Study protocol – Prospective case-control trial – Impact of significant carotid stenosis on retinal perfusion measured with automated retinal oximetry

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Background. Large vessel carotid stenosis is a significant cause of ischaemic stroke. Indications for surgical revascularisation depend on the severity of the stenosis and clinical symptoms. However, mild symptoms such as TIA (Transient ischaemic attack), amaurosis fugax or minor stroke precede large strokes in only 15% of cases.
Aim. The aim of this prospective study is to evaluate whether retinal perfusion is impacted in significant carotid stenosis. Automated retinal oximetry will be used to better assess perfusion in the post-stenotic basin. We presume the more stenotic the blood vessel, the more reduced the retinal perfusion is, resulting in adaptive changes such as greater arteriovenous saturation difference due to greater oxygen extraction. This could broaden the indication spectrum for revascularisation for carotid stenosis.
Methods. We plan to enroll yearly 50 patients with significant carotid stenosis and cross-examine them with retinal oximetry. The study group will provide stenotic vessels and, non-stenotic vessels will form the control group. Patients with significant carotid stenosis will undergo an MRI (Magnetic Resonnance imaging) examination to determine the presence of asymptomatic recent ischaemic lesions in the stenotic basin, and the correlation to oximetry parameters.
Statistics. The stenosis severity and retinal oximetry parameters will be compared for study and control groups with a threshold of 70%, respectively 80% and 90% stenosis. Results will be then reevaluated with emphasis on MRI findings in the carotid basin.
Conclusion. This prospective case control study protocol will be used to launch a multicentre trial assessing the relationship between significant carotid stenosis and retinal perfusion measured with automated retinal oximetry. Despite these differences, the findings indicate the potential of retinal oximetry for noninvasive real-time measurements of oxyhaemoglobin saturation in central nervous system vessels. Following calibration upgrade and technological improvement, verification retinal oximetry may potentially be applied to critically ill and anaesthesia care patients. The study on combined scanning laser ophthalmoscope and retinal oximetry supports the feasibility of the technique for oximetry analysis in newly born babies.
Trial Registration: ClinicalTrials.gov, ID: NCT06085612

Key words: ischaemic stroke, carotid stenosis, automated retinal oximetry, arterio-venous difference, magnetic resonance imaging

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INTRODUCTION

Ischemic stroke is a devastating neurological condition, second most frequent cause of death and a leading cause of long-term invalidity[1]. The incidence of ischaemic strokes in the Czech Republic is 241/100000 inhabitants per year[2]. Over 3600 patients a year develop ischaemic stroke due to significant carotid stenosis. Correctly timed surgical intervention significantly reduces a patients' risk of stroke recurrence in one procedure, compared to the treatment of other causes of stroke such as atrial fibrillation[3].

Stenosis under 50% is not a significant risk. The 10–15 year cumulative risk of a stroke event is 5.7% and 8.7% respectively. However, stenosis over 50% represents a higher risk of stroke – 9.6%, and 16.6% respectively[4]. The risk of stroke depends on the preceeding stenosis symptoms. While asymptomatic stenosis represents only a 1.5times higher risk of large stroke compared to healthy populations, the 5-year risk of stroke recurrence in the symptomatic stenosis varies from 10% to more than 50% depending on other factors, as summarized in Fig. 1. (ref.[5,6]).

This would mean that symptoms corresponding to an ischaemic event are a key variable in predicting stroke recurrence risk. However, classic symptoms such as TIA, amaurosis fugax, or minor stroke are detectable in only 15% of cases[7].

