, Potter J et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. Lancet 2004; 363(9420):1491-1502.

(3) Riles TS, Imparato AM, Jacobowitz GR, Lamparello PJ, Giangola G, Adelman MA et al. The cause of perioperative stroke after carotid endarterectomy. J Vasc Surg 1994; 19(2):206-214.

(4) de Borst GJ, Moll FL, van de Pavoordt HD, Mauser HW, Kelder JC, Ackerstaf RG. Stroke from carotid endarterectomy: when and how to reduce perioperative stroke rate? Eur J Vasc Endovasc Surg 2001; 21(6):484-489.

(5) Naylor AR, Hayes PD, Allergen H, Lenard N, Gaunt ME, Thompson MM et al. Reducing the risk of carotid surgery: a 7-year audit of the role of monitoring and quality control assessment. J Vasc Surg 2000; 32(4):750-759.

(6) Smith JL, Evans DH, Gaunt ME, London NJ, Bell PR, Naylor AR. Experience with transcranial Doppler monitoring reduces the incidence of particulate embolisation during carotid endarterectomy. Br J Surg 1998; 85(1):56-59.

(7) Naylor AR. Making carotid surgery safer. Br Med Bull 2000; 56(2):539-548.

(8) van Mook WN, Rennenberg RJ, Schurink GW, van Oostenbrugge RJ, Mess WH, Hofman PA et al. Cerebral hyperperfusion syndrome. Lancet Neurol 2005; 4(12):877-888.

(9) Spetzler RF, Wilson CB, Weinstein P, Mehdorn M, Townsend J, Telles D. Normal perfusion pressure breakthrough theory. Clin Neurosurg 1978; 25:651-672.

(10) Sundt TM, Sandoz BA, Whisnant JP. Carotid endarterectomy. Complications and preoperative assessment of risk. Mayo Clin Proc 1975; 50(6):301-306.

(11) Dalman JE, Beenakkers IC, Moll FL, Leusink JA, Ackerstaff RG. Transcranial Doppler monitoring during carotid endarterectomy helps to identify patients at risk of postoperative hyperperfusion. Eur J Vasc Endovasc Surg 1999; 18(3):222-227.

(12) Sundt TM, Jr., Sharbrough FW, Piepgras DG, Kearns TP, Messick JM, Jr., O'Fallon WM. Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy: with results of surgery and hemodynamics of cerebral ischemia. Mayo Clin Proc 1981; 56(9):533-543.

(13) Ogasawara K, Yukawa H, Kobayashi M, Miami C, Konno H, Teriyaki K et al. Prediction and monitoring of cerebral hyperperfusion after carotid endarterectomy by using single-photon emission computerized tomography scanning. J Neurosurg 2003; 99(3):504-510.

(14) Piepgras DG, Morgan MK, Sundt TM, Jr., Yanagihara T, Mussman LM. Intracerebral hemorrhage after carotid endarterectomy. J Neurosurg 1988; 68(4):532-536.

(15) Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982; 57(6):769-774.

(16) Poulin MJ, Robbins PA. Indexes of flow and cross-sectional area of the middle cerebral artery using doppler ultrasound during hypoxia and hypercapnia in humans. Stroke 1996; 27(12):2244-2250.

(17) Jansen C, Springer's AM, Moll FL, Vermilion FE, Hamerlijnck RP, van GJ et al. Prediction of intracerebral hemorrhage after carotid endarterectomy by clinical criteria and intraoperative transcranial Doppler monitoring. Eur J Vasc Surg 1994; 8(3):303-308.

(18) Powers AD, Smith RR. Hyperperfusion syndrome after carotid endarterectomy: a transcranial Doppler evaluation. Neurosurgery 1990; 26(1):56-59.

(19) Jorgenson LG, Schroeder TV. Defective cerebrovascular autoregulation after carotid endarterectomy. Eur J Vasc Surg 1993; 7(4):370-379.

(20) Ogasawara K, Inoue T, Kobayashi M, Endo H, Yoshida K, Fukuda T et al. Cerebral hyperperfusion following carotid endarterectomy: diagnostic utility of intraoperative transcranial Doppler ultrasonography compared with single-photon emission computed tomography study. AJNR Am J Neuroradiol 2005; 26(2):252-257.

(21) Jansen C, Moll FL, Vermilion FE, van Haelst JM, Ackerstaff RG. Continuous transcranial Doppler ultrasonography and electroencephalography during carotid endarterectomy: a multimodal monitoring system to detect intraoperative ischemia. Ann Vasc Surg 1993; 7(1):95-101.

(22) Stoneham MD, Thompson JP. Arterial pressure management and carotid endarterectomy. Br J Anaesth 2009; 102(4):442-452.

(23) Zachrisson H, Blomstrand C, Holm J, Mattsson E, Volkmann R. Changes in middle cerebral artery blood flow after carotid endarterectomy as monitored by transcranial Doppler. J Vasc Surg 2002;

36(2):285-290.
(24) Giller CA, Bowman G, Dyer H, Mootz L, Krippner W. Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. Neurosurgery 1993; 32(5):737-741.
(25) Serrador JM, Picot PA, Rutt BK, Shoemaker JK, Bondar RL. MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. Stroke 2000; 31(7):1672-1678.
(26) Bishop CC, Powell S, Rutt D, Browse NL. Transcranial Doppler measurement of middle cerebral artery blood flow velocity: a validation study. Stroke 1986; 17(5):913-915.
(27) Clark JM, Skolnick BE, Gelfand R, Farber RE, Stierheim M, Stevens WC et al. Relationship of 133Xe cerebral blood flow to middle cerebral arterial flow velocity in men at rest. J Cereb Blood Flow Metab 1996; 16(6):1255-1262.
(28) Sbarigia E, Speziale F, Giannoni MF, Colonna M, Panico MA, Fiorani P. Post-carotid endarterectomy hyperperfusion syndrome: preliminary observations for identifying at risk patients by transcranial Doppler sonography and the acetazolamide test. Eur J Vasc Surg 1993; 7(3):252-256.

Chapter 7

The value of near-infrared spectroscopy measured cerebral oximetry during carotid endarterectomy in perioperative stroke prevention. A review

Published in: European Journal of Vascular and Endovascular Surgery. 2009;38(5):539-45

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Abstract

Background
Transcranial Doppler (TCD) for identification of patients at risk for cerebral hyperperfusion syndrome (CHS) following carotid endarterectomy (CEA) cannot be performed in 10–15% of patients because of the absence of a temporal bone window. Near-infrared spectroscopy (NIRS) may be of additional value in these patients. We aimed to (1) compare the value of NIRS related to existing cerebral monitoring techniques in prediction of perioperative cerebral ischaemia and (2) compare the relation between NIRS and the occurrence of CHS.

Methods
A systematic literature search relating to NIRS and CEA was conducted in PubMed and EMBASE databases. Those included were: (1) prospective studies; (2) on NIRS for brain monitoring during CEA; (3) including comparison of NIRS to any other intra-operative cerebral monitoring systems; and (4) on either symptomatic or asymptomatic patients.

Results
We identified 16 studies, of which 14 focused on the prediction of intra-operative cerebral ischaemia and shunt indication. Only two studies discussed the ability of NIRS in predicting CHS. NIRS values correlated well with TCD and electroencephalography (EEG) values indicating ischaemia. However, a threshold for postoperative cerebral ischaemia could not be determined. Neither could a threshold for selective shunting be determined since shunting criteria varied considerably across studies. The evidence suggesting that NIRS is useful in predicting CHS is modest.

Conclusion
NIRS seems a promising monitoring technique in patients undergoing CEA. Yet the evidence to define clear cut-off points for the presence of perioperative cerebral ischaemia or identification of patients at high risk of CHS is limited. A large prospective cohort study addressing these issues is urgently needed.

Introduction

The benefit of carotid endarterectomy (CEA) is hampered by a 2–5% perioperative stroke rate.[1] Many etiologies of stroke following CEA have been proposed; of which the most significant are ischaemia from prolonged carotid artery clamping, intra-operative or postoperative thrombosis and embolism and postoperative cerebral hyperperfusion syndrome (CHS).[2] With the introduction of intra-operative cerebral monitoring during CEA, the intra-operative stroke rate declined, but the rate of postoperative stroke was not altered.[3] Postoperative CHS still occurs in 1–3% of CEA patients, and the knowledge of causes and prevention among physicians seems limited.[4] CHS that causes intracerebral hemorrhage is associated with a 40% mortality rate.

Currently, electroencephalography (EEG) and transcranial Doppler (TCD) are the most frequently used methods for intra-operative monitoring in the prevention of cerebral ischaemia.[5] EEG measures electrical activity produced by the brain recorded by electrodes placed on the scalp. TCD detects changes in cerebral blood flow (CBF) by measuring the flow velocity in the middle cerebral artery (V_{mca}) during and following CEA.[3,6] An increase of ≥100% of postoperative CBF, as compared to preoperative CBF values, has been associated with a 10 times higher risk for CHS. TCD however cannot be performed in all patients, since a temporal bone window is missing in 10–15% of CEA patients. Especially for this subgroup, a reliable alternative monitoring technique is required, but not yet available. Near-infrared spectroscopy (NIRS) has been suggested as an alternative cerebral monitoring technique. NIRS is a non-invasive technique that allows continuous monitoring of cerebral hemoglobin oxygen desaturation produced by systemic hypoxaemia.[5] Yet, the information on NIRS appears to be modest.[7-9] Therefore, in the present study, we performed a systematic literature review to (1) compare the value of NIRS related to existing cerebral monitoring techniques in prediction of intra- and postoperative cerebral ischaemia and (2) compare the relation between intra-operative NIRS values and risk of occurrence of postoperative CHS in patients undergoing CEA.

Methods

Search strategy

A literature search on all studies related to NIRS and CEA was conducted in December 2008. Studies were initially identified from PubMed and EMBASE databases using synonyms for the following search terms:

#1 (Carotid endarterectomy) OR (CEA) OR (carotid revascularization) OR (carotid desobstruction)
#2 (NIRS) OR (near-infrared spectroscopy) OR (infrared spectroscopy)
#3 (Hyperperfusion syndrome) OR (cerebral hyperperfusion)

Two researchers (CP and GB) independently screened the articles consecutively on title, abstract and full text. Additional studies were identified by searching the reference list of relevant studies identified. Titles and abstracts were retrieved by two independent reviewers separately (CWAP, GJdB). Doubts and differences of opinion were resolved by an open discussion.

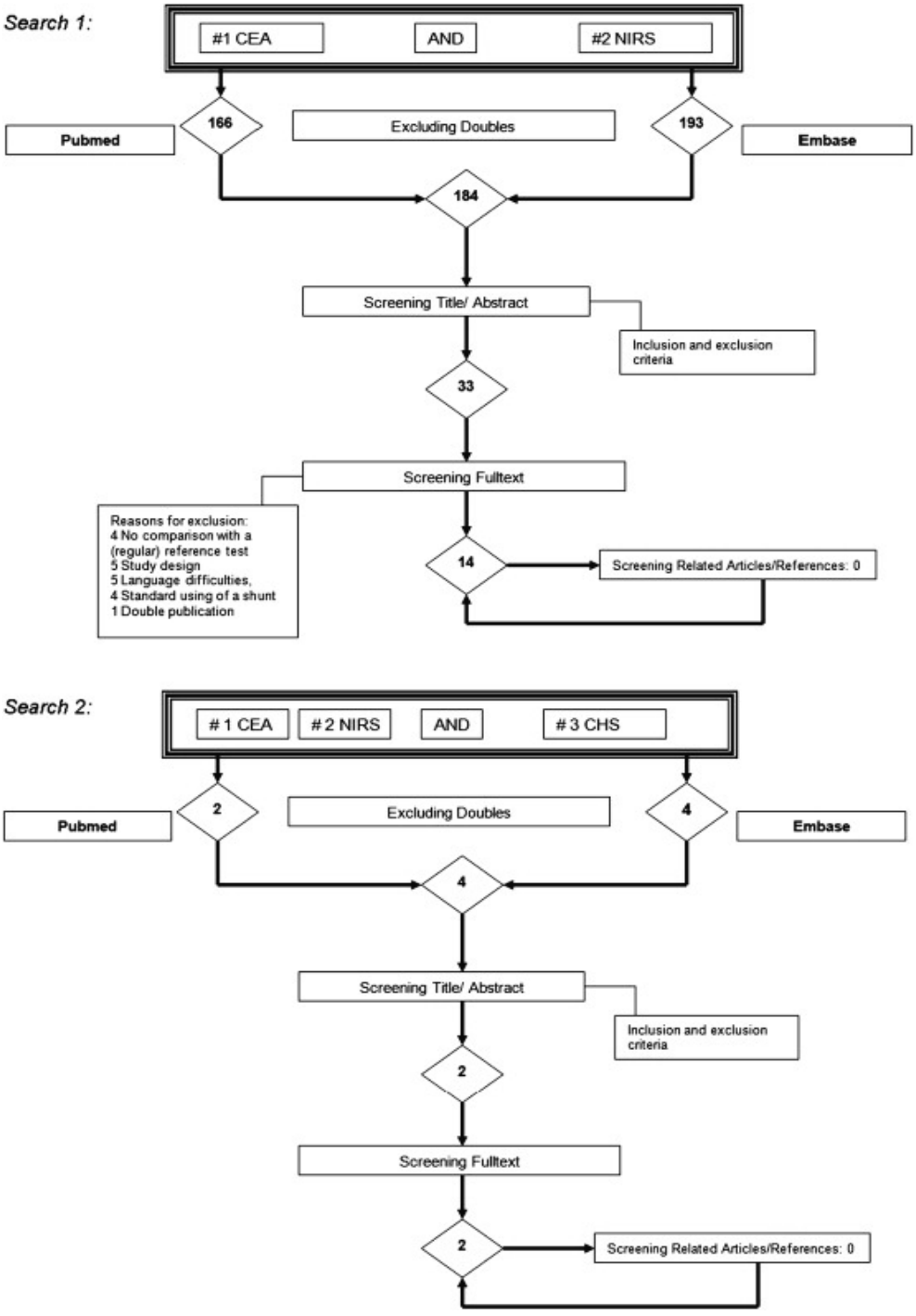

Figure 1. Flow charts for the search strategy and reasons for exclusion (March 2008)

The inclusion criteria were (1) prospective studies; (2) on NIRS for brain monitoring during CEA; (3) including comparison of NIRS to any other intra-operative cerebral monitoring systems; and (4) on either symptomatic or asymptomatic patients. Reasons for exclusion were (1) type of study design (retrospective, case report), (2) language difficulties (non-English papers), (3) full-text papers that were unavailable; (4) standardized intra-operative shunt insertion, or (5) a comparison with a non-regulatory monitoring method.

Results

Result of search strategy

To address our first objective, our search generated 166 and 193 hits in PubMed and EMBASE, respectively. Of these, following exclusion of double hits, 184 studies were screened on title and abstract and 33 studies were further assessed. Finally, 14 studies met the inclusion criteria and were included for further analysis (Figure 1; search 1). To address our second objective, we reviewed the relationship between intra-operative NIRS monitoring and the occurrence of CHS, and our search yielded two and four hits in PubMed and EMBASE, respectively. Only two studies fulfilled our search criteria and were included (Figure 1; search 2).

Data analytic approach

No effort was made to pool findings from the different studies into one estimate, because the studies varied too much in presentation, cut-off points used, study population and other characteristics. Therefore, results of the analysis of selected studies are presented in a descriptive manner.

Technical aspects of NIRS application

In nine of the 12 (search 1) studies, the Invos 3100 or the Invos 4100 (Somanetics Corp., Troy, MI, USA) or the OM220 (Shimadzu Co., Japan) were used. The remaining three studies used the NIRO 300 (Hamamatsu Photonics),[10] NIR 500 and NIR 1000 (Hamamatsu, London, UK), respectively, by penetrating the scalp and brain tissue whereby the skin, scull and other tissues are relatively transparent to near-infrared wavelengths of light. By using two detectors, the light reflected and transmitted by the superficial extracranial tissues is subtracted, resulting in a signal derived from brain tissue, the so-called regional hemoglobin oxygen saturation (rSO_2) index.[11] The changes in concentrations of oxygenated and deoxygenated hemoglobin are measured by a modified Beer–Lambert method. Because of the different wavelengths of the oxygenated and deoxygenated hemoglobin, these can be distinguished and the ratio of oxygenated hemoglobin to total tissue hemoglobin (TOI) can be defined.[12] The cerebral oximetry sensors were placed on the forehead, ipsilateral to the surgical site in seven studies, bilateral in five studies and an unspecified location in two studies.

NIRS compared with TCD sonography

In five of the 14 studies, NIRS was compared with TCD.[6,10,12-14] The results are described in Table 1. These studies comprised 352 patients with either symptomatic or asymptomatic but hemodynamically significant stenosis. In three studies, cerebral function monitoring (CFM)

was additionally used for detection of signs of cerebral ischaemia.[10, 13-15] An adequate TCD signal could not be obtained in 10%.[6,12,14] In 16.8% of the population, a shunt was placed on which thresholds for severe critical ischaemia measured by NIRS were determined in four studies. The indication for shunt insertion, however, varied considerably across studies: from a decrease in mean velocity less than 50% to less than 20% of the preclamp value. Some authors used a shunt only if CFM indicated cerebral ischaemia, defined as a persistent sustained fall in CBF of longer than 1 min.[10,14] In another study, a shunt was used only if it was based on signs of severe cerebral ischaemia measured both by TCD in combination with a sustained fall in CFM (>1 min).[13] Four out of five studies reported a significant positive relationship between changes in V_{mca} and rSO_2 on clamping.[6,10,12,13] The magnitude of the relationship between NIRS-measured rSO_2 and TCD-measured V_{mca} using linear regression ranged from 0.43 to 0.74. No conclusive data on the value of NIRS in the decision for shunt insertion could be obtained.

Study	Method	Indication	Rel. FV/ΔrSO_2	rSO_2 SCI	Sens.	Spec.	PPV	NPV
Al Rawi et al[10] n = 167	TCD CFM	<40% or CFM	r = 0.74, P < .01	Δ13%	100	93	76	100
Vets et al.[6] n = 14	TCD EEG	<20%	r = 0.72, P = .02	Δ13%	100	78	33	100
Grubhofer et al.[12] n = 55	TCD	<20%	r = 0.63, P < .01	Δ13% Δ12% Δ11%	100 100 100	87 83 83	22 18 25	100 100 100
Kirkpatrick et al[13] n = 76	TCD CFM	<40% and CFM	r = 0.73, P < .01	>6.8[a]	81	100	100	95
Kirkpatrick et al[14] n = 13	CFM	<50% and CFM	r = 0.61	NA	NA	NA	NA	NA

Table 1. NIRS compared with transcranial Doppler (TCD) to detect intraoperative ischemia
NIRS, Near-infrared spectroscopy; Methods, Used measuring methods: transcranial Doppler (TCD), cerebral function monitoring (CFM), electroencephalography (EEG); Indication, Indication for shunting. Threshold for performing a shunt measured in decrease of blood flow measured by TCD (of preclamp value) and/or a persistent respectively a sustained fall in CBF of longer than one minute measured by CFM; Rel. FV/ΔrSO_2, Relationship between flow volume in the middle cerebral artery and changes in regional cerebral oxygenation (rSO_2); rSO_2 SCI, rSO_2 Value measured by NIRS when severe critical ischemia (SCI) occurs identified by transcranial Doppler; Sens., Sensitivity (%); Spec., Specificity (%); PPV, Positive predictive value (%); NPV, Negative predictive value (%); NA, Not available. [a] ICA Hbdiff (μmol): total difference in concentrations of oxyhemoglobin and deoxyhemoglobine by clamping the internal carotid artery (ICA).

