SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Clinical studies in carotid endarterectomies performed under locoregional anesthesia

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1. Introduction

Every year, 50,000 patients in Hungary need medical treatment for acute cerebrovascular accidents, or strokes. In 15% of cases, the underlying cause is haemorrhage (or subarachnoid haemorrhage), but the vast majority - roughly 85% - are ischaemic.

The main causes of loss of blood supply to the brain are embolism and vascular disease. Embolisation is the most common cause of ischaemic stroke, the most common source of which is atherosclerotic disease or thrombosis of the heart or an artery. A common cause of ischaemic stroke is disease of the great arteries, which may affect the common carotid artery (CCA), internal carotid artery (ICA), vertebral artery, basilar artery and intracranial vessels. Invasive options for stroke prevention include carotid endarterectomy (CEA) carotid artery stenting (CAS) and surgical closure of the patent foramen ovale. The focus of clinical trials over the last decade has been on how to make carotid endarterectomies safer with the lowest possible complication rate. CEA is a prophylactic surgery aimed at preventing embolization from atherosclerotic plaque in the carotid bifurcation and reducing possible hemodynamic damage. It is important that the surgical risk should not be greater than the long-term stroke risk reduction gained by the surgery, as the prophylactic nature of the surgery would then be meaningless. The most commonly used surgical procedure is the so-called eversion endarterectomy, where the ICA is cut at its origin and then folded back like a sleeve, effectively pulling the vessel wall away from the plaque. Then, after the plaque is removed, the ICA is reattached. Recent large meta-analyses have shown that there is no difference between eversion and patch-plasty endarterectomy at either endpoint. After carotid artery dissection, the ipsilateral part of the brain can suffer from hypoperfusion if the collaterals do not function properly. To prevent this, shunt insertion is used by surgeons. This is actually a piece of plastic tubing with two ends attached to the CCA and ICA, ensuring continuity of blood flow between the two arteries. Some vascular surgeons routinely insert the shunt for every carotid operation (routine shunt-users), some never use it, while others use it selectively to monitor brain function or blood flow (selective shunt-users). The use of a shunt is dangerous in itself, as a piece of plaque can drift away when it is inserted, which can also cause a stroke. The main aim of selective shunt use is to ensure that, as far as possible, all patients get a shunt who need a shunt and none of them get who do not need. General anaesthesia is supposed to minimise cerebral oxygen demand and metabolism and is therefore cerebroprotective. Regional anaesthesia is the gold standard for monitoring neurological symptoms and offers the possibility of selective shunting. In the anaesthetised patient, various neuromonitoring techniques can help to assess the need for shunt, such as transcranial Doppler (TCD), near-infrared spectroscopy (NIRS), somatosensory evoked potential (SSEP) or electroencephalography (EEG). The cerebrum is supplied bilaterally by three large arteries, the anterior cerebral artery (ACA), the middle cerebral artery (MCA) and the posterior cerebral artery (PCA), whose origins are connected by the collateral system of the circle of Willis, and whose distal connections are made by the Heubner leptomeningeal network. In case of occlusion or severe narrowing of the extracranial vertebral and carotid arteries supplying the brain, the collateral system of the circle of Willis can compensate for the impaired perfusion.

Heubner's leptomeningeal network can reduce the extent of ischemic damage in the event of occlusion of arteries distal to the circle of Willis. The circle of Willis and Heubner's leptomeningeal network can differ considerably from individual to individual, so that occlusion of an artery supplying a particular brain can cause different degrees of ischaemia in the area supplied by that artery. When the operated internal carotid artery (ACI) is occluded, the main source of blood flow to the same hemisphere is eliminated and the intact Willis circle collateral system is supplied from the opposite side and the basilar artery via the anterior communicating