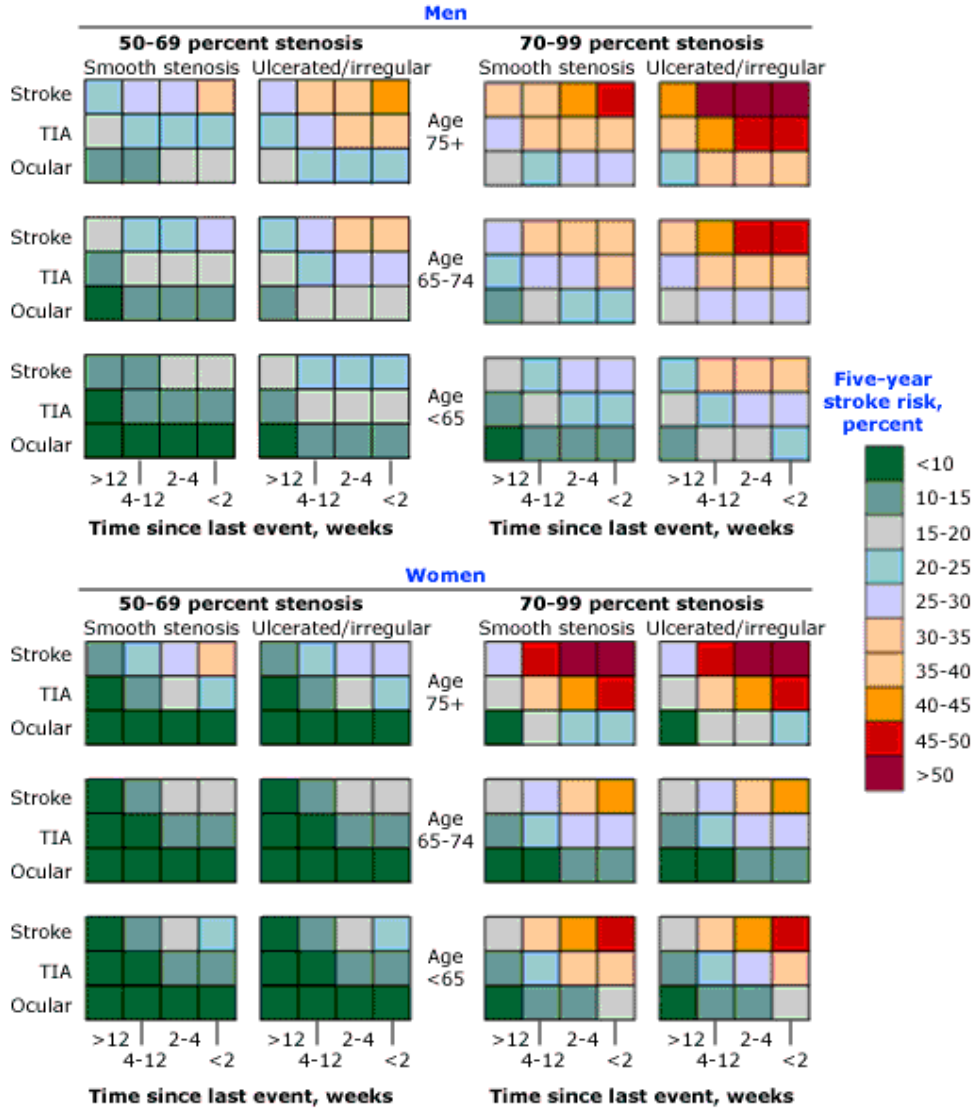

Fig. 1. Analysis of the ischaemic event. in various risk factors, Rothwell PM et al. 2005.

The research is now shifting towards developing methods with the ability to uncover clinically inapparent symptomatic events allowing more patients to undergo carotid revascularisation and thus reduce the global burden of stroke. Following progress in neuroradiology, a combination of several MRI protocols such as: perfusion-weighted imaging, total cerebral blood volume, absence of atherosclerotic plaque calcification, severity of vascular leukoencephalopathy, and detection of intramural vascular hemoglobin deposits appear to be congruent with the general risk of ischaemic stroke recurrence[8].

However, there are pragmatic limitations to MRI examinations due to financial, temporal, and logistical challenges for both patient and healthcare systems.

Automated retinal oximetry on the other hand, is a technology enabling direct evaluation of perfusion parameters in retinal blood vessels. These vessels are the terminal part of the carotid basin and retinal oximetry is the only available method for directly analyzing these poststenotic vessels.

The main physical principle of retinal oximetry is based on the different absorption properties of oxyhemoglobin and deoxyhemoglobin. While oxyhemoglobin does not absorb wavelengths of 570 nm, deoxyhemoglobin does. Both molecules absorb wavelengths of 600 nm (ref.[9]). Dual absorption maximum is later used to calculate oxygen saturation thus differentiating arteries from veins.