NIRS compared with electroencephalography (EEG)

In four of 15 studies, both EEG and NIRS were used for brain monitoring during CEA.[7,15-17] In three of these, EEG was compared with NIRS in detection of intra-operative severe cerebral ischaemia (Table 2).[7,16,17] Yamamoto et al. only shunted their last 15 patients selectively and this report was left out of analysis.[15] The other three studies comprised 228 patients with symptomatic or asymptomatic carotid stenosis. The threshold for critical ischaemia used was the asymmetry of the ipsilateral and contralateral EEG, further defined with a cut-off value of

>0.7 Hz[17] and asymmetry >20%.[16] A significant correlation between EEG and rSO_2 was found in all three studies. Shunt percentages varied from 6% to 17%. Thresholds for reduction in rSO_2 associated with severe critical ischaemia varied from 5% to 25%.

EEG	Indication	rSO_2 SCI	Sens.	Spec.	PPV	NPV
Rigamonti et al.[7] N = 49	Asymmetry NS	Δ15% P < .01	44	82	NA	94
Hirofumi et al.[17] N = 20	Asymmetry >0.7 Hz	Δ25%	100	100	100	100
De Letter et al[16] N = 101	Asymmetry >20%	Δ5%	100	44	27	100

Table 2. NIRS compared with electroencephalography (EEG) to detect intraoperative ischemia.
NIRS, Near-infrared spectroscopy; Indication, Indication for shunting: Threshold for performing a shunt measured by EEG; Asymmetry, asymmetry of the ipsi- and contralateral EEG; NS, Not specified; rSO_2 SCI, rSO_2 Value measured by NIRS if severe critical ischemia (SCI) occurred, identified by EEG; Sens., Sensitivity (%); Spec., Specificity (%); PPV, Positive predictive value (%); NPV, Negative predictive value (%); NA, Not available and could not be calculated from the available data.

NIRS compared with stump pressure (SP)
NIRS has been compared with stump pressure (SP) during CEA in two studies comprising 105 patients.[15,17] In one study, EEG was used as a third monitoring entity.[15] In both studies, a shunt was used when SP decreased below 40 mmHg. A shunt was placed in 13% of the patients reported by Kragsterman, whereas shunt use in the study by Yamamoto was irrelevant for our analysis, since only their last 15 patients were shunted selectively. A significant correlation was shown between the change of the regional saturation of the frontal lobe (SdO_2) and the stump pressure after cross-clamping the common carotid artery (CCA)[15] or the internal carotid artery (ICA).[17] In the study by Yamamoto, a SP of 40 mmHg was equivalent to an SdO_2 decrease of 4.1%, whereas in the Kragsterman study no threshold could be defined.

NIRS compared with somatosensory evoked potentials (SSEPs)
NIRS has been compared with SSEP as a monitoring method for cerebral ischaemia in two studies.[18,19] However, since the reliability of SSEP is under discussion and its use in CEA nowadays is scarce, and since there is no consensus about the cut-off point in detecting cerebral ischaemia, we felt that a comparison with NIRS was not appropriate.

NIRS compared with clinical signs of ischaemia
Regional anesthesia allows the use of clinical signs of cerebral ischaemia as a monitoring method. In two studies, clinical signs and NIRS were used.[5,7] Moritz and co-workers studied 48 patients.[5] A shunt was used following the occurrence of any new neurological deficit such as speech abnormalities, motor weakness or impaired consciousness. In 17% of patients, an intravascular shunt was placed. An absolute rSO_2 cut-off value below 59% in NIRS was

defined as a threshold for severe cerebral ischaemia indicative for shunt placing, with a positive predictive value of 39%.

NIRS and prediction of cerebral hyperperfusion syndrome (CHS)
In two studies (139 patients) NIRS was related to the risk of CHS.[8,9] No intraluminal shunts were used in this patient group. Neurological expression of CHS was clinically diagnosed by either decreased consciousness level, occurrence of seizures and development of focal neurological signs, such as motor weakness, or a combination of these symptoms. Using monitoring techniques, CHS was suspected in case of evidence of hyperperfusion on single photon emission computed tomography (SPECT), or doubling of cerebral blood flow (CBF) on TCD performed during CEA. Post-CEA hyperperfusion was reported in 11%[8] and 12%[9] of patients, whereas 1.4% of the patients developed CHS (Table 3). In all patients with CHS the rSO_2 values exceeded 105% of the post-clamping value and exceeded the 110% of preclamping values by the end of the procedure (Table 4). A reduced cerebrovascular reactivity (CVR) and reduced SO_2 ratio (SO_2 5 min before clamping/SO_2 lowest value during clamping) were significant independent predictors of the development of hyperperfusion after CEA.

	Mean age (yrs)	Ischemia post-CEA	Post-CEA hyperperfusion	CHS 6th day postop. (%)
Komoribayashi et al.[8] n = 89	68	2	10 (11%)	2 (2.2%)
Ogasawara et al.[9] n = 50	69	0	6 (12%)	1 (2%)

Table 3. Post-CEA hyperperfusion based on SPECT-imaging post-CEA.
CEA, Carotid endarterectomy; Ischemia post-CEA., New postoperative neurological deficit; Post-CEA hyperperfusion, Hyperperfusion, defined as an increase of cerebral blood flow of >100%, compared with preoperative values after carotid endarterectomy; CHS 6th day postop., Cerebral hyperperfusion syndrome on the 6th day after operation.

Ogasawara et al.[9] n = 50	$\%rSO_2$ increase of preclamping value	Sens.	Spec.	PPV	NPV
rSO_2 post-CEA	>5%, $r^2 = 0.247$, $P < .01$	100	86.4	50	100
rSO_2 at the end of the procedure	> 10%, $r^2 = 0.822$, $P < .01$	100	100	100	100

Table 4. Relationship between the cerebral blood flow (CBF) and the rSO_2 ratio after cross-clamping for patients with hyperperfusion.
$\%rSO_2$ Increase of preclamping value: relative increase of regional cerebral oxygen saturation compared with the preclamping value; Sens., Sensitivity (%); Spec., Specificity (%); PPV, Positive predictive value (%); NPV, Negative predictive value (%).

Discussion

TCD and EEG are currently the gold standard in brain monitoring during CEA.[3,20] However, both modalities have certain disadvantages. TCD monitoring cannot be performed in around 10% of the patients, because of missing a temporal bone window. Moreover, TCD is expensive and dependent on the skills of the technicians. EEG monitoring is time consuming, sometimes difficult to interpret and influenced by certain anesthetics.

As an alternative cerebral monitoring entity, NIRS offers a non-invasive technique, which is easy and quick to apply.[21] Especially for the subgroup in which TCD cannot be applied, NIRS might be helpful in identifying a threshold for postoperative risk for CHS. NIRS however has its own disadvantages: only the local conditions of the frontal lobe, supplied by the anterior cerebral artery, are measured and perfusion changes in other brain areas might escape detection.

In the present review, only 14 studies discussing the potential of NIRS in predicting intra-operative cerebral ischaemia could be identified. In several studies performed for intra-operative monitoring during CEA, NIRS values were significantly related to the results of TCD and EEG. Nevertheless, the reviewed studies had certain drawbacks, thereby limiting the quality of analysis of the reviewed data. In most reports, the investigated study cohort was small and the reference test chosen did not reflect the gold standard. Furthermore, different cut-off values were used. The most reliable cut-off value to determine severe critical ischaemia was obtained in an awake patient, using regional anesthesia. A TCD-measured reduction of 70%[3] of CBF provided a PPV of 71%, whereas EEG provided a PPV of 86.4%.[22,23] A threshold for obtained NIRS values below which shunting should be indicated could not be determined in a valid manner, since criteria used for shunting varied considerably across studies. Similarly, a NIRS value, based upon which cerebral ischaemia was likely to occur postoperatively, could not be determined from the literature due to large variability in patients and approaches taken. The evidence suggesting that NIRS is useful in predicting CHS is modest. However, the two reports focusing on NIRS application and the occurrence of CHS are consistent in their findings: in all patients with diagnosed CHS the rSO_2 values exceeded 105% of the post-clamping value and exceeded 110% of preclamping values by the end of the procedure. In other words, the positive predictive value of NIRS in predicting CHS based on only two prospective studies seems high. NIRS therefore might offer a promising technique in the detection of post-CEA patients at risk for CHS development, which should be reaffirmed in further future clinical trials.

Conclusion

NIRS seems a promising perioperative cerebral monitoring technique in CEA. Yet the evidence to define clear cut-off points for either presence of intra- or postoperative cerebral ischaemia or for identification of patients at high risk of a CHS is limited. A large cohort study addressing these issues in a prospective and systematic manner is urgently needed, before NIRS can be possibly used as a standard monitoring technique for the prevention of peri- and postoperative stroke from CEA.

References

(1) Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991; 325(7):445-453.

(2) Riles TS, Imparato AM, Jacobowitz GR, Lamparello PJ, Giangola G, Adelman MA et al. The cause of perioperative stroke after carotid endarterectomy. J Vasc Surg 1994; 19(2):206-214.

(3) Jansen C, Moll FL, Vermilion FE, van Haelst JM, Ackerstaff RG. Continuous transcranial Doppler ultrasonography and electroencephalography during carotid endarterectomy: a multimodal monitoring system to detect intraoperative ischemia. Ann Vasc Surg 1993; 7(1):95-101.

(4) Naylor AR, Evans J, Thompson MM, London NJ, Abbott RJ, Cherryman G et al. Seizures after carotid endarterectomy: hyperperfusion, dysautoregulation or hypertensive encephalopathy? Eur J Vasc Endovasc Surg 2003; 26(1):39-44.

(5) Moritz S, Kasprzak P, Arlt M, Taeger K, Metz C. Accuracy of cerebral monitoring in detecting cerebral ischemia during carotid endarterectomy: a comparison of transcranial Doppler sonography, near-infrared spectroscopy, stump pressure, and somatosensory evoked potentials. Anesthesiology 2007; 107(4):563-569.

(6) Vets P, ten BP, Adriaensen H, Van SP, De HS. Cerebral oximetry in patients undergoing carotid endarterectomy: preliminary results. Acta Anaesthesiol Belg 2004; 55(3):215-220.

(7) Rigamonti A, Scandroglio M, Minicucci F, Magrin S, Carozzo A, Casati A. A clinical evaluation of near-infrared cerebral oximetry in the awake patient to monitor cerebral perfusion during carotid endarterectomy. J Clin Anesth 2005; 17(6):426-430.

(8) Komoribayashi N, Ogasawara K, Kobayashi M, Saitoh H, Teriyaki K, Inoue T et al. Cerebral hyperperfusion after carotid endarterectomy is associated with preoperative hemodynamic impairment and intraoperative cerebral ischemia. J Cereb Blood Flow Metab 2006; 26(7):878-884.

(9) Ogasawara K, Konno H, Yukawa H, Endo H, Inoue T, Ogawa A. Transcranial regional cerebral oxygen saturation monitoring during carotid endarterectomy as a predictor of postoperative hyperperfusion. Neurosurgery 2003; 53(2):309-314.

(10) Al-Rawi PG, Kirkpatrick PJ. Tissue oxygen index: thresholds for cerebral ischemia using near-infrared spectroscopy. Stroke 2006; 37(11):2720-2725.

(11) Davies LK, Janelle GM. Con: all cardiac surgical patients should not have intraoperative cerebral oxygenation monitoring. J Cardiothorac Vasc Anesth 2006; 20(3):450-455.

(12) Grubhofer G, Plochl W, Skolka M, Czerny M, Ehrlich M, Lassnigg A. Comparing Doppler ultrasonography and cerebral oximetry as indicators for shunting in carotid endarterectomy. Anesth Analg 2000; 91(6):1339-1344.

(13) Kirkpatrick PJ, Lam J, Al-Rawi P, Smielewski P, Czosnyka M. Defining thresholds for critical ischemia by using near-infrared spectroscopy in the adult brain. J Neurosurg 1998; 89(3):389-394.

(14) Kirkpatrick PJ, Smielewski P, Whitfield PC, Czosnyka M, Menon D, Pickard JD. An observational study of near-infrared spectroscopy during carotid endarterectomy. J Neurosurg 1995; 82(5):756-763.

(15) Yamamoto K, Miyata T, Nagawa H. Good correlation between cerebral oxygenation measured using near infrared spectroscopy and stump pressure during carotid clamping. Int Angiol 2007; 26(3):262-265.

(16) de Letter JA, Sie HT, Thomas BM, Moll FL, Algra A, Eikelboom BC et al. Near-infrared reflected spectroscopy and electroencephalography during carotid endarterectomy--in search of a new shunt criterion. Neurol Res 1998; 20 Suppl 1:S23-7.:S23-S27.

(17) Hirofumi O, Otone E, Hiroshi I, Satosi I, Shigeo I, Yasuhiro N et al. The effectiveness of regional cerebral oxygen saturation monitoring using near-infrared spectroscopy in carotid endarterectomy. J Clin Neurosci 2003; 10(1):79-83.

(18) Beese U, Langer H, Lang W, Dinkel M. Comparison of near-infrared spectroscopy and somatosensory evoked potentials for the detection of cerebral ischemia during carotid endarterectomy. Stroke 1998; 29(10):2032-2037.

(19) Duffy CM, Manninen PH, Chan A, Kearns CF. Comparison of cerebral oximeter and evoked potential monitoring in carotid endarterectomy. Can J Anaesth 1997; 44(10):1077-1081.

(20) Dalman JE, Beenakkers IC, Moll FL, Leusink JA, Ackerstaff RG. Transcranial Doppler monitoring during carotid endarterectomy helps to identify patients at risk of postoperative hyperperfusion. Eur J Vasc Endovasc Surg 1999; 18(3):222-227.

(21) Strangman G, Franceschini MA, Boas DA. Factors affecting the accuracy of near-infrared spectroscopy concentration calculations for focal changes in oxygenation parameters. Neuroimage 2003; 18(4):865-879.

(22) Cao P, Giordano G, Zannetti S, De RP, Maghini M, Parente B et al. Transcranial Doppler monitoring during carotid endarterectomy: is it appropriate for selecting patients in need of a shunt? J Vasc Surg 1997; 26(6):973-979.
(23) Hans SS, Jareunpoon O. Prospective evaluation of electroencephalography, carotid artery stump pressure, and neurologic changes during 314 consecutive carotid endarterectomies performed in awake patients. J Vasc Surg 2007; 45(3):511-515.

Chapter 8

Near-infrared spectroscopy to indicate selective shunt use during carotid endarterectomy

Accepted for publication in:

The European Journal of Vascular and Endovascular Surgery

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Abstract

Background
This prospective cohort study assessed the value of cerebral near-infrared spectroscopy (NIRS) and transcranial Doppler (TCD) in relation to electroencephalography (EEG) changes for the detection of cerebral hypoperfusion necessitating shunt placement during carotid endarterectomy (CEA).

Methods
Patients with a sufficient TCD window undergoing CEA from February 2009 to June 2011 were included. All patients were continuously monitored with NIRS and EEG. An intraluminal shunt was placed selectively determined by predefined EEG changes in alpha, beta, theta, or delta activity. Relative changes in regional cerebral oxygen saturation (rSO_2) in the frontal lobe and mean blood flow velocity (V_{mean}) 30 seconds before carotid cross-clamping versus 2 minutes after carotid cross-clamping were related to shunt placement. Receiver operating characteristic curve analysis was performed to determine the optimal thresholds. Diagnostic values were reported as positive and negative predictive value (PPV and NPV).

Results
Of a cohort of 151 patients 17(11%) showed EEG changes requiring shunt placement. The rSO_2 and V_{mean} decreased more in the shunt-group than in the non-shunt group (mean± standard error of the mean) 21%±4% versus 7%±5% and 76%±6% versus 12%±3%, respectively ($p<0.005$). Receiver operating characteristic curve analysis revealed a threshold of 16% decrease in rSO_2 (PPV 76% and NPV 99%) and 48% decrease in V_{mean} (PPV 53% and NPV 99%) as the optimal cut-off value to detect cerebral ischemia during CEA under general anesthesia.

Conclusion
Compared with EEG, we found moderate PPV but high NPV for NIRS and TCD to detect cerebral ischemia during CEA under general anesthesia. Therefore, NIRS and TCD could independently be helpful to reduce unnecessary shunt use. Both techniques may be suitable to direct the use of selective shunting during CEA; however, the optimal thresholds remain to be determined.

Background

Carotid endarterectomy (CEA) is the treatment of choice to prevent future cerebrovascular events in symptomatic patients with a high-grade stenosis of the internal carotid artery.[1] However, the procedure itself carries a risk of stroke. Strokes with an onset during CEA are mainly caused by thrombosis, embolism, or intraoperative ischemia related to hypoperfusion during cross-clamping of the carotid artery.[2] Cerebral ischemia during cross-clamping may be prevented by placement of an intraluminal shunt, which may reduce the duration that blood flow to the brain is interrupted. However, routine shunting may result in unnecessary shunt use in approximately 85% of patients because most patients have sufficient collateral cerebral perfusion during cross-clamping. Further potential disadvantages of shunting include carotid artery dissection, shunt plaque embolisation, and inadequate shunt flow or shunt thrombosis. A shunt may also limit the exposure of the distal portion of the plaque. Many surgeons therefore prefer selective shunting, but this necessitates the use of a monitoring method to detect cerebral ischemia during a test cross-clamping. Use of locoregional anesthesia allows monitoring of neurologic function in an awake patient and can be regarded as the accepted standard for detection of cerebral ischemia during cross-clamping.[3-5] In contrast, objective detection of cerebral ischemia in patients under general anesthesia is more challenging. In experienced hands, interpretation of changes in electroencephalography (EEG) is the most commonly applied technique to detect cerebral ischemia and to decide whether a shunt is needed, with a high positive predictive value (PPV) and high negative predictive value (NPV).[6-9] However, implementation of EEG is associated with high procedural costs, and proper interpretation requires personnel experienced in clinical neurophysiology. Moreover, pre-existing EEG abnormalities in patients presenting with severe stroke or anesthetic-induced changes make interpretation of the EEG more difficult, or even impossible.[10]Transcranial Doppler (TCD) ultrasound monitoring of the mean blood flow velocity (V_{mean}) in large cerebral arteries, such as the middle cerebral artery (MCA), is widely used to obtain additional information regarding cerebral hemodynamics. Although TCD measurements are related to EEG changes, they are not a parameter of cerebral oxygenation.[11] Moreover TCD monitoring fails in up to 15% of patients because of an insufficient temporal bone window. A third non-invasive technique to detect cerebral ischemia is by monitoring changes in regional cerebral oxygen saturation (rSO_2) in the frontal lobe by near-infrared spectroscopy (NIRS). NIRS is easy to apply in all patients and is relatively low in cost because it offers information about cerebral oxygenation without the need for specialized personnel. NIRS has been widely applied in cardiac surgery, providing some evidence that NIRS-guided brain protection protocols might lead to reduced neurologic complications and improved patient outcomes.[12] In the present study, we assessed the value of NIRS and TCD in relation to EEG changes for the detection of cerebral hypoperfusion necessitating shunt placement during CEA.

Methods

Patients

This prospective cohort study included patients with a sufficient TCD window undergoing

CEA from February 2009 to June 2011 in the University Medical Centre Utrecht (UMCU). A maximum of two patients per day could be studied because of logistic reasons concerning personnel qualified in clinical neurophysiology. Indications for carotid revascularization were symptomatic or asymptomatic carotid stenosis >70%, as discussed in a multidisciplinary team. The severity of the carotid artery stenosis was assessed by carotid color Doppler-assisted duplex ultrasound imaging and confirmed by magnetic resonance angiography or computed tomography angiography. Stenosis was categorized on a 4-point scale as <50%, 50% to 70%, 70% to 99% stenosis, or occlusion.

CEA protocol

All patients underwent CEA under general anesthesia. Induction of anesthesia was achieved with sufentanil (0.3-0.7 μg/kg), propofol (0.5-2.0 mg/kg), and rocuronium (0.3-0.5 mg/kg), and was maintained with sevoflurane, aiming at a minimum alveolar concentration value of between 0.5 and 1%. Mean arterial pressure (MAP) was measured invasively using a 20-gauge catheter (1.1 mm internal diameter) placed in the radial artery. Until the carotid artery was declamped, MAP was kept between preoperative baseline values and 20% above. If required, vasoactive medication was administered to increase MAP. CEA was performed in a standardized way by an experienced vascular surgeon or by a vascular trainee under supervision. Heparin (5000 U) was administered intravenously three minutes before cross-clamping the carotid artery. An intraluminal Javid shunt was placed selectively and based solely on predefined EEG changes during at least two minutes of test cross-clamping. Sevoflurane administration was discontinued at the end of the procedure. The patient was extubated after the return of spontaneous respiration and was transferred to the recovery ward.