artery (ACoA) and posterior communicating artery (ACoP). If either of the communicating arteries is non-functional due to hypolasia or other causes (occlusion), the blood flow lost due to the occluded ICA cannot be replaced by the Willis circuit with adequate perfusion pressure and the low perfusion pressure in the operated hemisphere will cause ischaemic damage within a short time. The integrity and functionality of the circle of Willis can be determined from preoperative CT/MR angiography and transcranial colour-coded Doppler (TCCD). From a study by Hoksbergen and colleagues published in 2000, it is known that functional collaterals have a diameter of 1.1 mm while non-functional ones are between 0.4-0.6 mm. This suggests that collateral arteries with a diameter of less than 0.5 mm can be considered non-functional. A circle of Willis with hypoplastic, non-functioning segments is more likely to experience ischaemic neurological symptoms after ICA occlusion during surgery, more likely to require intraluminal shunt insertion and more likely to have a postoperative stroke. With this in mind, the surgeon can prepare for shunt insertion and choose the type of surgery accordingly, because it is technically easier to insert a shunt in a longitudinal incision than in a transverse arteriotomy for an everion endarterectomy. In our studies, we performed carotid endarterectomies under regional anaesthesia using transcranial Doppler (TCD) and near-infrared spectroscopy (NIRS). During surgery under regional anesthesia, the patient is in a mild sedated state, cooperates well, and clinical signs of cerebral ischemia are easily assessed: aphasia, contralateral paresis and impaired consciousness. Pre-operative CT and/or MR angiography scans were analysed by an independent radiologist colleague and patients were classified according to the integrity of the Willis circle. Some of the patients showed neurological symptoms after clamp, while the remaining patients were asymptomatic. The patients were thus divided into symptomatic and asymptomatic groups. We examined changes in regional brain oxygen saturation (rSaO2) measured by TCD and NIRS at 8 important time points of surgery and compared these between symptomatic and asymptomatic patients.
The timing of the measurements during surgery was as follows: 1. baseline (before regional anaesthesia), 2. after regional anaesthesia before incision 3. immediately after the start of surgery, 4. immediately after clamping the carotid artery, 5. at the fifth minute of clamp, 6. at the tenth minute of clamp, 7. Immediately after declamp, 8. postoperative period (4-6 hours after surgery). For surgical anaesthesia, an ultrasound-guided intermediate cervical plexus block was used, during which 20ml of 0.375mg/ml ropivacaine was administered from the lateral edge of the middle of the sternocleidomastoid muscle towards the medial muscle belly under the muscle.

2. Objectives

In our studies, we used combined monitoring (clinical signs + transcranial Doppler + NIRS) during carotid surgery under regional anaesthesia.
We sought to answer the following questions:

1. How does the flow rate change in the ipsilateral and contralateral middle cerebral artery measured by TCD during clamp regarding the neurological symptoms that may occur?
2. To what extent can a change in the mean flow rate in the middle cerebral artery be considered an indication for a shunt? What is the sensitivity and specificity of certain middle cerebral artery mean flow rate cut-off values?
3. How does brain tissue oxygen saturation measured by near-infrared spectroscopy (NIRS) reflect clinical symptoms in symptomatic and asymptomatic patients? At what degree of regional brain oxygen saturation reduction should a cut-off value be

established as an indication for shunt insertion, and what sensitivity and specificity is associated with it?
4. What was the incidence of incomplete circle of Willis among our patients?
5. Is there a correlation between an incomplete circle of Willis and the onset of neurological symptoms after carotid occlusion?
6. To what extent do variations in the circle of Willis predispose to ischemic neurological symptoms during CEA surgery?

3. Patients and methods

In our research, we followed the relevant national and institutional regulations and the principles of the Helsinki Document, which were approved by the Institute's editorial board. We registered our study as NCT02665104 in ClinicalTrials.gov. The Research Ethics Committee of the University of Debrecen approved our research under the number DE RKEB/IKEB:4364/2015.
All patients signed informed consent forms after detailed information.