There is altered oxygen metabolism in various systemic diseases such as chronic obstructive pulmonary disease, hypertension, diabetes mellitus as well as neurological disorders such as multiple sclerosis and dementia[10-13].

Even though the impact of carotid stenosis on retinal perfusion is self evident, it has not been systemmatically investigated to date. One study was performed using the data of 17 patients with significant carotid stenosis. The results indicated relative arterial hyperoxia and a significantly higher arterio-venous oxygen difference in the stenosis group[4].

Hypothesis

Reduced retinal blood flow due to significant carotid stenosis will result in adaptive changes measurable by retinal oximetry such as increased AV (Arteriovenous)

difference measured by retinal oximetry corresponding to increased oxygen extraction and/or dilation of post-capillary venules as a morphological correlate of blood circulation adaptation.

So far, studies with optical coherence tomography have confirmed reduced blood flow in the case of stenotic basin[15].

It is unknown whether these changes correspond to the clinical symptoms of carotid stenosis. Since 85% of ischaemic strokes due to carotid stenosis are not preceded by clinical warning signs (TIA, amaurosis fugax, minor stroke), the aim of this study is to evaluate changes in oximetry parameters compared to MRI verified ischaemic lesions regardless of their clinical significance. Retinal oximetry could provide a simple technique enabling the early detection of asymptomatic hemodynamically significant stenosis, thus allowing intervention prior to an ischaemic stroke event.

Aims of the study

Primary aim:

- To establish whether AV difference in the stenotic basin increases with the severity of stenosis and/or these changes vary depending on the severity of the stenosis.

Secondary aims:

- Evaluate the difference in retinal oximetry and ultrasonographic parameters in patients with clinically symptomatic and clinically asymptomatic carotid stenosis correlated to MRI findings of ipsilateral ischaemic lesions in the stenotic basin.

MATERIALS AND METHODS

Patient enrollment

In this prospective case-control study we estimate an enrollment of 50 patients a year. Inclusion criteria are ultrasonographic detection of significant carotid stenosis over 50%. Participants who give informed consent will undergo thorough ophthalmological examination prior to the retinal oximetry. Patients with high-degree refraction error, advanced cataract, glaucoma, proliferative diabetic retinal angiopathy or exsudative form of macular degeneration, undergoing treatment with vascular endothelial growth factor based treatment, laser photocoagulation or pars plana vitrectomy will be excluded due to technological limitations of retinal oximetry[11].

Baseline characteristics of the patients

Participants who give informed consent will undergo complete neurological examination with emphasis on subtle clinical sings of premorbid stroke. Patients with no history of prior ischaemic stroke will be referred to brain MRI stroke protocol as discussed below.

Patient medical history will be taken with emphasis on cardiovascular and atherosclerosis risk factors.

- Acute stroke symptoms – correlated with neuroimaging
- Dyslipidemia and treatment, values of blood lipid spectrum
- Diabetes Mellitus – type, actual pharmacotherapy, glycated hemoglobin value if possible
- Any cardiovascular events – these include prior myocardial infarction or history of ischaemic heart disease, peripheral arterial disease, prior stroke (more than 6 months before the examination) and revascularisation procedures in relation to these diagnoses
- Hypertension and treatment
- Atrial fibrillation and treatment – as a leading cause of ischaemic stroke
- Smoking and alcoholism

Prior to each examination, blood pressure will be taken, and peripheral blood oxygen saturation will be measured by finger oximeter (Pulse Oximeter PM 60, Cheiron i.n. CR-7A185379).

Ultrasonographic examination

Standard examination will be performed by machine GE-Logiq-S8, linear probe 9L-D frequency 2–8 MHz, sector probe M5S-D, frequency 1.8–4.4 MHz. Located at the Department of Neurology at Olomouc University Hospital.

Ultrasonographic examination describes the parameters of atherosclerotic plaque in carotid bulbus in B mode, such as plaque thickness, structure, presence and diameter of ulceration and instability signs, such as intraplaque hemorrhage, thrombus, neovascularisation, or rupture. Plaque calcifications and fibrosis is noted.