Monitoring techniques

Patients were continuously monitored using EEG, TCD, and NIRS during the entire procedure. Blood pressure, TCD, and NIRS data were stored on a hard disk for off-line analysis by an investigator blinded for shunt use and clinical outcome.

EEG protocol

Scalp electrodes were positioned before CEA according to the 10-20 International System. A 16-channel montage ($Fp_{1/2}$,$F_{7/8}$, $T_{3/4}$, $T_{5/6}$, $O_{1/2}$, $F_{3/4}$, $C_{3/4}$, and $P_{3/4}$) with C_z as common reference was used.[13] A preoperative EEG was obtained for all patients on the nursing ward or in the operating room. EEG signals were continuously monitored during surgery using a Micromed System device (Micromed Inc., Treviso, Italy) with a sample rate of 512 Hz. During the two minutes of test cross-clamping, changes in the EEG were assessed under supervision of a clinical neurophysiologist. The occurrence of new delta or theta activity was considered indicative for the development of cerebral ischemia in a predefined way.[13]

TCD assessment

For measurement of the V_{mean} in the MCA, a DWL Multidop X4 pulsed Doppler transducer (DWL Elektronische Systeme GmbH, Singen, Germany), gated at a focal depth of 45 to 60 mm, was placed over the temporal bone to insonate the main stem of the ipsilateral MCA. In the contralateral hemisphere, the V_{mean} in the anterior cerebral artery was monitored. Once

the optimal signal-to-noise ratio was obtained, the TCD transducer was fixed in place with a head frame, and V_{mean} was recorded continuously.

NIRS assessment
Two sensors were placed on the forehead, and continuous, bilateral rSO_2 measurements were performed using an Invos Cerebral Oximeter (Somanetics Corp, Troy, MI). NIRS allows continuous monitoring of regional cerebral oxygen saturation by penetrating the scalp and brain tissue, whereby the skin, skull, and other tissues are relatively transparent to near-infrared wavelengths of light. Changes in concentrations of oxygenated and deoxygenated hemoglobin are measured by a modified Beer-Lambert method. Oxygenated and deoxygenated hemoglobin have different wavelengths, which can be used to define the ratio of oxygenated hemoglobin to total tissue hemoglobin. By using two detectors, the light reflected and transmitted by the superficial extracranial tissues is subtracted.

Study parameters and data analysis
The percentage change in rSO_2 (ΔrSO_2), V_{mean} (ΔV_{mean}), and MAP (ΔMAP) elicited by CC was calculated by subtracting the averaged values of rSO_2, V_{mean}, and MAP for 30 seconds before the cross-clamping test (preclamping) from the averaged values for rSO_2 30 seconds assessed two minutes after cross-clamping (postclamping). This was divided by the preclamping value. Subsequently, ΔrSO_2, ΔV_{mean}, and ΔMAP were related to shunt placement, our primary end point, and to clinical outcome of stroke or death, our secondary end point.

Statistical analysis
For dichotomized factors, we used cross tabs and χ^2 tests ($n > 5$) or Fisher exact tests ($n < 5$) to calculate p-values. Continuous characteristics, presented as mean ± standard deviation, were analyzed using a paired or unpaired Student t tests when appropriate, Subsequently ΔrSO_2, ΔV_{mean}, and ΔMAP were calculated and are presented as mean ± standard error of the mean. To determine the optimal ΔrSO_2 and ΔV_{mean} cut-off value for cerebral hypotension requiring shunt placement, receiver-operating characteristic (ROC) curves were analyzed. The diagnostic performance is expressed as the PPV and NPV with the 95% confidence interval (CI). All analyses were performed using SPSS 20.0 software (SPSS Inc, Chicago, Il). Values of $p < 0.05$ were considered significant.

Results

Patient characteristics
Within the study timeframe, 294 patients underwent CEA, of which 274 (93%) had a sufficient TCD window. Because of logistic reasons, the study included 151 patients, who were a mean age of 70 ± 9 years. Most patients underwent CEA because of a high degree of symptomatic stenosis (Table 1). The median time between the last neurologic symptoms and subsequent CEA in our tertiary referral centre was 27 days (interquartile range, 18-51 days). The excluded patients did not significantly differ from the study population regarding shunt usage. Relevant EEG changes occurred in 17 patients (11%), and an intraluminal shunt was inserted. As reported in Table 1, baseline characteristics of patients who did and who did not receive an

intraluminal shunt did not differ significantly, with the exception of occlusion of the contralateral internal carotid artery, which was more frequently present in the shunt group (10% versus 29%; p = 0.03). The 30-day death/stroke rate was 3.3% (n = 5). One patient (0.7%) died 13 days after surgery because of vegetative endocarditis, without cerebrovascular complications. Four patients (2.6%) sustained a stroke with an intraoperative onset, of which three were defined as minor strokes and one as a major stroke (without useful recovery of function). No postoperative stroke occurred. More strokes occurred in the shunted group (n= 2, 11.7%) than in the nonshunted group (n= 2, 1.5%; Table 2). Three of four intraoperative strokes were identified with EEG.

Measurements

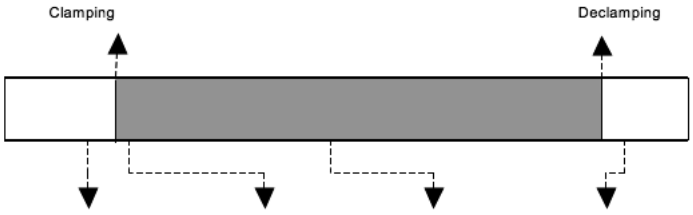
The changes in rSO_2, V_{mean}, and MAP elicited by cross-clamping are presented in Figure 1. In the 134 patients who did not receive a shunt, the ΔrSO_2 and ΔV_{mean} of –7% ± 0% and –12% ± 3% were smaller than the respective values of –20% ± 1% and 76% ± 6% in the 17 patients who did receive a shunt (both $p < 0.05$).

Variable	All patients (n= 151)	Shunt group (n= 17)	Non-shunt group (n= 134)	p- value
Gender (M)	117 (78%)	15 (88%)	102 (76%)	0.26
Side (right)	63 (42%)	6 (35%)	57 (43%)	0.57
Age (years; mean±SD)	70±9	69±8	70±10	0.72
Atrial fibrillation	14 (9%)	1 (6%)	13 (10%)	0.61
Angina pectoris/ myocardial infarction	49 (33%)	5 (29%)	44 (33%)	0.78
Diabetes Mellitus	36 (24%)	4 (24%)	32 (24%)	0.97
Hypercholesterolemia	134 (89%)	16 (94%)	118 (88%)	0.46
Peripheral artery disease	34 (23%)	6 (35%)	28 (21%)	0.18
Hypertension	127 (84%)	16 (94%)	111 (83%)	0.23
History of CEA				
ipsilateral	1 (1%)	0	1 (1%)	0.72
contralateral	17 (11%)	2 (12%)	15 (11%)	0.94
Indication (symptomatic)	133 (88%)	14 (82%)	119 (89%)	0.44
Degree of ipsilateral stenosis				
50- 70%	9 (6%)	2 (12%)	7 (5%)	0.28
>70%	142 (94%)	15 (88%)	127 (95%)	
Degree of contralateral stenosis				
<50%	72 (48%)	7 (41%)	65 (49%)	0.57
50-70%	25 (17%)	3 (18%)	22 (16%)	0.90
70- 99%	24 (16%)	2 (12%)	22 (16%)	0.62
Occlusion	19 (13%)	5 (29%)	14 (10%)	0.03
Unknown	11 (7%)	0	11 (8%)	0.2

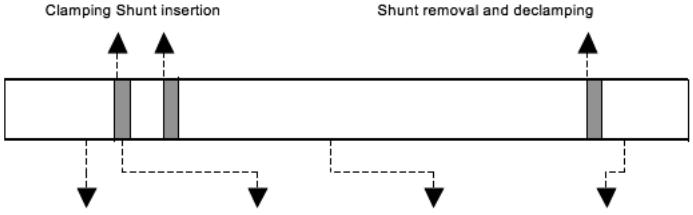
Table 1. Characteristics of all patients at baseline and according to shunt use

Variable		All patients (n= 151)	Shunt group (n= 17)	Non-shunt group (n= 134)	p- value
Stroke < 30 days		4 (2.6%)	2 (11.8%)	2 (1.5%)	0.06
Type	Major stroke	1 (0.6%)	1 (5.9%)	0	0.11
	Minor stroke	3 (2.0%)	1 (5.9%)	2 (1.5%)	0.30

Table 2. Clinical 30-day outcome



Non- shunted (n= 134)	Preclamping	Clamping (2 min)	Clamping (10min)	Postclamping
MAP (mmHg)	95 ± 15	101 ± 15	100 ±15	88 ± 8
V_{mean} (cm·s^{-1})	51 ± 16	45 ± 21	44 ± 19	57 ± 22
rSO_2 (%)	70 ± 8	66 ± 8	66 ± 8	70 ± 9



Shunted (n= 17)	Preclamping	Clamping (2 min)	Clamping (10min)	Postclamping
MAP (mmHg)	96 ± 15	99 ± 11	101 ±16	86 ± 14
V_{mean} (cm·s^{-1})	58 ± 24	13 ± 10	61 ± 25	70 ± 28
rSO_2 (%)	70 ± 10	56 ± 8	67 ± 13	69 ± 12

Figure 1. Timeframe
At the following time points, mean arterial pressure (MAP), mean middle cerebral artery blood velocity (V_{mean}), and regional cerebral oxygen saturation (rSO_2) in the frontal lobe were recorded and calculated. The grey area indicates clamping period; data are shown as mean ± standard deviation.

ROC curve analysis

Analysis of the ROC curve showed an area under the curve of 0.98 (95% CI: 0.96-1.00) for ΔrSO_2 to indicate shunt requirement as determined from EEG changes by the current protocol.(Figure 2) An optimal ΔrSO_2 cut-off value of a 16% decrease of preclamping rSO_2 was also calculated. With this cut-off value, a PPV of 76% (95% CI: 54%-89%) and an NPV of 99% (95% CI: 96%-100%) were obtained. To indicate shunt placement by TCD, a cut-off value of a 48% decrease in V_{mean} was found, with an area under the curve of 0.94 (95% CI: 0.860-1.00), a PPV of 53% (95% CI: 36%-70%), and an NPV of 99% (95% CI: 96%-100%; Table 3). In 21 patients, the threshold of ΔrSO_2 of –16% or less resulted in 5 patients with false-positive results, and with a threshold of ΔV_{mean} –48% or lower, nine more patients would have been wrongly identified. No new neurologic deficits were found when these false-positive patients recovered from anesthesia. In addition to EEG changes, the two patients in the shunt group who sustained a stroke also showed decreases below ΔrSO_2 and ΔV_{mean} thresholds.

	Shunt + (n= 17)	**Shunt – (n= 134)**	**Sens.(%) (95% CI)**	**Spec.(%) (95% CI)**	**PPV (%) (95% CI)**	**NPV (%) (95% CI)**
$\Delta rSO_2 \leq$ - 16%	16	5	94	96	76	99
$\Delta rSO_2 >$ - 16%	1	129	(73-99)	(92-98)	(55-89)	(96-100)
$\Delta V_{mean} \leq$ - 48%	16	14	94	90	53	99
$\Delta V_{mean} >$ - 48%	1	120	(73-99)	(83-94)	(36- 70)	(96-100)

Table 3. Cross-table of diagnosing electroencephalogram changes requiring shunt placement by near-infrared spectroscopy and transcranial Doppler. Sens.: sensitivity, spec.: specificity, PPV: positive predictive value, NPV: negative predictive value, CI: confidence interval. EEG: electroencephalography, NIRS: near infrared spectroscopy, rSO_2: regional cerebral oxygen saturation, TCD: transcranial Doppler sonography, V_{mean}: mean middle cerebral artery blood velocity.

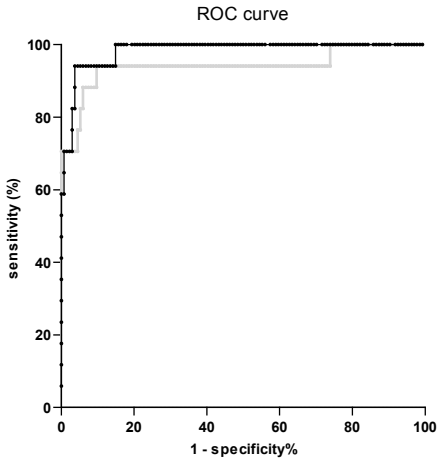


Figure 2. Receiver operating characteristic (ROC) curves. It shows the accuracy of intraoperative regional cerebral oxygen saturation (rSO_2; dark line) compared with mean middle cerebral artery blood velocity (V_{mean}; light line) in detecting cerebral ischemia requiring shunt use detected by electroencephalogram (EEG).

Discussion

In this study, we determined the diagnostic value of intraoperative NIRS and TCD monitoring to diagnose cerebral hypoperfusion detected by EEG during test clamping of the carotid artery in patients undergoing CEA under general anesthesia. We found moderate PPV but high NPV values for NIRS and TCD.

The existing literature does not elucidate whether selective or routine shunting has a more beneficial clinical outcome, and the consensus is that the individual surgeon should select the method with which he or she is most comfortable.[7;14;15] If shunting will be performed selectively, we propose that NIRS and TCD could independently exclude cerebral ischemia in patients undergoing CEA under general anesthesia and that both monitoring techniques could therefore be helpful in reducing unnecessary shunt use. In fact, if the thresholds we found in our study of a 16% decrease in rSO_2 and a 48% decrease in V_{mean} had been used instead of routine shunting, the number of patients who were shunted unnecessarily could have been reduced by 85% (from 134 to 21) and 78% (from 134 to 30), respectively.

NIRS may become the preferred monitoring technique in the near future because TCD requires specialized personnel and fails in up to 15% of patients as a result of an insufficient temporal bone window. Both techniques may be suitable to direct the use of selective shunting during CEA. The number of false-positive results for both techniques is high, however, and further data collection and analysis are required to define the optimal and most accurate NIRS threshold. Until this threshold is defined, we suggest the use of EEG monitoring for selective shunt use.

Several studies have discussed the value of TCD in the detection of hypoperfusion based on EEG changes in patients undergoing CEA under general anesthesia. Two studies, however, based the decision for shunt use purely on previously defined TCD thresholds.[16;17] In another study, a cut-off value of a 65% decrease in V_{mean} was determined, and a sensitivity of 80% and a specificity of 95% was found.[18] Furthermore, a reduction in blood flow velocity of 70% was associated with a PPV of 56% and an NPV of 99%.[5]

We previously conducted a systematic review that compared the value of NIRS during CEA in relation to existing cerebral monitoring techniques.[19] Several studies aimed to determine whether NIRS could be used to determine the need for shunt placement.[20-25] However, only two studies described the relationship between NIRS and EEG changes requiring shunt placement in patients undergoing CEA under general anesthesia with selective shunt use and determined cut-off values. Hirofumi et al found a decrease of 30% in cerebral oxygenation, with a PPV and NPV of 100%.[26] Shunt placement was performed selectively in only one patient (10%). De Letter et al included 101 patients, of whom 17 (17%) required shunt insertion.[27] They found a PPV of 27% for a cut-off value of a 5% decrease in rSO_2 in their search for a cut-off value, with an NPV of 100%, which we also consider most important because cerebral hypoperfusion without intraluminal shunt placement may result in irreversible cerebral infarction. A meta-analysis of these data by pooling these studies results in a PPV of 40% and an NPV of 100%. Because the case numbers in most studies are small, individual patient data to perform meta-analysis may be a step forward to a higher level of evidence. The use of individual patient data meta-analysis will allow evaluating accuracy of NIRS in relation to other patient characteristics. Ultimately, this could increase the accuracy of NIRS. For example, an occlusion of the contralateral carotid artery may be associated with

the need for shunt placement.[28,29]
The number of patients in our study may seem limited; yet, compared with other studies, we included a relatively high number of patients receiving an intraluminal shunt. Furthermore, the number of strokes in the shunted group was relatively high. This cannot be explained by shunt malfunctioning, because TCD monitoring was also used all patients, providing direct information to the surgeon on actual shunt function, and no shunt malfunctioning was noticed. In addition, the high stroke rate might be explained by the high-risk patients who undergo operations in our tertiary referral centre. The use of EEG as a reference standard may have influenced our results because the performance of NIRS was studied relative to EEG. Because the neurologic examination in the awake patient allows an absolute determination of cerebral ischemia, it will be interesting to define a rSO_2 threshold in patients who develop neurologic deficits during CC under local anesthesia. However, whether these data would be transferable to patients undergoing CEA under general anesthesia is disputable as McCleary et al suggest that local anesthesia preserves cerebral autoregulation whereas general anesthesia does not.[30]
Another consideration of our study concerns the technique used for the rSO_2 measurements. By using two sensors placed on the forehead, the frontal lobe oxygenation was measured in the cerebral tissue mainly perfused by the anterior cerebral artery, whereas the territory of the MCA is more laterally localized. Nevertheless, a comparison of frontally versus temporally placed sensors found that NIRS measurements using a frontal probe are at least as representative as a lateral probe for monitoring cerebral ischemia during CC.[31] Furthermore, the interindividual and intraindividual baseline variability in rSO_2 is high.[12] We accounted for this by correlating outcome to the relative and not the absolute change in rSO_2.

In conclusion, NIRS may offer an effective monitoring tool to exclude a relevant number of patients for shunt use under general anesthesia. Moreover, to selectively indicate the individual patient that needs a shunt may be safe, but the optimal threshold remains to be determined.

Acknowledgements
We would like to thank Dr. C.H. Ferrier and Mr. D.J. Van Vriesland of the Department of Clinical Neurophysiology for their contribution and specialized assistance.
The Invos Cerebral Oximeter (Somanetics Corporation, Troy, MI) was provided free of charge for the duration of the study by Covidien Nederland B.V., Zaltbommel, The Netherlands. However, Covidien had no influence on decisions concerning the study design, on the enrolment of patients, on the collection, analysis, and interpretation of data, on the writing of the report, or on the decision to submit the paper for publication.

References

(1) Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomized controlled trial. Lancet 2010; 375(9719):985-997.

(2) de Borst GJ, Moll FL, van de Pavoordt HD, Mauser HW, Kelder JC, Ackerstaf RG. Stroke from carotid endarterectomy: when and how to reduce perioperative stroke rate? Eur J Vasc Endovasc Surg 2001; 21(6):484-489.

(3) Benjamin ME, Silva MB, Jr., Watt C, McCaffrey MT, Burford-Foggs A, Flinn WR. Awake patient monitoring to determine the need for shunting during carotid endarterectomy. Surgery 1993; 114(4):673-679.

(4) Blume WT, Ferguson GG, McNeill DK. Significance of EEG changes at carotid endarterectomy. Stroke 1986; 17(5):891-897.

(5) Jansen C, Vriens EM, Eikelboom BC, Vermilion FE, van GJ, Ackerstaff RG. Carotid endarterectomy with transcranial Doppler and electroencephalographic monitoring. A prospective study in 130 operations. Stroke 1993; 24(5):665-669.

(6) Facco E, Deriu GP, Dona B, Ballotta E, Munari M, Grego F et al. EEG monitoring of carotid endarterectomy with routine patch-graft angioplasty: an experience in a large series. Neurophysiol Clin 1992; 22(6):437-446.

(7) Rerkasem K, Rothwell PM. Local versus general anesthesia for carotid endarterectomy. Cochrane Database Syst Rev 2008;(4):CD000126.

(8) Salvian AJ, Taylor DC, Hsiang YN, Hildebrand HD, Litherland HK, Humer MF et al. Selective shunting with EEG monitoring is safer than routine shunting for carotid endarterectomy. Cardiovasc Surg 1997; 5(5):481-485.