3.1. Patient selection, methods and instruments of measurement:

This prospective study was conducted in patients with hemodynamically significant unilateral carotid artery stenosis undergoing elective CEA surgery at the University of Debrecen Institute of Surgery. Regional anaesthesia was performed by ultrasound (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Nanshan, Shenzhen, China) using an L 12-4s linear transducer. 22G thick 50mm long plexus needle (Vygon Echoplex, Ecouen, France) was used. An intermediate plexus cervical block combined with a superficial block was applied under ultrasound guidance. The puncture was made at the posterior edge of the SCM muscle at the level of the 4th cervical vertebra at the Erb point (Erb point: the point along the posterior edge of the SCM muscle where the external jugular vein intersects the SCM, where the superficial branches of the cervical plexus enter). From the puncture point, we proceeded postero-laterally under the SCM in an antero-medial direction under the "investing layer" of the deep cervical fascia system. 20ml Ropivacaine (Naropin, Aspen Pharma Ltd., Dublin, Ireland) was administered at a concentration of 0.375mg/mg over 5 minutes under ultrasound guidance. Routine intraoperative monitoring included ECG, pulse oximetry, and invasive blood pressure measurement, as usual in carotid surgery. During carotid artery (interna and externa) dissection, patients were asked to press a whistle toy in the opposite hand to the operation to control the isometric force. The patient's neurological status was monitored by the anaesthesiologist throughout the operation. The patient was considered symptomatic if there was a loss of consciousness, contralateral upper limb paresis/paralysis or aphasia after clamping the carotid artery. In these cases, the surgeon opted for a shunt. Bilateral TCD was performed using the Rimed Digilite TCD device (Rimed Ltd., Israel). The temporal bone window was used for the insonation of the middle cerebral artery, at a depth of 45-55 mm, based on the best quality signal. Two fixed TCD probes were used to measure the systolic, diastolic and mean arterial flow velocities (MCAV) on both sides during surgery. Flow velocities (MCAV) and their percentage changes during surgery were analysed later. Flow velocities were recorded at different time points during surgery: (1) baseline, before regional block, (2) post-block, before surgical incision (3) immediately before artery clamping (4) immediately after clamping (5) 5 min. after clamping (6) 10 min. after clamping (7) immediately after artery declamping (8) post-operative period (4-6 h after).

Bilateral near-infrared spectroscopy (NIRS) was used to monitor oxygen saturation of brain tissue using an INVOS 5100C Cerebral Oximeter System (Somanetics Corporation, Troy, MI, USA) throughout surgery. The sensors of the device were placed on the patients' foreheads on both sides. Although measurements were taken continuously, only data measured at certain times during surgery (at the same time as the TCD measurement) were recorded for further processing: (1) baseline, before regional block, (2) post-block, before surgical incision (3) immediately before artery clamping (4) immediately after clamping (5) 5 min. after clamping (6) 10 min. after clamping (7) immediately after artery declamping (8) post-operative period (4-6 h after).
In all cases, computed tomography angiography (CTA) was performed before surgery. Later, after surgery, the CT angiography images were analysed by 3 independent neuroradiologists who did not know which group the patients belonged to (symptomatic or asymptomatic after clamping).
After analysing the CTA scans, the neuroradiologists classified the patients into functional and non-functional groups for the Willis circle.
We considered the circle of Willis as incomplete if any anatomical variation or pathological condition inhibited its collateral function (missing communicating arteries, occluded segments) and/or the diameter of the communicating arteries was less than 0.5mm. The categorisation was based on previous observations that a diameter of the communicating arteries below 0.5mm was considered to be the lower threshold for collateral function. The neuroradiologists analysed the CTA images independently, reaching consensus on the categorisation after reviewing the images together again in controversial cases.