Asessment of the severity of stenosis will be performed according to Grant et al. Radiologic guidelines from 2003 (ref.[16]) and will rely on a combination of findings. These criteria rely heavily on the haemodynamic findings and plaque morphological characteristics. Combination of these factors such as PSV (peak systolic velocity increase), EDV (endiastolic velocity increase) in the stenotic segment and pre-stenosis/post-stenosis (Common carotid artery) /ICA (Internal carotid artery) ratio[17].

Since the changes of blood velocity are non linear with the increasing severity of stenosis, the most prominent changes are detectable in higher stenoses i.e. over 70% and undetectable or with poor predictive value in lower stenosis i.e. under 40%. Stenoses have none to limited changes to haemodynamics with wide inter individual variability despiteuse of a combination of parameters[18].

Ultrasonographic parameters gain more predictive value in stenoses over 50%, 70% respectively. As the lumen diameter decreases, blood flow increases exponentially leading to more profound changes. However above 95% stenosis the situation changes and obstruction leads to significant reduction of blood flow and decrease in systolic velocities[19]. Combination of absolute values of flow velocities and ACI/ACC velocity ratio seems to be the best option for evaluating the stenosis severity with the sensitivity and specificity over 90% in stenosis over 70% (ref.[17]).

All characteristics of carotid stenosis are summarized in Table 1.

Table 1. Assessing the severity of stenosis using multiple parameters, Grant et al. 2003, Gerhard-Herman et al. 2006.

% stenosis	ICA PSV (cm/s)	Plaque estimate % *	ICA EDV (cm/s)	Ophtalhmic circulation	PSVICA/PSVCCA
<50%	<125	<50	<40	orthograde	<2.0
50–69%	125–230	≥50	40–100	orthograde	2–4
70–95%	>230	≥50	>100	ortho/retrograde	>4
Near occlusion 95–99%	high, low or undetectable	variable	variable	mostly retrograde	variable
Total occlusion	undetectable	not applicable	not applicable	mostly retrograde	not applicable

*Plaque estimate (diameter reduction) based on Duplex ultrasound B-mode and on additional color mode ultrasound
CCA, common carotid artery; DUS, duplex ultrasound; EDV, end diastolic velocity; ICA, internal carotid artery; PSV, peak systolic velocity.

Combination of the above if used in assessing the severity of carotid stenosis.

In addition to the above, PSV and EDV in ECA, OA (Ophtalmic artery) and intracranially MCA (Middle cerebral artery) will be noted as well. OA velocities will be measured in depth of 1–5 centimeters behind the ocular fundus where physiological crossing with optic nerve occur. Insonation angle will be noted. Central retinal artery parameters will be taken in the fundus irrespective of the insonation angle presuming the 90° direction of blood flow through the eye wall[18].

MCA velocities will be taken in the M1 segment also with the insonation angle.

These findings will be used for evaluation of ophthalmic perfusion as well as correlation for incidental MRI findings of ischaemic laesions.