(9) Schneider JR, Droste JS, Schindler N, Golan JF, Bernstein LP, Rosenberg RS. Carotid endarterectomy with routine electroencephalography and selective shunting: Influence of contralateral internal carotid artery occlusion and utility in prevention of perioperative strokes. J Vasc Surg 2002; 35(6):1114-1122.

(10) Isley MR, Edmonds HL, Jr., Stecker M. Guidelines for intraoperative neuromonitoring using raw (analog or digital waveforms) and quantitative electroencephalography: a position statement by the American Society of Neurophysiological Monitoring. J Clin Monit Comput 2009; 23(6):369-390.

(11) Halsey JH, Jr. Risks and benefits of shunting in carotid endarterectomy. The International Transcranial Doppler Collaborators. Stroke 1992; 23(11):1583-1587.

(12) Highton D, Elwell C, Smith M. Noninvasive cerebral oximetry: is there light at the end of the tunnel? Curr Opin Anaesthesiol 2010; 23(5):576-581.

(13) Visser GH, Wieneke GH, van Huffelen AC. Carotid endarterectomy monitoring: patterns of spectral EEG changes due to carotid artery clamping. Clin Neurophysiol 1999; 110(2):286-294.

(14) Schechter MA, Shortell CK, Scarborough JE. Regional versus general anesthesia for carotid endarterectomy: the American College of Surgeons National Surgical Quality Improvement Program perspective. Surgery 2012; 152(3):309-314.

(15) Lewis SC, Warlow CP, Bodenham AR, Colam B, Rothwell PM, Torgerson D et al. General anesthesia versus local anesthesia for carotid surgery (GALA): a multicentre, randomized controlled trial. Lancet 2008; %20;372(9656):2132-2142.

(16) McDowell HA, Jr., Gross GM, Halsey JH. Carotid endarterectomy monitored with transcranial Doppler. Ann Surg 1992; 215(5):514-518.

(17) Arnold M, Sturzenegger M, Schaffler L, Seiler RW. Continuous intraoperative monitoring of middle cerebral artery blood flow velocities and electroencephalography during carotid endarterectomy. A comparison of the two methods to detect cerebral ischemia. Stroke 1997; 28(7):1345-1350.

(18) Jansen C, Moll FL, Vermilion FE, van Haelst JM, Ackerstaff RG. Continuous transcranial Doppler ultrasonography and electroencephalography during carotid endarterectomy: a multimodal monitoring system to detect intraoperative ischemia. Ann Vasc Surg 1993; 7(1):95-101.

(19) Pennekamp CWA, Bots ML, Kappelle LJ, Moll FL, De Borst GJ. The Value of Near-Infrared Spectroscopy Measured Cerebral Oximetry During Carotid Endarterectomy in Perioperative Stroke Prevention. A Review. European Journal of Vascular and Endovascular Surgery 2009; 38(5):539-545.

(20) Pedrini L, Magnoni F, Sensi L, Pisano E, Ballestrazzi MS, Cirelli MR et al. Is Near-Infrared Spectroscopy a Reliable Method to Evaluate Clamping Ischemia during Carotid Surgery? Stroke Res Treat 2012; 2012:156975. doi: 10.1155/2012/156975. Epub;%2011 Nov 9.:156975.

(21) Shang Y, Cheng R, Dong L, Ryan SJ, Saha SP, Yu G. Cerebral monitoring during carotid endarterectomy using near-infrared diffuse optical spectroscopies and electroencephalogram. Phys

Med Biol 2011; 56(10):3015-3032.
(22) Tambakis CL, Papadopoulos G, Sergentanis TN, Lagos N, Arnaoutoglou E, Labropoulos N et al. Cerebral oximetry and stump pressure as indicators for shunting during carotid endarterectomy: comparative evaluation. Vascular 2011; 19(4):187-194.
(23) Uchino H, Nakamura T, Kuroda S, Houkin K, Murata J, Saito H. Intraoperative dual monitoring during carotid endarterectomy using motor evoked potentials and near-infrared spectroscopy. World Neurosurg 2012; 78(6):651-657.
(24) Yoshimoto T, Shirasaka T, Yoshizumi T, Fujimoto S, Kaneko S, Kashiwaba T. Evaluation of carotid distal pressure for prevention of hyperperfusion after carotid endarterectomy. Surg Neurol 2005; 63(6):554-557.
(25) Zogogiannis ID, Iatrou CA, Lazarides MK, Vogiatzaki TD, Wachtel MS, Chatzigakis PK et al. Evaluation of an intraoperative algorithm based on near-infrared refracted spectroscopy monitoring, in the intraoperative decision for shunt placement, in patients undergoing carotid endarterectomy. Middle East J Anesthesiol 2011; 21(3):367-373.
(26) Hirofumi O, Otone E, Hiroshi I, Satosi I, Shigeo I, Yasuhiro N et al. The effectiveness of regional cerebral oxygen saturation monitoring using near-infrared spectroscopy in carotid endarterectomy. J Clin Neurosci 2003; 10(1):79-83.
(27) de Letter JA, Sie HT, Thomas BM, Moll FL, Algra A, Eikelboom BC et al. Near-infrared reflected spectroscopy and electroencephalography during carotid endarterectomy--in search of a new shunt criterion. Neurol Res 1998; 20 Suppl 1:S23-S27.
(28) Green RM, Messick WJ, Ricotta JJ, Charlton MH, Satran R, McBride MM et al. Benefits, shortcomings, and costs of EEG monitoring. Ann Surg 1985; 201(6):785-792.
(29) Phillips MR, Johnson WC, Scott RM, Vollman RW, Levine H, Nabseth DC. Carotid endarterectomy in the presence of contralateral carotid occlusion: the role of EEG and intraluminal shunting. Arch Surg 1979; 114(11):1232-1239.
(30) McCleary AJ, Dearden NM, Dickson DH, Watson A, Gough MJ. The differing effects of regional and general anesthesia on cerebral metabolism during carotid endarterectomy. Eur J Vasc Endovasc Surg 1996; 12(2):173-181.
(31) de Letter JA, Sie TH, Moll FL, Algra A, Eikelboom BC, Ackerstaff GA. Transcranial cerebral oximetry during carotid endarterectomy: agreement between frontal and lateral probe measurements as compared with an electroencephalogram. Cardiovasc Surg 1998; 6(4):373-377.

Chapter 9

Near-infrared spectroscopy can predict the onset of cerebral hyperperfusion syndrome after carotid endarterectomy

Published in:

Cerebrovascular Diseases, 2012;34(4):314-21

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Abstract

Background
Cerebral hyperperfusion syndrome (CHS) after carotid endarterectomy (CEA) is a potential life-threatening complication. Therefore, early identification and treatment of patients at risk is essential. CHS can be predicted by a doubling of postoperative transcranial Doppler (TCD)-derived mean middle cerebral artery blood velocity (V_{mean}) compared to preoperative values. However, in approximately 15% of CEA patients, an adequate TCD signal cannot be obtained due to an insufficient temporal bone window. Moreover, the use of TCD requires specifically skilled personnel. An alternative and promising technique of noninvasive cerebral monitoring is relative frontal lobe oxygenation (rSO_2) measured by near-infrared spectroscopy (NIRS), which offers on-line information about cerebral oxygenation without the need for specialized personnel. In this study, we assess whether NIRS and perioperative TCD are related to the onset CHS following CEA.

Methods
Patients who underwent CEA under general anesthesia and had a sufficient TCD window were prospectively included. The V_{mean} and rSO_2 measured before induction of anesthesia were compared to measurements performed in the first postoperative hour (ΔV_{mean}, ΔrSO_2, respectively). Logistic regression analysis was performed to determine the relationship between ΔV and ΔrSO_2 and the occurrence of CHS. Subsequently, receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off values. Diagnostic values were shown as positive and negative predictive values (PPV and NPV).

Results
In total, 151 patients were included, of which 7 patients developed CHS. The ΔV_{mean} and ΔrSO_2 differed between CHS and non-CHS patients (median, interquartile range), i.e. 74% (67–103) versus 16% (–2 to 41), p = 0.001, and 7% (4–15) versus 1% (–6 to 7), p = 0.009, respectively. The mean arterial blood pressure did not change. Postoperative ΔV_{mean} and ΔrSO_2 were significantly related to the occurrence of CHS [odds ratio (OR) 1.40 (95% CI 1.02–1.93) per 30% increase in V_{mean} and OR 1.82 (95% CI 1.11–2.99) per 5% increase in rSO_2]. ROC curve analysis showed an area under the curve of 0.88 (p = 0.001) for ΔV_{mean} and an optimal cut-off value of 67% increase (PPV 38% and NPV 99%), and an area under the curve of 0.79 (p = 0.009) for ΔrSO_2 and an optimal cut-off value of 3% rSO_2 increase (PPV 11% and NPV 100%). The combination of both monitoring techniques provided a PPV of 58% and an NPV of 99%.

Conclusions
Both TCD and NIRS measurements can be used to safely identify patients not at risk of developing CHS. It appears that NIRS is a good alternative when a TCD signal cannot be obtained.

Background

Perioperative cerebrovascular complications of carotid endarterectomy (CEA) can be divided into intra- and postoperative complications, depending on the time of onset. Intraoperative adverse events, mostly caused by thromboembolic events or hypoperfusion,[1] have significantly declined following the introduction of intraoperative cerebral monitoring,[2-4] whereas the postoperative rate of cerebrovascular complications remained more or less stable with approximately 3%.[2] Besides local thrombosis at the level of the endarterectomy or thromboembolism, cerebral hyperperfusion syndrome (CHS) is an important postoperative complication. CHS, defined as a cerebral hyperperfusion in addition to neurological symptoms, occurs in approximately 3–5% of patients undergoing a CEA procedure and is potentially life threatening.[5] When not recognized timely and treated adequately, CHS can lead to intracerebral hemorrhage, the most feared complication associated with a mortality of 40%, and therefore warrants early identification of patients at risk.[6] Currently, postoperative transcranial Doppler (TCD) monitoring is considered the gold standard in CHS prediction. A TCD value which is the double of preoperative middle cerebral artery (MCA) mean blood velocity (V_{mean}) is associated with onset of CHS in about 40% of patients and can reliably exclude patients at risk of developing CHS.[7] However, in 10–15% of CEA patients, an adequate TCD signal cannot be obtained because of an insufficient temporal bone window. At present, for this subgroup of patients, there is no reliable alternative monitoring tool to predict CHS. As a consequence, patients at high risk might be missed by the current monitoring strategy, while patients might be incorrectly identified as high risk for CHS leading to superfluous treatment and additional costs. An alternative approach is perioperative monitoring of the frontal lobe oxygenation of the brain (rSO_2) with near-infrared spectroscopy (NIRS). This technique may be a promising alternative cerebral monitoring technique since it is easy to apply, applicable in all patients and relatively low in costs. However, the existing evidence on perioperative use of NIRS in relation to the onset of CHS is limited.[8]
In the present study, we questioned whether NIRS could be used for identification of patients at risk of developing CHS. Therefore, we prospectively gathered NIRS-measured rSO_2 before, during and after CEA and related NIRS and TCD to the development of CHS following CEA.

Methods

Patients
This study was designed as a single-centre cohort study. Patients who underwent CEA between February 2009 and June 2011 in the University Medical Center Utrecht and had a temporal window suitable for TCD monitoring were prospectively included. The severity of the carotid artery stenosis on preoperative imaging by computed tomography angiography or magnetic resonance angiography was categorized on a 4-point scale: <50%, 50–70%, 70–99% stenosis or occlusion.

Measurements
One day before surgery, baseline oscillometric blood pressure (BP) and bilateral V_{mean} were measured (Figure 1). Baseline rSO_2 was determined bilaterally before induction of anesthesia

and continued till the end of surgery. Peroperatively and in the recovery ward, intra-arterial BP was monitored through a catheter (1.1 mm ID, 20 gauge) placed in the radial artery. Intraoperative V_{mean} monitoring was started after induction, but before incision, and continued till the end of surgery. Postoperative TCD and NIRS measurements were performed for a period of 20 min in the first postoperative hour.

Transcranial Doppler
For measurement of the V_{mean} in the MCA, a pulsed Doppler transducer (DWL Multidop X4, Sipplingen, Germany) gated at a focal depth of 45–60 mm was placed over the temporal bone to insonate the main stem of the ipsilateral MCA and V_{mean} was recorded continuously.

Near-Infrared Spectroscopy
The rSO_2 measurement was performed using Invos Cerebral Oximeter (Somanetics Corporation, Troy, Mich., USA) with the aid of two sensors placed on the forehead.

Intraoperative Management
After application of routine monitoring devices (ECG and pulse oximetry), induction of anesthesia was achieved with sufentanil (0.3–0.7 μg/kg), propofol (0.5–2.0 mg/kg) and rocuronium (0.3–0.5 mg/kg). Anesthesia was maintained using sevoflurane, with a minimum alveolar concentration of 0.5–1. Before cross-clamping the carotid artery, 5,000 U of heparin was given intravenously. The CEA was performed by an experienced vascular surgeon or by a vascular trainee under supervision in a standardized way. An intraluminal shunt was used selectively in case of electroencephalographic (Micromed Inc., Treviso, Italy) asymmetry.

Postoperative Management
Postoperatively, patients stayed in the recovery ward for continuous BP monitoring for at least 6 h. After the postoperative NIRS and TCD measurements had been performed, patients with a systolic BP >160 mm Hg, a BP of 20% above the preoperative BP, a postoperative V_{mean} >100% compared to preoperative V_{mean}, or an absolute V_{mean} >120 $cm \cdot s^{-1}$ with or without symptoms were treated with intravenous infusion of labetalol (5–20 $mg \cdot h^{-1}$) to decrease BP and/or V_{mean}. After 6 h, patients were moved to the general ward. However, if BP was not controlled appropriately or if signs of CHS were present during the 6-hour time frame in the recovery ward, patients were transferred to the medium care unit for continuous monitoring and intravenous therapy.

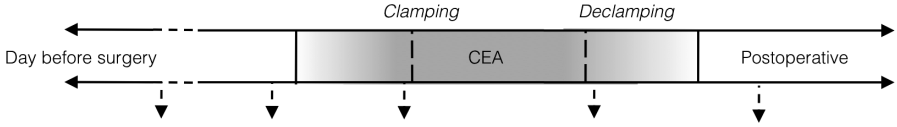
Definition of CHS
CHS was defined as the postoperative occurrence of headache, confusion, seizures, focal neurological deficits or an intracranial hemorrhage, in addition to TCD-registered postoperative cerebral hyperperfusion (>100% increase of the preoperative V_{mean} or an absolute V_{mean} >120 $cm \cdot s^{-1}$).

Data Analysis
The BP signal and the envelope curve of the TCD spectrum were A/D converted at 100 Hz, while bilateral frontal lobe rSO_2 was determined at 0.14 Hz. To calculate the mean arterial blood pressure (MAP) and V_{mean}, the diastolic pressure or velocity, respectively, was multiplied

by two and added to the systolic pressure or velocity. Subsequently, the results were dived by three. A 30-second averaged value of MAP, V_{mean} and rSO_2 was calculated at the following time points: baseline, preclamping, postclamping and postoperative. Subsequently, relative differences between baseline and postoperative MAP, V_{mean} and rSO_2 and between pre- and postclamping MAP, V_{mean} and rSO_2 were defined as ΔMAP, ΔV_{mean} and ΔrSO_2 respectively.

Statistical Analysis

Data are presented as median and interquartile range (IQR). The Wilcoxon signed rank test was used to compare the different measurements. To calculate the differences between CHS and non-CHS patients, the Mann-Whitney *U* test was used. A p-value <0.05 was considered significant. To determine the relationship between ΔV_{mean} and ΔrSO_2 and outcome, logistic regression analysis was performed. The optimal cut-off point of both ΔV_{mean} and ΔrSO_2 in relation to the onset of CHS was chosen using the receiver operating characteristic (ROC) curve and Youden's index (sensitivity + specificity – 1). Predictive values are shown as positive predictive value (PPV) and negative predicative value (NPV).



	Baseline	Preclamping	Postclamping	Postoperative
MAP (osc.)	102 (93-110)	n/a	n/a	n/a
MAP	n/a	95 (85-104)	88 (78-96)	84 (76-99)
V_{mean}	55 (45-65)	48 (42-59)	55 (42-67)	65 (53-79)
rSO_2	70 (65-76)	70 (65-77)	71 (65- 77)	71 (65-75)

Figure 1. Timeframe.
At the following time points, MAP (mm Hg), V_{mean} ($cm \cdot s^{-1}$) and rSO_2 (%) were recorded and calculated. At baseline, MAP was measured using an oscillometric (osc.) method. Transition from white turns to gray indicates anesthetizing of the patient. n = 151; data are shown as median (IQR). Baseline values: 1 day before surgery. Preclamping values: averaged value of a 30-second measurement, 30 s before preclamping. Postclamping values: averaged value of 30-second measurement, 3 min after declamping Postoperative values: averaged value of 30-second measurement, in the first postoperative hour. N/a: not applicable

Results

Patient Characteristics

patients fully recovered. All CHS patients developed hypertension prior to the development of CHS.

Hemodynamic and Cerebral Measurements
Intraoperatively, MAP decreased from 95 mm Hg (85–104) before cross-clamping the carotid artery to 88 mm Hg (IQR 78–96 mm Hg) $p < 0.001$, after declamping. V_{mean} increased from 48 $cm \cdot s^{-1}$ (IQR 42–59) to 55 $cm \cdot s^{-1}$ (IQR 42–67), $p < 0.001$. (Figure 1; Tables 2 and 3) Three patients had an intraoperative ΔV_{mean} of >100%; none of them developed CHS. rSO_2 did not change significantly after declamping the carotid artery. The ΔrSO_2 did not differ between patients with and without an intraoperative ΔV_{mean} of >100%. Intraoperative ΔMAP, ΔV_{mean} and ΔrSO_2 did not differ significantly between patients who did or did not develop CHS.

Variable	All patients (n=151)	CHS (n=7)	Non - CHS (n= 144)	p- value
Gender (M)	117 (78%)	5 (71%)	112 (78%)	0.695
Side (right)	63 (42%)	3 (43%)	60 (42%)	0.950
Age (median, IQR)	70 (64-78)	59 (54- 69)	70 (64- 78)	0.079
History of CEA				
ipsilateral	1 (1%)	0	1 (1%)	0.825
contralateral	17 (11%)	1 (14%)	16 (11%)	0.795
Indication (symptomatic)	133 (88%)	6 (86%)	127 (88%)	0.843
Degree of ipsilateral stenosis				
50- 70%	9 (6%)	1 (14%)	8 (6%)	0.341
>70%	142 (94%)	6 (86%)	136 (94%)	
Degree of contralateral stenosis				
<50%	72 (48%)	2 (29%)	70 (49%)	0.300
50-70%	25 (17%)	1 (14%)	24 (17%)	0.869
70- 99%	24 (16%)	2 (29%)	22 (15%)	0.348
Occlusion	19 (13%)	1 (14%)	18 (13%)	0.889
Unknown	11 (7%)	1 (14%)	10 (7%)	0.465
Peroperative shunt use	17 (11%)	2 (29%)	15 (10%)	0.138
Perioperative stroke	4 (3%)	0	4 (3%)	0.655
Perioperative TIA	1 (1%)	0	1 (1%)	0.825
Postoperative hypertension	32 (21%)	7 (100%)	25 (17%)	< 0.001
Death < 30 days	1 (1%)	0	1 (1%)	0.825

Table 1. Patient characteristics of all patients and according to the onset of CHS

Pt.		Baseline	Pre-clamping	Post-clamping	Post-CEA	ΔIntra (%)	ΔPost (%)	Symptoms
1.	rSO_2	72	62	68	74	9.0	3	Dysphasia and headache on 3rd post-operative day
	V_{mean}	35	42	37	59	-12	69	
	MAP	110	132	64	114	-52	4	
2.	rSO_2	70	68	67	74	-1	6	Dysphasia and confusion on 5th post-operative day
	V_{mean}	77	68	70	86	3	12	
	MAP	109	96	96	116	0	6	
3.	rSO_2	63	77	76	69	-3	10	Headache on 1st post-operative day
	V_{mean}	39	47	59	79	26	103	
	MAP	115	110	81	64	-26	-44	
4.	rSO_2	67	72	71	72	-1	7	Headache on 1st post-operative day
	V_{mean}	35	28	26	71	-1	103	
	MAP	93	69	86	91	25	-2	
5.	rSO_2	75	68	71	87	3	16	Headache and hypertension on 1st post-operative day
	V_{mean}	88	73	82	153	-12	74	
	MAP	119	111	83	115	-25	-3	
6.	rSO_2	75	80	82	88	3	17	Headache and hypertension on 6th post-operative day
	V_{mean}	76	75	90	127	20	67	
	MAP	100	100	96	107	-4	7	
7.	rSO_2	64	54	67	66	24	3	Headache and vomiting on 1st post-operative day
	V_{mean}	67	62	103	120	66	79	
	MAP	97	146	102	100	-30	3	

Table 2. Intraoperative (ΔIntra) and postoperative (ΔPost) relative changes in MAP (mmHg), mean MCA blood velocity (V_{mean}, $cm \cdot s^{-1}$) and frontal lobe oxygenation (rSO_2, %) for all patients who developed CHS separately and their symptoms.