3.2. Statistical analysis:

Arteria cerebri media flow velocities (MCAV) were analysed. We also calculated the percentage change in MCAV during the intervention and compared the values on the operated side with those on the contralateral side. After testing for normal distribution and analysis of area under the distribution and slope curve, data were presented as mean ± standard deviation or median and interquartile range (IQR) of 25-75%. Comparisons were performed using t-tests and Kruskal-Wallis tests. Categorical values were compared using $\chi 2$ test. Differences were considered statistically significant at $p<0.05$.
NIRS and Willis circle test data were presented as mean and standard deviations. Categorical variables were compared using the corresponding $\chi 2$ (chi-square) test. Repeated measures ANOVA test was used to compare NIRS values measured at different time points of surgery. Differences were considered statistically significant if the P value was <0.05.

4. Results:

4.1. Study of flow velocity values using transcranial Doppler:

80 patients were planned to be included in the study, but 14 patients were found to be ineligible due to the lack of a transtemporal acoustic window. In the end, 66 patients were included, 43 men and 23 women. During CEA surgery, 55 patients were neurologically asymptomatic and 11 were symptomatic. There was no significant difference between the two groups of patients in terms of age and cardiovascular risk factors. 7 patients were classified ASA II and 59 patients ASA III. One early (<48 h) surgical-site ischemic stroke occurred in both patient groups.

4.1.1. Brain blood flow velocity (MCAV) values in asymptomatic patients during CEA:

In the neurologically asymptomatic group, cerebral blood flow velocity (MCAV) was significantly reduced during clamping on the operated side and significantly increased after artery unclamping, compared to the non-operated side. It is worth noting that temporarily higher flow velocity values were measured on the operated side in the postoperative period, which may indicate hyperperfusion.

4.1.2. Cerebral blood flow velocity (MCAV) values in symptomatic patients during CEA

Flow velocity changes in patients with neurological symptoms requiring shunting during carotid artery occlusion behaved differently from those in asymptomatic patients. Comparing the operated and intact sides, the decrease in flow velocity was more pronounced on the operated side compared with the asymptomatic patients, but this difference was significantly reduced after shunt insertion. On the opposite side, flow velocities were slightly lower. After artery declamping, there was no significant difference in flow velocities between the operated side and the opposite side.

4.1.3. Comparison of the percentage change in flow rates in symptomatic and asymptomatic patients

Comparing the percentages of MCAV change in symptomatic and asymptomatic patients, we found that the decrease in symptomatic patients exceeded 70%, while in asymptomatic patients the decrease was less than 50% on average. After shunt insertion, the percentage decrease in MCAV on the surgical side was smaller in symptomatic patients than in asymptomatic patients. On the surgical side, the increase in MCAV after artery declamp, a sign of hyperperfusion, was slightly more pronounced in the symptomatic group than in the asymptomatic group (25% versus 17.6%).

4.2. Study of the circle of Willis and regional brain saturation values

107 patients were included in our study. NIRS monitoring was performed in all cases, CTA images were available in 94 cases. The missing 13 patients were all asymptomatic (no new neurological symptoms after exclusion).

4.2.1. Results of the Willis Circle study

Correlation between Willis Circle complete/incomplete status and symptoms after clamp:
Based on CT angiography, 67 incomplete Willis circle were found among the patients, 54 were asymptomatic 13 were symptomatic after carotid occlusion.
No complete circle of Willis was found among patients with symptoms after carotid artery occlusion (n=13). Among asymptomatic patients (n=81), 54 incomplete and 27 complete circles of Willis were found. A statistically significant difference was found between symptomatic and asymptomatic patient groups in the number of complete and incomplete Willis circles (Chi-square: 6.08; p=0.013).

The relationship between communicating artery functionality and neurological symptoms after carotid artery occlusion:
The anterior communicating artery was absent or hypoplastic (<0.5 mm) in 5 of 13 symptomatic patients. No non-functioning arteria communicans anterior was found in the asymptomatic group (Chi-square: 32.9; p=10-8).