MRI examination characteristics

The MRI will be performed on a Siemens Aera 1.5-T (Siemens, Erlangen, Germany) with quantum gradients (syngo2004A) and a standard head coil (CP head array coil). The protocol will contain the following sequences: 1. localizer, 2. T2-weighted turbo spin echo (TSE), 3. fluid-attenuated inversion recovery (FLAIR), 4. diffusion-weighted imaging (DWI), 5. 3-D time of flight magnetic resonance angiography (TOF MRA). The total acquisition time (AT) is 11 min 28 s. Sequences 2–4 will be applied to acquire data from the same set of slices (standard number of slices 19, slice thickness 5 mm, distance factor 30%). The standard slice orientation is oblique axial, approximately parallel to the skull base in order to minimize the susceptibility to artifacts in echo-planar imaging (EPI) sequences. The sequence parameters are as follows: T2-TSE TR/TE/ETL 4,000/99/9 ms, FOV 230×173 mm, matrix 256×256, AT 1 min 34 s; FLAIR 8,050/112/ETL 21/2 concatenation, FOV 230 mm, FOV phase 76.6%, matrix 256×151, AT 2 min 26 s. These sequences are used to assess hemorrhage and detect local demyelination changes, including sites of ischemic demyelination. The EPI-DWI sequence parameters are as follows: 3,200/94/EPI factor 128/3 averages, FOV 230×230 mm, matrix 128×128 with interpolation, TA 1 min 20 s. MRI data is acquired with three diffusion weightings: b=0, b=500, and b=1,000. The fourth type of image is an automatically created apparent diffusion coefficient (ADC) map. DWI traces show average local diffusivity in the brain tissue examined when b is 500 and 1,000. This sequence is applied to assess hemorrhage (b=0: T2*–EPI, susceptibility-sensitive sequence) and detect sites of reduced diffusion (DWI, b=500 and 1,000). The 3D-TOF MRA sequence parameters are as follows: 43/7.15, 3 slabs, 32 partitions/slab, slice thickness 1 mm, FOV 200×150 mm, matrix 512×192, AT 5:59 min. The images obtained – maximum intensity projection (MIP) and sublayers – would illustrate the closure of the main arterial trunk of the circle of Willis or its branches. Infarct volumes are measured on DWI trace images (b=1,000) and calculated as a total hyperintense area in single slices multiplied by effective slice thickness [(actual slice thickness + distance factor)/ interslice gap].

A radiologically symptomatic patient will be considered if ischaemic lesions are foundin the stenotic basin.

Ophthalmological examination + automated retinal oximetry

First, the ophthalmological history is taken and a detailed physical examination of the anterior and posterior segments of the bulbus is performed using the slit lamp. Later optic coherent tomography (OCT) and retinal oximetry of both eyes are performed.

Physical examination includes:

- Examination of visual acuity using optotype ETDRS (Early Treatment Diabetic Retinopathy Study)
- Non-contact measurement of intraocular pressure (Canon TX-20P, CMI ORA III)
- Anterior segment examination using the slit lamp
- Fundus examination in artificial mydriasis using 1% tropicamide drops. Pupil dilation of at least 5 mm must be achieved

OCT (optic coherent tomography) examination

This examination is a non-contact, non-invasive method displaying the tomographic images of the retina. Targeting the layers of retina, scans of the macular region (macular cube 200x200) and retinal nerve fiber layer (RFNL) are measured. OCT non-contrast angiography of the macular region will be performed to capture the retinal and choroidal blood vessel network with high resolution. Examination is performed on a Spectralis SD-OCT (Heidelberg-Engineering, Heidelberg, Germany) machine.

Retinal oximetry

Examination occurs in standardised conditions in a dark room, eliminating the visible light spectrum bias.

Fundus photograph is taken at 50° width, centered on the temporal edge of the optic nerve. Flash intensity 50 Ws is used. At least 2 photographs of the same eye are taken. The higher quality photograph is later used for analysis. The measured area is marked by 2 concentric circles in 1.5PD (pupilar diameter) and 3PD diameter, centered on the center of the optic nerve papilla. An automated analytic protocol is used to compute the values of oxygen saturation. The machine type is Retinal Oximeter Oxymap T1 (Oxymap ehf. Reykjavik, Iceland) that is paired with retinal camera TRC-50DX, Topcon Corporation, Tokyo, Japan.

An automated analytic protocol is used to compute the values of oxygen saturation. The machine automatically detects blood vessels in a predefined area, and differentiates arteries from veins. Blood vessel diameter is also noted. Physiological crossings of arteries and veins have to be excluded manualy due to the risk of mixing of the absorbance spectrum of both types of blood vessels circles in 1.5PD and 3PD diameter, centered on the center of the optic nerve papillaThe machine type is Oxymap (Oxymap ehf. Reykjavik, Iceland).

There are a few limitations to performing retinal oximetry, including pre-existing patient conditions and technical measurement errors. These however do not overlap with the limitations of MRI. First, a patient needs to be cooperative and capable of a seated position. Second, some ocular diseases preclude the examination of the fundus: high-degree refraction error, advanced cataract, glaucoma, and diabetic retinal changes (such as proliferative angiopathy and exsudative form of macular degeneration). Patients treated with anti-vascular endothelial growth factor drugs, undergoing laser photocoagulation or pars plana vitrectomy have to be excluded[19].