	Intraoperative increase			Postoperative increase		
	ΔMAP (%)	ΔV_{mean} (%)	ΔrSO_2 (%)	ΔMAP (%)	ΔV_{mean} (%)	ΔrSO_2 (%)
All	-7 (-16- 3)	7 (-5-29)	0 (-3- 4)	-15 (-26- -3)	17 (0-44)	1 (-5- 7)
CHS (n=7)	-26 (-30- 0)	13 (-6- 25)	3 (-1- 9)	3 (-3- 6)	74 (67- 102)	7 (4- 15)
Non- CHS (n=144)	-7 (-16 – 3)	7 (-5 -30)	0 (-4 – 4)	-16 (-27- -3)	16 (-2 – 41)	1 (-6- 7)
p-value	.174	.846	.246	.058	.001	.009

Table 3. Intraoperative and postoperative relative increase in mean blood pressure (ΔMAP), mean middle cerebral artery blood velocity (ΔV_{mean}) and frontal lobe oxygenation (ΔrSO_2) in patients who developed cerebral hyperperfusion syndrome (CHS) and who did not. Data are shown as median (IQR).

Postoperatively, MAP decreased from 102 mm Hg (IQR 93–110) preoperatively to 84 mm Hg (IQR 76–99) after surgery (p = 0.001), while V_{mean} increased from 55 cm·s^{-1} (IQR 45–65) to 65 cm·s^{-1} (IQR 53–79), p < 0.001, in combination with a stable rSO_2, being 70% (IQR 65–76) versus 71% (IQR 65–75), p = 0.340. Pre- and postoperative MAP did not differ between CHS and non-CHS patients. However, patients who developed CHS had both a larger ΔV_{mean} and a larger ΔrSO_2 than patients without CHS (74% [IQR 67–103] vs. 16% [IQR –2 to 41] and 7% [IQR 4–15] vs. 1% [IQR –6 to 7], p < 0.01, respectively). Six patients had a postoperative ΔV_{mean} of >100%, four patients had a postoperative V_{mean} of >120 cm·s^{-1} and two patients had both. Two of these 12 patients developed CHS. Patients with a postoperative ΔV_{mean} of >100% or a postoperative V_{mean} of >120 cm·s^{-1} had a higher ΔrSO_2, i.e. 8% (IQR 2–15), than patients who had not, i.e. 0% (IQR –5 to 6), p = 0.019. The MAP did not change postoperatively compared to preoperative measurements.

Variable	OR	95% CI
Gender (M)	1.40	0.26 - 7.56
Side (right)	1.05	0.23 -4.86
Age (median, IQR)	0.93	0.86 -1.01
History of CEA		
ipsilateral	0	
contralateral	1.33	0.15 - 11.79
Indication (symptomatic)	0.80	0.09 - 7.08
Degree of ipsilateral stenosis		
50- 70%	2.83	0.30 - 26.45
>70%	0.13	0.04 - 3.30
Degree of contralateral stenosis		
<50%	0.42	0.08 - 2.25
50-70%	0.83	0.10 - 7.24
70- 99%	2.22	0.41 - 12.16
Occlusion	1.17	0.13 - 10.26
Unknown	2.23	0.24 - 20.41
Peroperative shunt use	3.44	0.61 - 19.30
Intraoperative ΔV_{mean} , per 1% increase	1.00	0.98 - 1.02
Intraoperative ΔrSO_2, per 1% increase	1.10	0.92 - 1.19
Postoperative ΔV_{mean}, per 1% increase	1.01*	1.00 - 1 .03
Postoperative ΔrSO_2, per 1% increase	1.13*	1.02 - 1.25
Post-operative ΔV_{mean}, per 30% increase	1.48*	1.08 - 2.03
Postoperative ΔrSO_2, per 5% increase	1.82*	1.11 - 2.99

Table 4. Univariate predictors of the development of CHS. Statistically significant predictors of CHS are indicated by an asterisk (*).

Logistic Regression Analysis

As shown in Table 4 univariate analysis demonstrated that both postoperative ΔV_{mean} (odds ratio [OR)] 1.40 [95% CI 1.02–1.93] per 30% increase) and postoperative ΔrSO_2 (OR 1.82 [95% CI 1.11–2.99] per 5% increase) were related to the development of CHS postoperatively.

ROC Curve Analysis

Based on ROC curve analysis an increase in V_{mean} of 67% was identified as the cut-off value most related to the onset of CHS, with an area under the curve of 0.88 (p = 0.001). (Figure 2) With this cut-off value, a PPV of 38% and an NPV of 99% were found. (Table 5) A cut-off value of 2% rSO_2 increase with an area under the curve of 0.79 (p = 0.009) had a PPV of 11% and an NPV of 100%. As shown in table 5, a combination of both monitoring techniques provides a PPV of 58% and an NPV of 99%. Of all 15 patients with ΔV_{mean} >67%, nine patients had a ΔrSO_2 >2%.

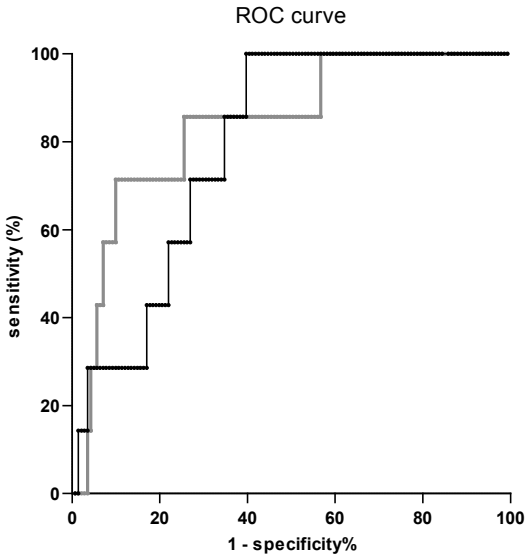


Figure 2. ROC curves comparing the postoperative increases in relative frontal lobe oxygenation (rSO_2; dark line) measured using NIRS and TCD-derived mean MCA blood velocity (V_{mean}; light line) for prediction of CHS following CEA.

	CHS+	CHS-	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Monitoring technique						
NIRS +	7 (5%)	59 (39%)	100	58	11	100
NIRS -	0 (0%)	82 (5%)				
TCD+	6 (4%)	10 (7%)	86	93	38	99
TCD-	1 (1%)	131 (9%)				
Combined monitoring techniques						
TCD +, NIRS +	6 (4%)	3 (2%)	86	98	67	99
TCD -, NIRS –	0 (0%)	74 (49%)	0	54	0	10
TCD + or NIRS+	7 (5%)	64 (4%)	100	46	10	100

Table 5. Diagnostic cross-table for the number of patients that developed CHS after CEA correctly diagnosed by NIRS and/or TCD measurements. Sens: sensitivity. Spec: specificity. PPV: positive predictive value. NPV: negative predictive value.

Discussion

In this study, we evaluated the relationship between changes in both rSO_2 and V_{mean} during CEA and the development of postoperative CHS. We showed that both rSO_2 and V_{mean} were more increased in patients who did develop CHS than in those who did not. Both measurements could independently relate to the occurrence of CHS. Based on our results, the combination of TCD and NIRS seems to most reliably select patients at risk for the development of CHS, while NIRS monitoring alone can safely exclude patients at risk of developing CHS.

Exclusion of patients being at risk of developing CHS is essential as treatment of patients in the early phase can potentially prevent life-threatening symptoms.[6] Several risk factors have been proposed to be associated with the occurrence of CHS, including longstanding hypertension, poor collateral flow high-grade ipsilateral stenosis and contralateral carotid occlusion, but no clear preoperative prediction model exists today.[5] Moreover, both a reduced cerebral blood flow and cerebral vasoreactivity have been shown to be independently related to the onset of CHS.[9,10] Increases in cerebral blood flow can be measured using SPECT[11,12]; however, as this method has several disadvantages including high procedural costs, TCD increase is currently mostly used as a surrogate for cerebral blood flow measurements.

We recently observed that TCD measurements in the postoperative phase more precisely predict the onset of CHS than intraoperative TCD measurements.[7] We attributed this finding to the influence of the administered anesthetic agents during the intraoperative measurement. To avoid the influence of anesthetics on the measurements, we used the same time frame in the current study and compared the preoperative and postoperative awake values. As described elsewhere, the value of NIRS related to the onset of CHS has been promising, but the evidence is poor since there are no clearly defined rSO_2 cut-off values.[8] Ogasawara et al.[13] compared declamping rSO_2 with preclamping values and found a significant correlation between rSO_2 increases after declamping and the onset of CHS. However, in their

study, only one patient developed CHS. Komoribayashi et al.[14] also used intraoperatively measured NIRS values. They found a significant association between cerebral hyperperfusion, patients without clinical symptoms, and a reduced rSO_2 during clamping as compared to preclamping values. Moreover, the association between intraoperative ischemia and cerebral hyperperfusion following CEA has been shown previously.[15]

Our study has several limitations. Firstly, early antihypertensive treatment of patients at risk might have prevented the later development of CHS. In 12 patients, cerebral hyperperfusion was observed (ΔV_{mean} of >100%, or a postoperative V_{mean} of >120 $cm \cdot s^{-1}$), but only in eight of these patients an increase in rSO_2 of >2% was found. Nevertheless, the other four patients did not develop CHS. This might be explained by the use of antihypertensive therapy in the selected patients. It is thought that patients with a high-degree carotid stenosis have an impaired cerebral autoregulation. As in these patients the cerebrovascular resistance is reduced and the V_{mean} (as a surrogate measure of the cerebral blood flow) has become BP dependent,[16] antihypertensive treatment might have prevented the later development of CHS in these patients. However, in our analysis, we assumed that all hypertensive patients would have developed CHS (worst case scenario). In such a scenario, the magnitude of the ORs remained similar, and therefore we feel that the treatment of hypertension of patients whose blood pressure rose did not affect our findings. Therefore, we conclude that the use of antihypertensive medication has not influenced our results. Secondly, the utility of TCD was limited by the need for a sufficient bone window; moreover, TCD measurements required experienced personnel. NIRS can partly compensate for the disadvantages of TCD, since it is easy to apply and can be performed in all patients. Nevertheless, the interindividual and intraindividual baseline variability is high[17]; therefore, we correlated outcome to the relative and not the absolute change in rSO_2. Furthermore, the reproducibility of NIRS measurements has previously been questioned.[17] To reduce the interindividual variation, we used NIRS as a trend monitor and to reduce the intraindividual variation, we did not remove the sensor between the end of surgery and the measurement in the recovery room.

The third and most relevant limitation of our study is the limited number of cases. Because of the small number of patients who develop CHS following CEA, this number is not easy to expand. Therefore, we used a limited number of predictors and no adjustment for multiple testing was made. Where the small numbers limited the precision of our estimates, it is unlikely that it affected the validity of our findings.

Based on our results, we conclude that NIRS is a reliable monitoring technique to exclude patients at risk of developing CHS. Furthermore, for the detection of patients at risk of developing CHS, the combination of NIRS and TCD monitoring provides the highest predictive value. However, as increase in the number of cases is needed to confirm our results, it is too premature to recommend a widespread application of use for the detection of patients at risk of developing CHS. Nevertheless it strengthens us to continue the evaluation of both NIRS and TCD and we added NIRS to our standard cerebral monitoring protocol.

Acknowledgements

Invos Cerebral Oximeter (Somanetics Corporation, Troy, Mich., USA) was costless provided for the duration of the trial by Covidien Nederland B.V., Zaltbommel, The Netherlands.

References

(1) Riles TS, Imparato AM, Jacobowitz GR, Lamparello PJ, Giangola G, Adelman MA et al. The cause of perioperative stroke after carotid endarterectomy. J Vasc Surg 1994; 19(2):206-214.

(2) de Borst GJ, Moll FL, van de Pavoordt HD, Mauser HW, Kelder JC, Ackerstaf RG. Stroke from carotid endarterectomy: when and how to reduce perioperative stroke rate? Eur J Vasc Endovasc Surg 2001; 21(6):484-489.

(3) Naylor AR, Hayes PD, Allergen H, Lenard N, Gaunt ME, Thompson MM et al. Reducing the risk of carotid surgery: a 7-year audit of the role of monitoring and quality control assessment. J Vasc Surg 2000; 32(4):750-759.

(4) Smith JL, Evans DH, Gaunt ME, London NJ, Bell PR, Naylor AR. Experience with transcranial Doppler monitoring reduces the incidence of particulate embolisation during carotid endarterectomy. Br J Surg 1998; 85(1):56-59.

(5) van Mook WN, Rennenberg RJ, Schurink GW, van Oostenbrugge RJ, Mess WH, Hofman PA et al. Cerebral hyperperfusion syndrome. Lancet Neurol 2005; 4(12):877-888.

(6) Dalman JE, Beenakkers IC, Moll FL, Leusink JA, Ackerstaff RG. Transcranial Doppler monitoring during carotid endarterectomy helps to identify patients at risk of postoperative hyperperfusion. Eur J Vasc Endovasc Surg 1999; 18(3):222-227.

(7) Pennekamp C.W.A., Tromp S.C., Ackerstaff R.G., Bots M.L., Immink R.V., Spiering W. et al. Prediction of cerebral hyperperfusion after carotid endarterectomy by Transcranial Doppler. Submitted 2011.

(8) Pennekamp CW, Bots ML, Kappelle LJ, Moll FL, de Borst GJ. The value of near-infrared spectroscopy measured cerebral oximetry during carotid endarterectomy in perioperative stroke prevention. A review. Eur J Vasc Endovasc Surg 2009; 38(5):539-545.

(9) Hosoda K, Kawaguchi T, Ishii K, Minoshima S, Shibata Y, Iwakura M et al. Prediction of hyperperfusion after carotid endarterectomy by brain SPECT analysis with semiquantitative statistical mapping method. Stroke 2003; 34(5):1187-1193.

(10) Ogasawara K, Yukawa H, Kobayashi M, Miami C, Konno H, Teriyaki K et al. Prediction and monitoring of cerebral hyperperfusion after carotid endarterectomy by using single-photon emission computerized tomography scanning. J Neurosurg 2003; 99(3):504-510.

(11) Chida K, Ogasawara K, Aso K, Suga Y, Kobayashi M, Yoshida K et al. Postcarotid endarterectomy improvement in cognition is associated with resolution of crossed cerebellar hypoperfusion and increase in 123I-iomazenil uptake in the cerebral cortex: a SPECT study. Cerebrovasc Dis 2010; 29(4):343-351.

(12) Fujimura M, Inoue T, Shimizu H, Saito A, Mugikura S, Tominaga T. Efficacy of prophylactic blood pressure lowering according to a standardized postoperative management protocol to prevent symptomatic cerebral hyperperfusion after direct revascularization surgery for moyamoya disease. Cerebrovasc Dis 2012; 33(5):436-445.

(13) Ogasawara K, Konno H, Yukawa H, Endo H, Inoue T, Ogawa A. Transcranial regional cerebral oxygen saturation monitoring during carotid endarterectomy as a predictor of postoperative hyperperfusion. Neurosurgery 2003; 53(2):309-314.

(14) Komoribayashi N, Ogasawara K, Kobayashi M, Saitoh H, Teriyaki K, Inoue T et al. Cerebral hyperperfusion after carotid endarterectomy is associated with preoperative hemodynamic impairment and intraoperative cerebral ischemia. J Cereb Blood Flow Metab 2006; 26(7):878-884.

(15) Kawamata T, Okada Y, Kawashima A, Yoneyama T, Yamaguchi K, Ono Y et al. Postcarotid endarterectomy cerebral hyperperfusion can be prevented by minimizing intraoperative cerebral ischemia and strict postoperative blood pressure control under continuous sedation. Neurosurgery 2009; 64(3):447-453.

(16) Reinhard M, Muller T, Guschlbauer B, Timmer J, Hetzel A. Dynamic cerebral autoregulation and collateral flow patterns in patients with severe carotid stenosis or occlusion. Ultrasound Med Biol 2003; 29(8):1105-1113.

(17) Highton D, Elwell C, Smith M. Noninvasive cerebral oximetry: is there light at the end of the tunnel? Curr Opin Anaesthesiol 2010; 23(5):576-581.

Chapter 10

Differential effect of phenylephrine and ephedrine on cerebral hemodynamics prior to carotid cross-clamping during carotid endarterectomy

Published in:

British Journal of Anaesthesia. 2012;109(5):831-3.

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Internal carotid artery stenosis is often associated with impaired cerebral autoregulation, implying that cerebral blood flow depends on arterial pressure.[1–3] To preserve cerebral perfusion and to prevent 'watershed' stroke during carotid endarterectomy (CEA), hypotension before and during cross-clamping needs to be avoided.[4] Several short-acting agents, such as phenylephrine or ephedrine, are commonly used to correct intraoperative hypotension, but have different hemodynamic effects. Phenylephrine, an α-agonist, increases arterial pressure by arterial vasoconstriction, whereas ephedrine, an a- and β-agonist, increases arterial pressure by arterial vasoconstriction combined with an increase in heart rate and cardiac output (CO).[5] In healthy anesthetized subjects with intact cerebral autoregulation, frontal lobe cerebral tissue oxygenation (rSO_2) declined after phenylephrine while it was preserved after ephedrine.[6,7]

To evaluate the effect of both ephedrine and phenylephrine on cerebral hemodynamics during CEA under general anesthesia, we analyzed the association between the increase in mean arterial pressure (MAP) induced by either ephedrine or phenylephrine and concurrent changes in cerebral hemodynamics using transcranial Doppler-derived mean middle cerebral artery blood velocity (V_{mean}) and near-infrared spectroscopy-derived rSO_2. All patients were anaesthetized using the same anesthetic regimen. In 11 patients undergoing CEA between February 2009 and June 2011, who all received either ephedrine (5–10 mg; n=7) or phenylephrine (50–100 μg; n=4) to correct relative hypotension (defined as >20% decrease in MAP when compared with preoperative MAP directly before cross-clamping).
Three minutes after ephedrine or phenylephrine administration, MAP increased from (mean ;SD) 79 (12) to 89(11) mm Hg or from 84 (6) to 102 (6) mm Hg (both p=0.025), respectively (Figure 1). Ephedrine raised heart rate from 55 (12) to 65 (17) beats min^{-1} (p=0.017), while phenylephrine declined heart rate from 74 (6) to 65 (5) beats min^{-1} (p=0.005). After ephedrine administration, rSO_2 increased from 70 (7)% to 73 (6)% (p=0.002); however, phenylephrine decreased rSO_2 from 71 (7)% to 66 (9)% (p=0.076). The V_{mean} remained constant after ephedrine (46 [14] cm $s^{-1)}$, but increased from 46 (13) to 49 (12) cm s^{-1} (p=0.035) after phenylephrine. The linear regression analysis showed that the absolute change from baseline in rSO_2 was positively related to the change in MAP with ephedrine (0.108% per mm Hg increase, 95% confidence interval [CI] 0.058–0.159). However, for a phenylephrine-induced increase in MAP, an inversely related change in rSO_2 compared with MAP (–0.202% per mm Hg increase, 95% CI –0.278 to 0.126) was found.
The mechanism of the reduction in rSO_2 after phenylephrine and not after ephedrine is unclear. In patients with intact cerebral autoregulation, the decrease in rSO_2 after phenylephrine was associated with concordant changes in CO, whereas rSO_2 remained unchanged when CO remained constant after treatment with ephedrine.[6] This observation confirms that changes in CO, even independently from arterial pressure, affect cerebral haemodynamics.[8] Cerebral arteries are abundantly innervated by sympathetic fibres.[9] Therefore, the decrease in rSO_2 after phenylephrine could be explained by a direct α-receptor-mediated cerebral vasoconstriction, as a decrease in middle cerebral artery diameter might result in a decreased blood flow, while V_{mean} remains constant or even increases.

To our knowledge, this is the first report on the differential influence of phenylephrine and ephedrine on cerebral hemodynamics in patients undergoing CEA. Although the data are

very limited, the observations were consistent, since no patients treated with phenylephrine showed an increase in cerebral oxygenation, and no patient in the ephedrine group showed a decrease. Therefore, based on this small case series, we conclude that the value of phenylephrine in terms of benefit for cerebral hemodynamics could be questioned. A controlled trial is warranted to clarify the effects of different vasoactive agents on cerebral oxygenation to determine the optimal agent to increase arterial pressure during CEA.

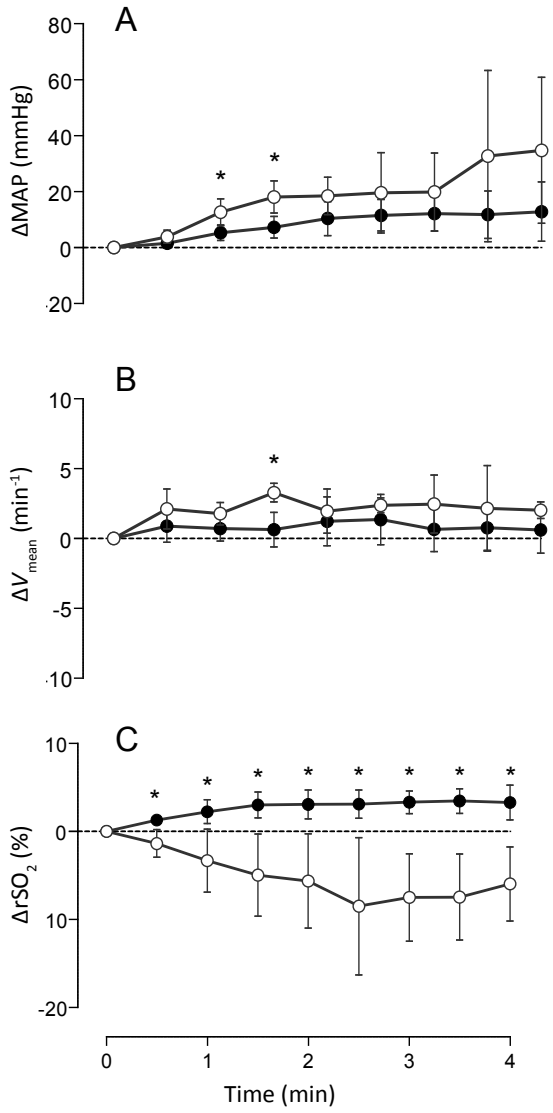

Figure 1. The effect of phenylephrine (o; n=4) versus ephedrine (●; n=7) on absolute changes (mean±SD) in mean arterial pressure (ΔMAP; panel A) Mean middle cerebral artery blood velocity (ΔV_{mean}; panel B) and frontal lobe oxygenation (ΔrSO_2; panel C). Statistically significant ($P < 0.05$) differences between the phenylephrine and ephedrine group determined by one-way analysis of variance are indicated by an asterisk (*).

Acknowledgements
The Invos Cerebral Oximeter (Somanetics Corporation, Troy, MI) was costless provided for the duration of the study by Covidien Nederland B.V., Zaltbommel, The Netherlands.

References

(1) Diehl RR, Linden D, Lucke D, Berlit P. Phase relationship between cerebral blood flow velocity and blood pressure. A clinical test of autoregulation. Stroke 1995; 26(10):1801-1804.

(2) Reinhard M, Gerds TA, Grabiak D, Zimmermann PR, Roth M, Guschlbauer B et al. Cerebral dysautoregulation and the risk of ischemic events in occlusive carotid artery disease. J Neurol 2008; 255(8):1182-1189.

(3) Reinhard M, Roth M, Muller T, Czosnyka M, Timmer J, Hetzel A. Cerebral autoregulation in carotid artery occlusive disease assessed from spontaneous blood pressure fluctuations by the correlation coefficient index. Stroke 2003; 34(9):2138-2144.

(4) Stoneham MD, Thompson JP. Arterial pressure management and carotid endarterectomy. Br J Anaesth 2009; 102(4):442-452.

(5) Dyer RA, Reed AR, van DD, Arcache MJ, Hodges O, Lombard CJ et al. Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. Anesthesiology 2009; 111(4):753-765.

(6) Meng L, Cannesson M, Alexander BS, Yu Z, Kain ZN, Cerussi AE et al. Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. Br J Anaesth 2011; 107(2):209-217.

(7) Nissen P, Brassard P, Jorgensen TB, Secher NH. Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension. Neurocrit Care 2010; 12(1):17-23.

(8) Ogoh S, Brothers RM, Barnes Q, Eubank WL, Hawkins MN, Purkayastha S et al. The effect of changes in cardiac output on middle cerebral artery mean blood velocity at rest and during exercise. J Physiol 2005; 569(Pt 2):697-704.

(9) Sandor P. Nervous control of the cerebrovascular system: doubts and facts. Neurochem Int 1999; 35(3):237-259.

Chapter 11

Phenylephrine versus ephedrine on cerebral perfusion during carotid endarterectomy (PEPPER): study protocol for a randomized controlled trial

Published in: Trials. 2013;14(1):43

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Abstract

Background
Intraoperative arterial hypotension can lead to severe complication in patients undergoing carotid endarterectomy, in particular if cerebral autoregulation is impaired. Short-acting agents, such as phenylephrine or ephedrine, commonly used to correct intra-operative hypotension, have different haemodynamic effects. Recently, it was reported that, in healthy anesthetized subjects with intact cerebral autoregulation, frontal lobe cerebral tissue oxygenation declined after phenylephrine bolus administration while it was preserved after ephedrine use.[1,2] However, the effect of both agents in patients undergoing carotid endarterectomy is unknown. The aim of this study is to assess the effect of two routinely randomly used vasopressors (phenylephrine and ephedrine) on the cerebral hemodynamics during carotid endarterectomy.

Methods/ Design
Patients undergoing carotid endarterectomy will be prospectively included and randomized for correction of intraoperative hypotension with either phenylephrine (50 to 100 µg) or ephedrine (5 to 10 mg). If hypotension persists for more than five minutes after treatment, the patient will be classified as a non-responder and escape medication as preferred by the anesthesiologist will be administered. Changes in cerebral hemodynamics will be quantified by changes in transcranial Doppler-derived middle cerebral artery blood velocity and near infra-red spectroscopy-derived frontal lobe cerebral tissue oxygenation, when intraoperative hypotension is treated with phenylephrine or ephedrine in patients who undergo carotid endarterectomy with or without an adequate functioning cerebral autoregulation. To quantify whether the intraoperative cerebral autoregulation is impaired or not, a decrease in breathing frequency from the normal 12 breaths per minute to 6 breaths per minute for an episode of three minutes will be performed.

Discussion
Phenylephrine and ephedrine are two of the most commonly used short-acting agents to increase blood pressure in clinical anesthesiologic practice. Monitoring of middle cerebral artery blood velocity with transcranial Doppler and frontal lobe cerebral tissue oxygenation with near infra-red spectroscopy are part of the standard of care. Furthermore, there are no reports that the three-minute modification in breathing frequency described in the intervention-section is harmful. Therefore, the risks for participating patients are negligible and the burden minimal.

Trail registration
Clinical trials.gov: NCT01451294

Background

Carotid endarterectomy (CEA) is the recommended treatment to prevent future cardiovascular events in patients with a symptomatic high degree stenosis of the internal carotid artery (ICA). Besides these symptoms, stenosis of the ICA jeopardizes the cerebral perfusion and may affect cerebral autoregulation (CA), indicating that cerebral perfusion becomes dependent on changes in blood pressure.[1] Therefore, to preserve cerebral perfusion during surgery and to prevent 'watershed' stroke, intraoperative hypotension needs to be avoided and the suggested blood pressure that should be maintained intraoperatively is an arterial pressure between baseline blood pressure measured on the nursing ward the day before surgery and 20% above this blood pressure.[2] To do so, different short-acting vasopressor agents can be used, such as phenylephrine or ephedrine.[3] If existing at all, preference for either of these agents is solely based on the discretion of the attending anesthesiologist. Furthermore, ephedrine and phenylephrine are widely accepted and, when heart rate is in the normal range, applied in cardiovascular surgery on the basis of individual preference. Both agents have a different mechanism of action. Phenylephrine (an α-agonist) increases blood pressure purely by vasoconstriction, whereas ephedrine (a combined α- and β-agonist) increases blood pressure by a combination of vasoconstriction and an increase in heart rate and a subsequent rise in cardiac output.[4]

Besides the difference in systemic hemodynamics, the perfusion of the brain reacts differently. In healthy subjects, with intact CA, the frontal lobe cerebral tissue oxygenation (rSO_2) decreases during phenylephrine administration while it is preserved with ephedrine use,.[4,5] It is suggested that the increase in cardiac output observed during ephedrine use can explain this difference in rSO_2.[5] It is unknown how in the situation of impaired CA, as often observed in patients undergoing a CEA, the rSO_2 and vasomotor tone react after administration of phenylephrine or ephedrine. Thus, the optimal drug to maintain cerebral perfusion in CEA patients, with an impaired CA is unknown. If during the use of one of the two agents cerebral perfusion would be better maintained or even increased this would clearly influence the choice for the desired agent.

In our institution, we routinely monitor rSO_2 using near infrared spectroscopy (NIRS) and middle cerebral artery blood velocity (V_{MCA}) measured by transcranial Doppler (TCD) during CEA. To study the effect of both vasopressors on these parameters, we retrospectively analyzed the effect of phenylephrine and ephedrine induced changes in mean arterial pressure (MAP) on rSO_2 and V_{MCA} in 11 CEA patients. We noticed that phenylephrine and ephedrine both increased MAP and V_{MCA} in patients undergoing carotid endarterectomy. However, an increase in MAP induced by phenylephrine has a lowering effect on the rSO_2, while ephedrine had an increasing effect on the rSO_2.[6] This pilot study indicated that the use of ephedrine should be preferred above the use of phenylephrine for correction of hypotension during CEA. However, the numbers of patients were small and the dose of agent applied not standardized. Therefore, a prospective study to analyze the effect of both ephedrine and phenylephrine on cerebral perfusion during CEA is needed to make a recommendation.

Methods

Study objectives

Our primary objective is to study the influence of two routinely used drugs to increase MAP (phenylephrine and ephedrine) on cerebral oxygenation and perfusion, estimated by changes in NIRS derived rSO_2 and TCD derived V_{MCA}, in patients undergoing carotid endarterectomy. Our secondary objective is to evaluate whether the influence of phenylephrine and ephedrine on cerebral perfusion and oxygenation is different between patients with and without an adequate functioning CA.

Participants

This study is designed as a prospective randomized trial in a tertiary referral vascular centre. As shown in Figure 1 we will include all patients indicated for CEA because of a symptomatic high degree stenosis of the ICA (discussed in a multidisciplinary meeting) in the University Medical Centre Utrecht (UMCU) who needs use of vasopressor to increase MAP during CEA. To be included in the current study all patients must meet the following criteria:

1. Undergoing CEA because of a symptomatic high degree stenosis of the ICA in the UMCU.
2. Having an appropriate temporal bone window for reliable perioperative TCD monitoring.
3. Having given written informed consent.
4. Having a decrease in MAP >20% during surgery.

Patients will be excluded if they meet one of the following criteria:

1. Not having a temporal bone window appropriate for TCD measurement.
2. Not willing to give informed consent.
3. No decrease in MAP >20%.
4. A heart rate less than 50 beats per minute at the time of administration.
5. Hypersensitivity to either ephedrine of phenylephrine.

Randomization and interventions

This study is designed as a prospective randomized trial in a tertiary referral vascular center. Currently, the preference of administering either phenylephrine or ephedrine for correction of intraoperative hypotension is mainly based on the physician's preferences. For this trial randomization based on a computer-generated randomization list will be performed during CEA to counteract changes in MAP more than 20% under baseline with either

- Phenylephrine (50 to 100 µg), or
- Ephedrine (5 to 10 mg)

If hypotension persists five minutes after administration of the randomized medication, this patient will be classified as a non-responder and escape medication as preferred by the anesthesiologist will be administered. Before surgery all patients will be informed about the trial procedure. Written informed consent will be obtained from all patients. As part of the standard of care cerebral monitoring, TCD, NIRS and electroencephalography (EEG) will be provided. To quantify whether the intraoperative CA is impaired or not, the breathing frequency will be decreased from the normal 12 breaths per minute to 6 breaths per minute for an episode of three minutes.

Study parameters

Our primary study parameters are the changes in rSO_2 measured using NIRS and V_{MCA} measured using TCD. Our secondary parameter is quantification of CA.

Sample size calculation

To determine the sample size, we conducted a power analysis based on a retrospective pilot study. In this pilot study (performed in the UMCU), the response within each subject group was normally distributed. After phenylephrine administration a decrease in rSO_2 of –1.5% (± 2) per 10 mmHg increase was seen, while after ephedrine use the rSO_2 increased 1% (± 2) per 10 mmHg increase. We calculated that 14 patients in each group would be required to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.9. The Type I error probability associated with this test of this null hypothesis is 0.05. Adjusting the sample size to drop out of patients (because of bad signal quality, medical reasons), 20 patients per group will be sufficient. In our vascular centre, CEA is performed weekly. We assume two patients can be included weekly. Therefore, the estimated length of the study will be approximately six months.

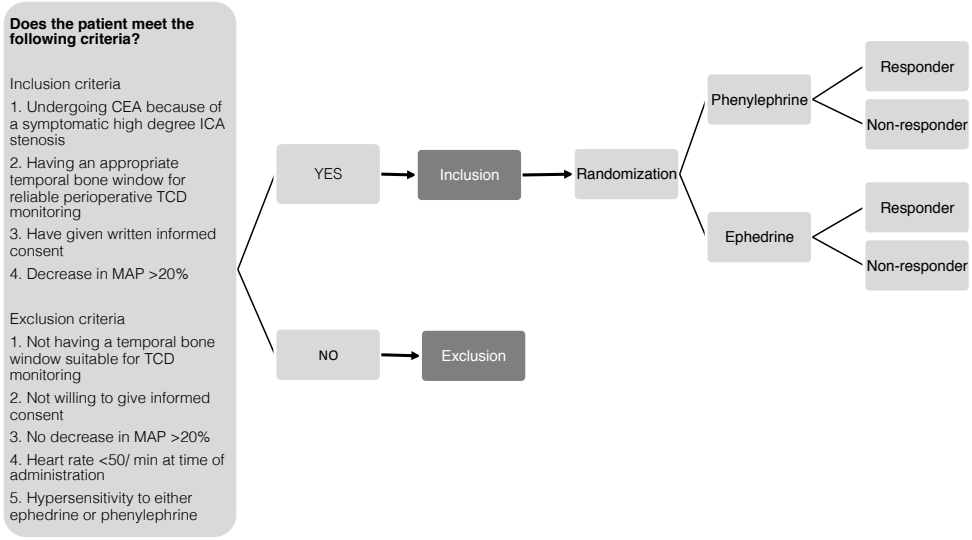

Figure 1 . Study protocol

Medication
Ephedrine is sympathomimetic amine acting directly on the α– and β-receptors and indirectly by increasing the release of norepinephrine by the sympathetic nerve endings. As with any sympathomimetic agent, ephedrine stimulates the central nervous system, the cardiovascular system, the respiratory system and the sphincters of the digestive and urinary tract. After intravenous administration, ephedrine is completely biologically available. Intravenous injections are effective within a minute and for up to about 20 minutes. Small quantities of ephedrine are metabolized in the liver, but the majority of ephedrine is excreted unchanged in the urine. Elimination of ephedrine is increased (and hence the half-life is decreased) with decreasing pH of the urine.
Phenylephrine hydrochloride is a sympathomimetic agent with mainly direct effects on adrenergic receptors. It has predominantly α-adrenergic activity and is without significant stimulating effects on the central nervous system at usual doses. After injection it produces peripheral vasoconstriction and increased arterial pressure. It also causes a baroreflex mediated bradycardia. Intravenous injections are effective within a minute and for up to about 20 minutes. Phenylephrine is metabolized in the liver by monoamine oxidase. The metabolites, their route and rate of excretion have not been identified. For both ephedrine and phenylephrine the preparation and labeling will be conducted as in the pharmacy department of the UMC Utrecht. The investigational products are part of the standard of care and, therefore, received, stored and disposed at the pharmacy of the University Medical Center Utrecht.

Intraoperative care

Anesthesia (no deviation of standard of care)
Following connection of the patient to the anesthesia monitor, an intra-arterial catheter in the radial artery is placed in each patient for arterial blood pressure measurement. Induction of anesthesia is achieved with sufentanil (0.3 to 0.7 mcg/kg) and propofol (0.5 to 2.0 mg/kg). Rocuronium (0.3 to 0.5 mg/kg) is used to facilitate tracheal intubation. Anesthesia is maintained using the volatile anesthetic sevoflurane, aiming at a Minimum Alveolar Concentration (MAC) value of 0.5 to 1. Anesthesia-related hypotension is treated with either phenylephrine or ephedrine administration (study medication). In case hypotension persists five minutes after administration of either ephedrine or phenylephrine, the patient will be classified as a non-responder and escape medication as preferred by the anesthesiologist will be administered. Outside the study period, the choice of treatment to correct hypotension will be based on the physician's preferences. After heparinization, MAP is maintained between –10% and +10% from baseline, until carotid artery cross clamping is performed. At the end of the procedure, the sevoflurane supply will be stopped, and after return of spontaneous respiration, the trachea will be extubated and the patient will be transferred to the recovery ward.

Measurement of cerebral autoregulation
To quantify whether the intraoperative CA is impaired or not, the breathing frequency is decreased from the normal 12 breaths per minute to 6 breaths per minute for an episode of three minutes. To maintain an unchanged minute alveolar ventilation of approximately six

liters per minute, the tidal volume has to be almost doubled. The intra-thoracic pressure oscillations created with this way of ventilating will be transferred to the arterial blood pressure signal since a higher intra-thoracic pressure during mechanical insufflation of the lungs will prohibit blood from entering the thoracic cavity. Approximately two heartbeats after the start of the inspiration the amount of blood delivered to the right side of the heart decreases and also the amount of blood leaving the left side of the heart (that is, cardiac output) declines. In the expiration phase the opposite occurs and cardiac output increases. This variation in cardiac output results in a concomitant oscillation in the beat-to-beat registered blood pressure and this is again transferred to the beat-to-beat V_{MCA} and rSO_2 signals. Intact CA implies that the cerebral perfusion remains constant despite changes in blood pressure. Hypothetically, this means that the V_{MCA} would remain totally unaltered despite the 6 per minute blood pressure oscillations as elicited with the ventilator in anesthetized subjects. In reality, CA behaves like a high pass filter. This means that oscillations with duration of 10 seconds in blood pressure will be present but dampened in the V_{MCA} signal. Furthermore, oscillations in V_{MCA} in this frequency area precede those in MAP by approximately two to three seconds. The better CA functions the more the amplitude of the oscillation in V_{MCA} will be dampened and the more the V_{MCA} signal precedes the blood pressure signal.

Intraoperative monitoring (no deviation of standard of care)

Blood pressure monitoring
A radial artery catheter is placed in each patient for continuous blood pressure measurement.