Technological limitations are represented by patient retinal pigmentation. Studies show that venous saturation in blue irises differs from brown irises[20]. This bias is minimalized using an automatic mathematic algorithm in oxygen saturation calculation.

Another factor influencing the measured values is retinal blood vessel thickness. In blood vessels larger than 200 um in diameter, a central halo can be seen called the central vessel reflex. Since the oxygen saturation is not a value directly measured by the machine but the result of a mathematical algorithm, it can report arterial saturation values over 100% due to this bias which is of course, physiologically impossible. However since the saturation value is calculated by common mathematical algorhythm for all values this bias becomes irrelevant in the AV difference.

Statistical analysis and expected results

Statistical evaluation will be performed at the Department of Medical Biophysics, Faculty of Medicine, Dentistry, Institute of Molecular and Translational Medicine, Palacký University, Olomouc.

SPSS statistical software (vertion 17:0; SPSS, Chicago, II, USA) was used to determine the sample size to reach statistical significance. Statistical analysis will be performed for an estimated pathological cut-off value of the AV difference. It will be necessary to include at least 50 patients in each group (stenosis over 50%, over 70% vs. non-stenotic control group formed by contralateral blood vessels from the same patient pool) to obtain a statistically significant difference (min. 20%) in a pathological cut-off value of AV difference.

First, linear correlation between the stenosis severity and retinal oximetry parameters will be evaluated using Pearson correlation coefficient and Shapiro-Wilk confirmation.

Two groups will then be formed depending on the severity with thresholds of 50%, 70%, 80% and 90% stenosis with the control group of non-stenotic blood vessels from the same participant pool. Retinal oximetry parameters of these 2 groups will be compared using the Wilcoxon pair test for AV-difference and blood vessel diameter as the most sensitive markers of retinal oxygen metabolism and vascular compensatory changes.

Depending on the size of the sample, logistic regression will be used to analyze the optimal value of the AV difference and/or blood vessel diameter for predicting stenosis severity and if possible for calculating the odds-ratio of percentage of stenosis depending on the AV difference.

In the second part, measured AV differences will be evaluated by comparing the asymptomatic patients against the clinically symptomatic patients and patients with MRI lesions ipsilateral to the stenosis.

All the statistical tests will be evaluated at a 5% significance level.

DISCUSSION

Despite recent progress in the acute treatment of ischaemic stroke, there are still a number of patients that do not benefit from reperfusionor are ineligible for the treatment. The long-term consequences of ischaemic stroke are devastating, severely reduce the quality of life making prevention a priority. The main pitfall of carotid endarterectomy lies now in its indication. Early detection of clinically inconspicuous yet in terms of stroke risk, highly dangerous stenosis appears to be the key for revascularisation indication. Retinal oximetry could be a technique for use in early detection of these symptoms, and assisting the indication of endarterectomy.

Published results from a pilot clinical trial have confirmed the increased oxygen extraction in retinal blood vessels in the stenotic basin in a small group of 17 patients[14]. However, larger groups of patients need to be examined with enmphasis on analysing more parameters of the retinal oximetry. Though higher oxygen extraction on the stenotic side are, on face value logical, other factors may influence retinal oxygen metabolism such as reduced metabolism rate or microvascular haemodynamic changes. Detailed study of the blood flow dynamics in the stenotic basin may prove to be crucial to identifying the individual risk variations in stroke manifestation in patients with the same degree of stenosis.

ABBREVIATIONS

TIA, Transient Ischaemic Attack; CT, Computer Tomography; MRI, Magnetic Resonance Imaging; PSV, Peak Systolic Velocity; EDV, End diastolic velocity; CCA, Common carotid artery; ICA, internal carotid artery; ECA, external carotid artery; OA, Ophtalmic artery; AV, arteriovenous; DWI, Diffusion weighted imaging; FLAIR, Fluid attenuated inversion recovery; TOF, time of flight; OCT, optic coherent tomography; PD, pupillar diameter.

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