Cardiac output monitoring
Non-invasive arterial pressure (NAP) will be measured using the Nexfin monitor (BMEYE B.V., Amsterdam, The Netherlands), which uses an improved finger cuff technology with high sensitivity optical components and fully digital control systems. In addition, brachial arterial blood pressure is reconstructed from the measured finger arterial pressure using waveform filtering to approximate a brachial pressure wave, together with pressure level correction compensating for the finger to radial pressure difference. An appropriate size finger cuff will be applied to the mid-phalanx of the middle finger ipsilateral to the invasive blood pressure catheter. The “heart reference system”, which measures and corrects the hydrostatic difference between the finger and the heart, will be set at the arterial pressure transducer level.

NIRS
Bilateral rSO_2 measurements will be performed using Invos Cerebral Oximeter (Somanetics Corporation, Troy, MI, USA), which allows continuous monitoring of cerebral oxygenation, by penetrating the scalp and brain tissue whereby the skin, scull and other tissues are relatively transparent to near-infrared wavelengths of light. Changes in concentrations of oxygenated and deoxygenated hemoglobin are measured by a modified Beer-Lambert method and because of the different wavelengths of the oxygenated and deoxygenated hemoglobin, these can be distinguished and the ratio of oxygenated hemoglobin to total tissue hemoglobin can be defined. By using two detectors the light reflected and transmitted by the superficial extra cranial tissues is subtracted.

TCD measurement
For all TCD registrations a pulsed Doppler transducer (DWL Multidop X4, Sipplingen, Germany) gated at a focal depth of 45 to 60 mm, will be placed over the temporal bone to insonate the main stem of the ipsilateral middle cerebral artery and the contralateral anterior cerebral artery. After tracheal intubation, TCD is applied. The TCD probes are fitted in a light metal frame, which is firmly fixed to the head with two earpieces and an adjustable nose saddle. The V_{MCA} will be measured continuously.

EEG measurement
For measuring the cerebral function state and detecting signs of cerebral ischemia, used as an indication for selective shunting during CEA, electroencephalography (EEG; Micromed Inc., Treviso, Italy) is used. Prior to starting anesthesia, EEG electrodes will be applied to the patient's skull and the EEG will be continuously registered during surgery.

Carotid endarterectomy (no deviation of standard of care)
A vascular surgeon or vascular trainee under supervision will perform carotid surgery in a standardized way. Patients will receive 5,000 IU heparin three minutes before cross-clamping the carotid artery. The decision for a venous, prosthetic or bovine patch will be made by preference of the surgeon. An intraluminal shunt will selectively be used based on TCD and/or EEG criteria as described in the literature.[7]

Recruitment and consent
The principal investigator, who will inform individual participants about the study, will do patient recruitment. Informed consent will be obtained as soon as possible, but must be acquired before surgery. The patient information letter and informed consent form are attached as a separate document.

Withdrawal of individual subjects
Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Any patient with incomplete data registration can be withdrawn and replaced by a consecutive patient.

Follow-up of subjects
Patients will receive no follow-up other than regular follow-up procedures following carotid endarterectomy (outpatient clinic visit combined with duplex ultrasound of the operated carotid bifurcation).

Adverse and serious adverse events
Adverse events, serious adverse events and suspected, unexpected, serious adverse reactions will be recorded and reported according to the requirements of the accredited medical ethical committee.

Statistical analysis
The MAP, TCD and NIRS measurements will be presented as continuous variables for both

of the randomized groups. To examine the effect of either ephedrine or phenylephrine on rSO_2 and V_{MCA} an intention-to-treat analysis will be used. For this analysis all patients that received either ephedrine or phenylephrine will be included (both responders and non-responders). Subsequently, a subanalysis will be performed to compare the changes in rSO_2 and V_{MCA} per 1 mmHg increase between patients that received either ephedrine or phenylephrine. For this subanalysis only the responders will be included. To compare the relationship between the phenylephrine and ephedrine group in an rSO_2 and $V_{MCA,}$ the Student's t-test will be used. The relationship will be calculated at two different time points:

- two minutes after either phenylephrine or ephedrine administration (t_2) and
- at the moment the maximum increase in blood pressure is reached (t_{max}).

To determine whether the influence of phenylephrine and ephedrine on cerebral perfusion and oxygenation is different between patients with and without an adequate functioning cerebral auto-regulation, another subanalysis within both groups will be performed using a Student's t-test.

The statistical analysis will be performed using the Statistical Package for Social Sciences version 20.0 (SPSS Inc, Chicago, Il, USA). A probability value of less than 0.05 ($p < 0.05$) is considered significant.

Discussion

Since both phenylephrine and ephedrine have been routinely used for years and all measurements are part of the standard of care, no side effects are expected. Furthermore, there are no reports that the three-minute modification in breathing frequency described in the intervention-section is harmful. Varying breathing frequencies while maintaining minute ventilation results in larger tidal volumes and, therefore, an unchanged oxygen uptake and carbon dioxide remove, which can be measured using a pulse oximeter. Larger tidal volumes, however, result in higher airway pressures during low frequency ventilation. Inspiratory and expiratory airway pressures in healthy lungs during 6 $mL \cdot kg^{-1}$ with a normal ventilatory frequency of 12 min^{-1} are approximately 15 and 5 mmHg, respectively. During a ventilatory frequency of 6 min^{-1} inspiratory and expiratory airway pressures will rise to approximately 25 and 5 mmHg. This is comparable to airway pressures observed during laparoscopic surgery when the abdomen is inflated with carbon dioxide or during surgery with the body in 20° Trendelenburg position. Therefore, the risks for participating patients are negligible and the burden minimal.

To our best knowledge this trial represents the first attempt to evaluate the differential effects of phenylephrine and ephedrine in correction of intraoperative hypotension during CEA. If either of these drugs is shown to be superior with respect to the cerebral hemodynamics, results from our study will provide clinical trial evidence for the management of blood pressure during CEA.

Trial status

The Medical Ethics Committee (METC) of the University Medical Centre Utrecht has approved this study protocol. The trial has already been started in October 2012; the estimated length of the study will be eight months.

Acknowledgements
The Invos Cerebral Oximeter (Somanetics Corporation, Troy, MI, USA) was provided at no cost for the duration of the study by Covidien Nederland B.V., Zaltbommel, The Netherlands. However, Covidien had no influence on decisions concerning the study design and on writing the protocol.

References

(1) Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomized controlled trial. Lancet 2010; 375(9719):985-997.

(2) Stoneham MD, Thompson JP. Arterial pressure management and carotid endarterectomy. Br J Anaesth 2009; 102(4):442-452.

(3) Meng L, Cannesson M, Alexander BS, Yu Z, Kain ZN, Cerussi AE et al. Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. Br J Anaesth 2011; 107(2):209-217.

(4) Dyer RA, Reed AR, van DD, Arcache MJ, Hodges O, Lombard CJ et al. Hemodynamic effects of ephedrine, phenylephrine, and the coadministration of phenylephrine with oxytocin during spinal anesthesia for elective cesarean delivery. Anesthesiology 2009; 111(4):753-765.

(5) Nissen P, Brassard P, Jorgensen TB, Secher NH. Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension. Neurocrit Care 2010; 12(1):17-23.

(6) Pennekamp CWA, Immink RV, Moll FL, Buhre WF, De Borst GJ. Differential effects of phenylephrine and ephedrine on cerebral hemodynamics prior to carotid cross-clamping during carotid endarterectomy. Br J Anaesth 2012;109(5):831-3.

(7) Jansen C, Moll FL, Vermilion FE, van Haelst JM, Ackerstaff RG. Continuous transcranial Doppler ultrasonography and electroencephalography during carotid endarterectomy: a multimodal monitoring system to detect intraoperative ischemia. Ann Vasc Surg 1993; 7(1):95-101.

Chapter 12

Summary and general discussion

Carotid endarterectomy (CEA) results in a significant reduction in stroke in symptomatic patients with a high degree stenosis of the carotid artery.[1] However, CEA itself is associated with a perioperative stroke rate of 2% to 5%, which limits the benefit of the procedure.[2] Besides thromboembolic causes, complications that occur with CEA are often related to changes in cerebral blood flow (CBF), which is the blood supply to the brain at a given time. One of the major suppliers of blood to the brain is cross-clamped during CEA, which may result in cerebral hypoperfusion. Subsequent restoration of blood flow after the carotid stenosis is removed may induce a sudden increase in CBF, possibly resulting in hyperperfusion of the brain.[3] Finding the balance in CBF is essential in the prevention of complications of CEA, but challenging. Surgical improvements and the introduction of cerebral monitoring have significantly reduced the intraoperative stroke rate: patients at risk for cerebral ischemia can be identified with the use of cerebral monitoring and a temporary shunt can be placed, if necessary.[2]

Under normal circumstances, with mean systemic arterial pressure between ~50 and 150 mm Hg, the CBF is maintained at a constant level by cerebrovascular pressure autoregulation mechanisms, a protective intrinsic control mechanism of the cerebral circulation.[4,5] The exact physiologic mechanism of cerebral autoregulation, however, has not yet been clarified, but several interacting mechanisms are proposed to play a regulatory role in the cerebral circulation, including metabolic or chemical mechanisms, a myogenic mechanism, and a neurogenic mechanism.[6] Although the exact role of the neurogenic mechanism is unclear, the nerve supply to the major cerebral arteries, which consists of sympathetic, parasympathetic, and sensory nerve fibers, is thought to play a regulatory role in the cerebral circulation. Cerebrovascular disease may result in flow-related alterations in nerve density. Because carotid artery stenosis has been associated with an impaired cerebral autoregulation,[7-9] we tried to evaluate the effect of bilateral carotid ligation on the nerve supply in an animal model. The results, which are described in **Chapter 2**, were remarkable: bilateral carotid ligation did not lead to hypoperfusion of the brain but did lead to redistribution of blood flow via the posterior circulation of the brain. Apparently, the adaptation range of the vascular system is extraordinarily high. Nerve density is dynamic, with the capacity to adapt to altering functional demands[10]; however, we also showed that these changes are concurrent with morphologic changes.

Conversely, in patients who are admitted for CEA, longstanding hypoperfusion due to carotid artery disease may have induced a decrease in nerve density of the major cerebral arteries. This can be hypothesized to be the underlying mechanism of the cerebral hypoperfusion syndrome (CHS), which may occur due to a sudden increase in CBF after restoration of blood flow when the carotid artery declamped. A reduced nerve supply of the basal cerebral arteries may hamper vasoconstriction of the cerebral vessels in response to an increased blood flow. It may therefore be highly interesting to develop a hypoperfusion animal model and assess for changes in nerve density and CO_2 reactivity. Improved understanding of the pathophysiologic mechanism of CHS may provide clues for future therapies.

Until this mechanism is clarified, identification of patients at risk for complications related to CEA is important to reduce CEA-associated morbidity and mortality.

Preoperative risk stratification of patients may allow the identification of patients who are at increased risk for complications of CEA. In **Chapter 3**, we found that that preoperative assessment of the cerebripetal arteries and of the configuration of the circle of Willis, but not

clinical characteristics, allow preoperative identification of patients who are unlikely to tolerate carotid cross-clamping during CEA. We also analyzed potentials risk factors for CHS but could not find an association between patient clinical characteristics and the onset of CHS postoperatively. A preoperative diminished cerebrovascular reactivity or reserve capacity measured by the acetazolamide test has been shown to be a risk factor for postoperative development of CHS.[11;12] The clinical applicability of these risk factors is, however, limited by several disadvantages, including radiation exposure, high procedural costs, and the expected high numbers of patients who have to be screened to prevent one case of CHS. With the current preoperative assessment, it is not possible to assess preoperatively whether a patient will not tolerate cross-clamping and requires shunt placement or will develop CHS. Perioperative monitoring therefore remains essential, also because cerebral monitoring during CEA can be used to detect shunt malfunction. The routine use of shunting is a subject of debate. There are several arguments against the use of routine shunts, including its associated morbidity.[13] However, we believe that the individual surgeon should select the method with which he or she is most comfortable.

Studies comparing CEA under general anesthesia and local anesthesia have not shown significant differences in the rates of procedural stroke or death. By operating with the patient under local anesthesia, awake testing can be used to indicate cerebral ischemia,[14] but many surgeons prefer to operate with the patient under general anesthesia. If general anesthesia is used, several methods of monitoring can be used for detection of hypoperfusion, including electroencephalography (EEG) and transcranial Doppler sonography (TCD), of which the latter can also be used for identification of patients at risk for CHS.[15-19] An increase in blood velocity measured the middle cerebral artery (V_{mca}) of >100% at 3 minutes after declamping the ICA, compared with the preclamping V_{mca}, is commonly used.[16;20] However, this intraoperative measurement will not identify all patients at risk for CHS, and others may be treated unnecessarily with invasive antihypertensive drugs and invasive blood pressure monitoring in the medium care unit.

In **Chapter 6**, we describe that additional preoperative and early postoperative TCD measurements allow improved identification of patients developing CHS, while the number of patients falsely identified and treated unnecessarily is negligibly small. To reduce CHS-related morbidity and mortality, we therefore recommend a preoperative and postoperative TCD measurement. EEG and TCD have several disadvantages, however, because both techniques require specialized personnel, are time-consuming, and are associated with additional costs. Moreover, TCD requires the availability of a suitable temporal bone window. With the use of near-infrared spectroscopy (NIRS) to measure regional oxygen saturation (rSO_2), these disadvantages can be overcome.[21] In **Chapter 8** and **Chapter 9**, we studied whether NIRS could reliably replace EEG for the detection of cerebral hypoperfusion requiring cross-clamping and whether NIRS could replace TCD for the identification of patients at risk for CHS, respectively. In **Chapter 8**, we evaluated NIRS and TCD compared with EEG to guide selective shunt use during CEA performed with the patient under general anesthesia. We found moderate positive predictive values but high negative predictive values for both techniques. We therefore propose that for clinicians who routinely shunt, NIRS and TCD could both be helpful to reduce unnecessary shunt use and thereby reduce shunt-related complications. Compared with EEG and TCD, NIRS is associated with low costs and may be preferred. However, because the number of false-positive results using NIRS is high, further

data collection and analysis is required to define the most appropriate threshold.
Based on the additional value of preoperative and postoperative TCD measurements discussed in **Chapter 6**, we also analyzed the value of postoperative NIRS-measured rSO_2 values in **Chapter 9**. Increased rSO_2 values were associated to the occurrence of CHS. When TCD and NIRS were used simultaneously, the highest positive predictive values were found, and therefore, a bimodality strategy is recommended. NIRS monitoring alone, however, can safely be used to exclude patients at risk of developing CHS to prevent superfluous treatment, and NIRS is a good alternative when a TCD signal cannot be obtained. Whether NIRS should be implemented in clinical practice also depends on its cost-effectiveness, which to date remains unclear. It might therefore be interesting to compare the costs of NIRS with the costs of the currently used techniques in a cost-effectiveness analysis.
If inadequate cerebral perfusion is detected by NIRS or other monitoring techniques during CEA, blood pressure has to be increased, because poor arterial pressure control has been associated with increased morbidity and mortality after CEA.[22-27] This can in part be explained by the relatively high comorbidity in these patients but also by watershed infarctions due to inadequate cerebral perfusion. In many patients undergoing CEA, cerebral perfusion has become dependent on arterial pressure because of an impaired cerebral autoregulation.[7-9]
Several vasoactive agents can be used to increase blood pressure. In **Chapter 10**, we describe that two different commonly used agents, phenylephrine and epinephrine, have a different effect on the cerebral hemodynamics in patients undergoing CEA. When phenylephrine is used, the blood pressure increased, while a decrease in rSO_2 was observed. An epinephrine-induced increase in blood pressure, on the other hand, was accompanied by an increased or unchanged rSO_2 and might therefore be preferred over phenylephrine. A randomized controlled trial, of which the protocol is described in **Chapter 11**, is warranted to determine the optimal agent to increase blood pressure during CEA and to find out whether this effect is confined to patients with an impaired autoregulation.
Although carotid artery stenting is gaining acceptance in subgroups, CEA remains the standard intervention for symptomatic carotid artery stenosis.[1;28;29] Ever since the first CEA performed in 1954, many applications have been proposed to improve the risk-to-benefit ratio of CEA. This thesis aimed to contribute to these efforts by improving the understanding of pathophysiologic mechanisms, risk stratification, diagnosing, and prevention of CEA-related complications. The variety of aspects involved in the perioperative management for CEA illustrates the importance of a multidisciplinary approach.

References

(1) Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet 2010; %20 ;375(9719):985-997.

(2) de Borst GJ, Moll FL, van de Pavoordt HD, Mauser HW, Kelder JC, Ackerstaf RG. Stroke from carotid endarterectomy: when and how to reduce perioperative stroke rate? Eur J Vasc Endovasc Surg 2001; 21(6):484-489.

(3) van Mook WN, Rennenberg RJ, Schurink GW, van Oostenbrugge RJ, Mess WH, Hofman PA et al. Cerebral hyperperfusion syndrome. Lancet Neurol 2005; 4(12):877-888.

(4) Lassen NA. Cerebral blood flow and oxygen consumption in man. Physiol Rev 1959; 39(2):183-238.

(5) Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. Cerebrovasc Brain Metab Rev 1990; 2(2):161-192.

(6) Regulation of the circulation of the brain. In: Bevan RD, Bevan JA, editors. The human brain circulation: functional changes in disease. Totowa, New Jersey: Humana Press; 1994. 291-318.

(7) Diehl RR, Linden D, Lucke D, Berlit P. Phase relationship between cerebral blood flow velocity and blood pressure. A clinical test of autoregulation. Stroke 1995; 26(10):1801-1804.

(8) Reinhard M, Roth M, Muller T, Czosnyka M, Timmer J, Hetzel A. Cerebral autoregulation in carotid artery occlusive disease assessed from spontaneous blood pressure fluctuations by the correlation coefficient index. Stroke 2003; 34(9):2138-2144.

(9) Reinhard M, Gerds TA, Grabiak D, Zimmermann PR, Roth M, Guschlbauer B et al. Cerebral dysautoregulation and the risk of ischemic events in occlusive carotid artery disease. J Neurol 2008; 255(8):1182-1189.

(10) Bleys RL, Cowen T. Innervation of cerebral blood vessels: morphology, plasticity, age-related, and Alzheimer's disease-related neurodegeneration. Microsc Res Tech 2001; 53(2):106-118.

(11) Hosoda K, Kawaguchi T, Ishii K, Minoshima S, Shibata Y, Iwakura M et al. Prediction of hyperperfusion after carotid endarterectomy by brain SPECT analysis with semiquantitative statistical mapping method. Stroke 2003; 34(5):1187-1193.

(12) Ogasawara K, Yukawa H, Kobayashi M, Mikami C, Konno H, Terasaki K et al. Prediction and monitoring of cerebral hyperperfusion after carotid endarterectomy by using single-photon emission computerized tomography scanning. J Neurosurg 2003; 99(3):504-510.

(13) Rerkasem K, Rothwell PM. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). Cochrane Database Syst Rev 2009;(4):CD000190.

(14) Benjamin ME, Silva MB, Jr., Watt C, McCaffrey MT, Burford-Foggs A, Flinn WR. Awake patient monitoring to determine the need for shunting during carotid endarterectomy. Surgery 1993; 114(4):673-679.

(15) Blume WT, Ferguson GG, McNeill DK. Significance of EEG changes at carotid endarterectomy. Stroke 1986; 17(5):891-897.

(16) Dalman JE, Beenakkers IC, Moll FL, Leusink JA, Ackerstaff RG. Transcranial Doppler monitoring during carotid endarterectomy helps to identify patients at risk of postoperative hyperperfusion. Eur J Vasc Endovasc Surg 1999; 18(3):222-227.

(17) Jansen C, Vriens EM, Eikelboom BC, Vermeulen FE, van GJ, Ackerstaff RG. Carotid endarterectomy with transcranial Doppler and electroencephalographic monitoring. A prospective study in 130 operations. Stroke 1993; 24(5):665-669.

(18) Jansen C, Sprengers AM, Moll FL, Vermeulen FE, Hamerlijnck RP, van GJ et al. Prediction of intracerebral haemorrhage after carotid endarterectomy by clinical criteria and intraoperative transcranial Doppler monitoring. Eur J Vasc Surg 1994; 8(3):303-308.

(19) Powers AD, Smith RR. Hyperperfusion syndrome after carotid endarterectomy: a transcranial Doppler evaluation. Neurosurgery 1990; 26(1):56-59.

(20) Ogasawara K, Inoue T, Kobayashi M, Endo H, Yoshida K, Fukuda T et al. Cerebral hyperperfusion following carotid endarterectomy: diagnostic utility of intraoperative transcranial Doppler ultrasonography compared with single-photon emission computed tomography study. AJNR Am J Neuroradiol 2005; 26(2):252-257.

(21) Moritz S, Kasprzak P, Arlt M, Taeger K, Metz C. Accuracy of cerebral monitoring in detecting cerebral ischemia during carotid endarterectomy: a comparison of transcranial Doppler sonography, near-infrared spectroscopy, stump pressure, and somatosensory evoked potentials. Anesthesiology 2007; 107(4):563-569.

(22) Asiddao CB, Donegan JH, Whitesell RC, Kalbfleisch JH. Factors associated with perioperative

complications during carotid endarterectomy. Anesth Analg 1982; 61(8):631-637.
(23) Naylor AR, Ruckley CV. The post-carotid endarterectomy hyperperfusion syndrome. Eur J Vasc Endovasc Surg 1995; 9(4):365-367.
(24) Reigel MM, Hollier LH, Sundt TM, Jr., Piepgras DG, Sharbrough FW, Cherry KJ. Cerebral hyperperfusion syndrome: a cause of neurologic dysfunction after carotid endarterectomy. J Vasc Surg 1987; 5(4):628-634.
(25) Schroeder T, Sillesen H, Boesen J, Laursen H, Sorensen P. Intracerebral haemorrhage after carotid endarterectomy. Eur J Vasc Surg 1987; 1(1):51-60.
(26) Stoneham MD, Thompson JP. Arterial pressure management and carotid endarterectomy. Br J Anaesth 2009; 102(4):442-452.
(27) Sundt TM, Jr., Sharbrough FW, Piepgras DG, Kearns TP, Messick JM, Jr., O'Fallon WM. Correlation of cerebral blood flow and electroencephalographic changes during carotid endarterectomy: with results of surgery and hemodynamics of cerebral ischemia. Mayo Clin Proc 1981; 56(9):533-543.
(28) Kakisis JD, Avgerinos ED, Antonopoulos CN, Giannakopoulos TG, Moulakakis K, Liapis CD. The European Society for Vascular Surgery guidelines for carotid intervention: an updated independent assessment and literature review. Eur J Vasc Endovasc Surg 2012; 44(3):238-243.
(29) Liapis CD, Bell PR, Mikhailidis D, Sivenius J, Nicolaides A, Fernandes e Fernandes et al. ESVS guidelines. Invasive treatment for carotid stenosis: indications, techniques. Eur J Vasc Endovasc Surg 2009; 37(4 Suppl):1-19.

Chapter 13

Summary in Dutch

Nederlandse samenvatting

Het brein is een van de best doorbloede organen van het menselijk lichaam. De bloedvoorziening wordt voor het grootste deel verzorgd door de twee halsslagaders (arteriae carotides), die naar de voorzijde van het brein verlopen. Twee kleine slagaders, die langs de nekwervels verlopen (arteriae vertebrales) verzorgen het overige deel van de bloedvoorziening. Via een ring van bloedvaten op de hersenbasis, de cirkel van Willis, worden de linker en rechter bloedcirculatie en de voorste en achterste bloedcirculatie met elkaar verbonden.
Het is cruciaal om de doorstroming van het bloed naar de hersenen op peil te houden, aangezien een onderbreking van de bloedtoevoer al snel kan leiden tot ernstige hersenschade. Een intrinsiek regelmechanisme, cerebrale autoregulatie genoemd, zorgt ervoor dat ondanks schommelingen in bloeddruk de bloedstroom in de hersenen gelijk blijft. Het precieze werkingsmechanisme is niet geheel opgehelderd, maar men veronderstelt dat de zenuwen in de vaatwand van de hersenvaten hierbij een belangrijke rol te spelen.
In de in **hoofdstuk 2** beschreven studie hebben wij het effect van veranderingen in bloedtoevoer naar het brein op de zenuwvoorziening in de vaatwand nader onderzocht. Wij hebben daarbij gebruik gemaakt van een diermodel waarbij beiderzijds de halsslagaders van ratten werden afgebonden en de ratten driemaal een MRI (magnetic resonsance imaging: een radiologisch onderzoek) scan ondergingen om veranderingen in morfologie te observeren en veranderingen in doorbloeding van het brein te meten. Wij maten vier weken na de ingreep geen verminderde doorbloeding van het brein maar constateerden wel een redistributie van bloedstromen via de achterste bloedcirculatie. Tevens bleek de diameter van de vaten sterk toegenomen evenals de zenuwdichtheid. Deze bevinding ondersteunt de gedachte dat de zenuwvoorziening in de vaatwand een functionele rol speelt in de regulatie van de bloeddoorstroming van het brein.
Bij een ernstige vernauwing van een van de halsslagaders of door het losschieten van een stolsel kan de bloedtoevoer tijdelijk worden onderbroken, waardoor neurologische symptomen in de vorm van een transient ischemic attack (TIA) of een beroerte kunnen optreden. Om het risico op een nieuwe TIA of beroerte te verminderen is bij dergelijke patiënten met een vernauwing van een van de halsslagaders van meer dan 70% revascularisatie van de vernauwde halsslagader door middel van een operatie, een carotisendarteriëctomie (CEA), geïndiceerd. Een CEA is echter niet geheel zonder risico. In circa 3% van de procedures treedt een complicatie op in de vorm van een beroerte. Als een beroerte tijdens de operatie ontstaat wordt dit een intraoperatieve beroerte genoemd en als een patiënt na een geslaagde operatie een beroerte krijgt, spreken we van een postoperatieve beroerte.
Om complicaties in een vroeg stadium op te kunnen sporen kan gebruik worden gemaakt van hersenmonitoring. De verschillende typen van monitoring en hun rol tijdens een CEA hebben wij beschreven in **hoofdstuk 4**.
In het UMCU wordt tijdens de operatie met behulp van transcraniële Doppler (TCD) monitoring de snelheid van de bloedstroom naar de hersenen gemeten en wordt met behulp van elektro-encefalografie (EEG) de hersenfunctie bepaald. Tijdens deze operatie wordt de halsslagader tijdelijk afgeklemd om de vernauwing met de binnenwand te kunnen verwijderen,. Als de bloedtoevoer tijdens het afklemmen niet goed wordt overgenomen via de cirkel van Willis kan als tijdelijke omleiding een shunt worden geplaatst, waardoor de doorstroming van het bloed gehandhaafd blijft. Aangezien het plaatsen van een shunt op

zichzelf ook een complicatie in de vorm van het losschieten van stolsels of het scheuren van de vaatwand tot gevolg kan hebben, wordt in het UMCU selectief gebruik gemaakt van een shunt. Op basis van veranderingen in het EEG die optreden tijdens het plaatsen van de vaatklem, wordt besloten al dan niet een shunt te plaatsen.
Om op basis van patiënteigenschappen en beeldvorming (CT of MRI) voor de operatie te kunnen voorspellen welke patiënten het afklemmen van de halsslagader niet zullen verdragen en dientengevolge een shunt nodig hebben, hebben wij het in **hoofdstuk 3** beschreven predictiemodel ontwikkeld. Afwijkingen in de cirkel van Willis en een volledig dichte halsslagader aan de andere zijde bleken geassocieerd te zijn met een hogere kans op een shunt. Met behulp van dit model is het in de toekomst mogelijk om op basis van preoperatieve beeldvorming vooraf een inschatting te maken van het risico op shuntgebruik tijdens een CEA, waardoor het risico op intraoperatieve complicaties beter kan worden ingeschat.
Postoperatieve beroertes worden meestal veroorzaakt door een stolsel of een te sterke doorbloeding van de hersenen na de operatie, het hyperperfusiesyndroom, dat wordt gekenmerkt door een combinatie van symptomen en ten minste een verdubbeling van de bloeddoorstroming voor de operatie, gemeten met TCD. Met behulp van TCD kan tevens worden voorspeld welke patiënten een verhoogde kans hebben op het ontwikkelen van het hyperperfusiesyndroom. Een overzicht hiervan is opgenomen in **hoofdstuk 5**. De huidige standaard voor het identificeren van patiënten die vanwege een verhoogd risico preventief behandeld dienen te worden voor het hyperperfusiesyndroom, is een TCD-meting tijdens de operatie.
In **hoofdstuk 6** laten wij zien dat een additionele TCD-meting in de vroege fase na de operatie een veel gevoeligere en specifiekere methode is voor het identificeren van patiënten met een verhoogd risico, zodat de behandeling gerichter kan worden toegepast.
Een belangrijk nadeel van monitoring met behulp van TCD en EEG is de behoefte aan ervaren personeel wat hoge kosten met zich meebrengt. Daarnaast is bij 15% van de patiënten een TCD-meting niet mogelijk vanwege het ontbreken van een zogenaamd akoestisch venster in de schedel, waardoor de geluidsgolven de bloedvaten in het hoofd niet kunnen bereiken.
Mogelijk biedt near infrared spectroscopy (NIRS), een techniek waarmee de lokale zuurstofsaturatie van het brein gemeten wordt, een goed alternatief voor de bestaande cerebrale monitoring, aangezien NIRS gemakkelijk toepasbaar is zonder extra personeel. De potentiële waarde van NIRS rondom CEA op basis van de beschikbare literatuur bespreken wij in **hoofdstuk 7**.
Vervolgens hebben wij in de **hoofdstukken 8 en 9** NIRS- metingen met EEG- en TCD-monitoring vergeleken en onderzocht of NIRS van toegevoegde waarde kan zijn bij het voorkomen van beroertes tijdens en na een CEA. In hoofdstuk 8 beschrijven wij dat veranderingen in NIRS, die optreden tijdens het plaatsen van de klem op de halsslagader tijdens CEA, redelijk goed overeenkomen met tegelijkertijd optredende veranderingen in het EEG. Met behulp van NIRS kan dus redelijk betrouwbaar worden bepaald of een patiënt een shunt nodig heeft tijdens het afklemmen van de halsslagader. Tevens kan betrouwbaar worden vastgesteld welke patiënten geen shunt nodig hebben. **Hoofdstuk 9** laat zien dat met behulp van NIRS het risico op het ontwikkelen van het hyperperfusiesyndroom na een CEA veilig worden uitgesloten. Voor patiënten bij wie een TCD meting niet mogelijk is kan NIRS dus een goed alternatief zijn, waardoor morbiditeit en mortaliteit ten gevolge van het

hyperperfusiesyndroom kan worden beperkt.
Als tijdens de operatie een verminderde doorbloeding van de hersenen optreedt, dient de bloeddruk verhoogd te worden, aangezien een slechte bloeddrukregulatie tijdens de procedure geassocieerd is met een verhoogde morbiditeit en mortaliteit. Er zijn verschillende middelen die gebruikt kunnen worden om de bloeddruk te verhogen tijdens een CEA, met een vergelijkbaar effect op de bloeddruk maar met een verschillend effect op de zuurstofsaturatie. In **hoofdstuk 10** beschrijven wij dat een efedrinegeïnduceerde stijging van de bloeddruk samengaat met een stijgende of gelijkblijvende zuurstofsaturatie van het brein, terwijl een fenylefrinegeïnduceerde bloeddrukstijging leidt tot een dalende zuurstofsaturatie van het brein. Als de bloeddruk wordt verhoogd om de doorbloeding van het brein te verbeteren, lijkt efedrine dus het te prefereren middel. Echter, voor een harde uitspraak gedaan kan worden over de keuze voor het middel dient een prospectief gerandomiseerde studie plaats uitgevoerd te worden. Deze studie, waarvan het protocol beschreven staat in **hoofdstuk 11**, hopen wij binnen enkele maanden af te ronden.

Chapter 14

Review committee

Dankwoord

Curriculum vitae auctoris

Review committee

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Dankwoord

Dit proefschrift was zeker niet tot stand gekomen zonder de hulp van vele anderen. Een aantal van hen wil ik in het bijzonder bedanken:

Prof. dr. F.L. Moll, als student kwam ik bij u omdat ik graag onderzoek wilde doen bij de vaatchirurgie en sindsdien heb ik me altijd zeer welkom gevoeld. Ik bewonder uw vermogen om alles te overzien en direct tot de kern te komen. Ik ben u zeer dankbaar voor het in mij gestelde vertrouwen.

Prof. dr. W.F. Buhre, veel dank voor de mogelijkheden die u mij hebt geboden om dit promotietraject te starten en om uiteindelijk de PEPPER trial voort te zetten.

Prof. dr. R.L.A.W. Bleys, beste Ronald, wat ben ik blij dat jij als promotor bij mijn onderzoek bent betrokken. Heel veel dank voor het in mij gestelde vertrouwen en de mogelijkheid om mijn proefschrift uit te breiden met een dierexperimentele studie. Je betrokkenheid, interesse en de tijd die je altijd wilde vrijmaken om iets te bespreken of even mee te kijken, heb ik zeer gewaardeerd.

Dr. G.J. de Borst, beste GJ, vanaf het moment dat ik als student bij jou kwam was ik geïnspireerd door jouw enthousiasme voor onderzoek. Ik ben je erg dankbaar voor je toegankelijkheid, tijd en steun: ondanks de tegenslagen die met het dierexperimentele werk gepaard gingen wist je mij steeds weer te motiveren. De manier waarop jij wetenschap, kliniek en privé combineert, bewonder ik zeer.

Prof. dr. L.J. Kappelle, uw waardevolle suggesties en kritische blik bij de opzet en het schrijven van de artikelen hebben veel bijgedragen aan meerdere artikelen. Dank voor uw bereidheid zitting te nemen in de leescommissie van dit proefschrift.

Prof. dr. M.L. Bots, beste Michiel, zeer veel dank voor je epidemiogische sturing bij de opzet, analyses en het opschrijven van meerdere studies en je bereidheid zitting te nemen in de leescommissie van dit proefschrift.

Prof. dr. J.T.A. Knape en prof. dr. W.H. Mess, hartelijk dank voor uw interesse en bereidheid deel zitting te nemen in de beoordelingscommissie van dit proefschrift.

Dr. R.V. Immink, beste Rogier, je tomeloze enthousiasme, grote wetenschappelijke interesse en kritische commentaren hebben veel bijgedragen aan dit proefschrift. Veel dank voor onze fijne samenwerking.

Dr. J. Hendrikse en dr. P.J. van Laar, beste Jeroen en Peter Jan, veel dank voor het analyseren van de 500 cirkels en jullie waardevolle suggesties bij het schrijven van hoofdstuk 3.

Dr. H.M. den Ruijter, beste Hester, veel dank voor de prettige samenwerking en je toegankelijkheid. Jouw epidemiologische input is van grote waarde geweest en hebben

verscheidene artikelen naar een hoger niveau getild.

Dr. R.G.A. Ackerstaff, dank voor uw ervaren en kritische blik op het TCD artikel.
Dr. S.C. Tromp, beste Selma, veel dank voor je hulp en grote betrokkenheid bij het opzetten en schrijven van de TCD (vervolg-) studie en onze prettige samenwerking.

Dr. R.M. Dijkhuizen, beste Rick, veel dank voor je hulp en begeleiding tijdens het opzetten, uitvoeren en opschrijven van onze dierstudie. Dr. A. van der Toorn, beste Annette, heel veel dank voor het scannen van de dieren, het analyseren van de data en je hulp bij het opschrijven van onze studie.

Afdeling KNF en in het bijzonder Nizare Henriquez, Daniel van Vriesland, Anja Ezendam, Barbara Piazza en Elise Wijburg. Ik ben jullie heel erg dankbaar voor de vele TCD-metingen die jullie hebben verricht tijdens en na de honderden CEA's, waarvoor jullie soms langer moesten blijven. Ik heb onze prettige samenwerking altijd zeer gewaardeerd.

Medewerkers van de afdeling anatomie, hartelijk dank voor jullie gastvrijheid en interesse in mijn onderzoek. Jan Willem en Suzanne, heel veel dank voor jullie geduld en hulp met alle kleuringen, zonder jullie was het nooit op tijd af geweest. Dr. T.A.P. Roeling, beste Tom, veel dank voor je hulp met de beeldanalyses.

Alle medewerkers van het GDL en in het bijzonder Anja van der Sar, veel dank voor je ondersteuning tijdens onze dierstudie.

René van de Vosse, dank voor je technische ondersteuning bij het gebruik van Signalbase. En sorry, ik kan er ook niks aan doen dat de outputbestanden steeds van format wijzigen.

Overige vaatchirurgen: dr. Van Herwaarden, dr. Toorop, drs. Berger drs. Hazenberg en dr. Waasdorp, dank voor jullie interesse en behulpzaamheid op de OK tijdens de metingen.

Cobie en Susan, heel veel dank voor jullie hulp en interesse.

Anesthesisten, anesthesiemedewerkers en recoveryverpleegkundigen, hartelijk dank voor jullie behulpzaamheid tijdens het uitvoeren van de metingen op de OK en de recovery.

Collega's en in het bijzonder mijn kamergenoten, Emily Postma, Margriet Fokkema, Jakob Kist, Laurien Waaijer, Klaas Govaert, Anne den Hartog, Charlotte van Kessel, Lutske Lodewijk, Jasper van Keulen, Ernst Steller, Benjamin Emmink, Roy Verhage, Sjoerd Nell, Martin Teraa, Pieter van der Sluis, Peter Paul Wisman, Okan Bastian, Marjolein Heeres, Herman Zandvoort, Bas Nelissen, Rob Hurks, Dave Koole, Guus van Lammeren, Kathelijne Groeneveld, Joyce Vrijenhoek, Samira Fegrachi en Femke Mauritz, heel veel dank voor alle gezelligheid, humor en interesse in mijn onderzoek en daarbuiten. Bedankt voor de leuke tijd die ik met jullie heb gehad.

Mijn paranimfen: Anika Tsuchida en Hanna Talacua. Lieve Anika, er zijn maar weinig woorden

nodig om elkaar te begrijpen. Lieve Hanna, er zijn maar weinig mensen die mij zo goed kennen als jij. Voor mij zijn jullie het voorbeeld van onvoorwaardelijke vriendschap en ik vind het fantastisch dat jullie mijn paranimfen zijn. Heel veel dank.

Lieve papa en mama, heel veel dank voor jullie onvoorwaardelijke liefde en steun en alle mogelijkheden die jullie mij hebben geboden om mij steeds verder te ontwikkelen. Lieve Mariette, ook al vliegen we elkaar als echte zussen soms in de haren, ik ben heel blij dat jij mijn zus bent. Ik vind het geweldig dat je vanuit Mexico hiernaartoe bent gekomen voor mij.

Lieve Sebastiaan, vanaf het eerst moment dat wij elkaar leerden kennen was het eigenlijk al feest. Heel veel dank voor al je liefde, geduld, steun, humor en relativeringsvermogen. Ik hoop op nog een heel lang leven samen.

Curriculum vitae auctoris

Claire Pennekamp was born in Gouda, the Netherlands, on May 18th 1985. After graduating at the Coornhert Gymnasium in Gouda, she initiated her medical study at Utrecht University. In 2007 she started scientific research on cerebral monitoring during carotid endarterectomy which has become the basis for this thesis.
After completing medical school at the end of 2009 she continued this scientific reseach as a PhD student supervised by prof. dr. F.L. Moll (department of vascular surgery), prof. dr. W.F. Buhre (department of anesthesiology), prof. dr. R.L.A.W. Bleys (department of anatomy) and dr. G.J. de Borst (department of vascular surgery). Parts of the work described in this thesis were presented and awarded on (inter)national congresses.
From October 2013 she will start her residency at the department of ophtalmology at the Academic Medical Center in Amsterdam, under supervision of prof. dr. M. Ph. Mourits.