Absent or non-functioning bilateral posterior communicating arteries were seen in 9/13 symptomatic patients and 9/81 asymptomatic patients (Chi-square: 24.4; p=10-7)
Non-functioning arteria communicans posterior on the surgical side was more frequent in symptomatic patients (9/13) than in asymptomatic patients (24/81, Chi-square: 7.71; p=0.005), and the same was observed in the opposite non-functioning arteria communicans posterior (symptomatic: 9/13; asymptomatic: 28/81; Chi-square: 5.64; p=0.017).
It should be noted that bilateral non-functioning posterior communicating artery occurred only in symptomatic patients.

4.2.2. Regional oxygen saturation of the brain during CEA

In asymptomatic patients, we observed slight but statistically significant differences in tissue oxygen saturation (rSO2) of the brain after carotid artery dissection between the surgical and the contralateral side. Brain oxygen saturation was significantly lower after carotid occlusion on the surgical side and this difference persisted even at the 10th minute of carotid occlusion. It should be noted that, although statistically significant, the relative reduction in oxygen saturation of brain tissue on the operated side was less than 20% compared with the baseline preoperative value.
In symptomatic patients, oxygen saturation of brain tissue gradually decreased after carotid clamp on the operated side and the difference between the two sides persisted until 10 minutes after clamping. Although not statistically significant, elevated oxygen saturation of brain tissue was found after carotid declamp, indicating hyperperfusion of the operated side. In the postoperative period, 4-6 hours after surgery, we found no difference in oxygen saturation of brain tissue between the operated side and the contralateral side.

5. Discussion

Previous studies of carotid artery surgery have shown that 12% of patients have ischaemic neurological symptoms after ICA clamping. Recognition of these alarming symptoms (aphasia, impaired consciousness, contralateral upper limb paresis or paralysis) is crucial, as the process can be reversed in the majority of cases by the removal of hemodynamic anomalies, namely by intraluminal shunt insertion, i.e., the intraoperative development of definitive ischemic cerebral lesion can be prevented by rapid and adequate shunt application.
In regional anaesthesia, the recognition of symptoms is easy, whereas in general anaesthesia, various neuromonitoring methods are used to assess the need for a shunt. The sensitivity and specificity of these methods is inferior to that of awake patient detection. In our studies, we performed measurements in carotid endarterectomies operated under regional anaesthesia and correlated the results with the occurrence of neurological symptoms occasionally experienced during surgery. Using NIRS and TCD, we measured cerebral regional oxygen saturation, cerebral arterial flow velocity, and assessed the status of the circle of Willis based on previous CTA results, and used these data to determine the predictive value of the measurement methods for shunt requirement. In our first study, we found that in symptomatic patients who required shunt insertion after carotid artery clamp, the flow velocity in the surgical side of the middle cerebral artery decreased by

more than 70%. After shunt insertion, this decrease was smaller than in asymptomatic patients who did not receive a shunt. To our knowledge, there are few studies that have measured cerebral blood flow velocities during carotid artery surgery under regional anaesthesia throughout the operation. In recent decades, there has been a lively debate about the appropriate method to indicate the need for shunt in carotid surgery. In a study, McCarthy and colleagues found that shunt insertion was required in 12% of cases of CEA surgery performed under regional anaesthesia because of the onset of neurological symptoms after carotid clamping.

This value is slightly lower than ours (11/66; 16.6%), but shunt insertion based on neuromonitoring can reach 25% in CEA performed under general anaesthesia. The relatively high shunt rate (16.7%) in our study should be mentioned. Shunt insertion was based on the appearance of neurological symptoms after carotid artery clamp. In a more recent study of CEA surgery in regional anaesthesia, the rate of shunt and patch placement due to neurological symptoms was 31.6%.

We should mention that in Hungary the rate of ischaemic stroke is 40 per 100,000 inhabitants per year, which shows the picture of a society with a significant cardiovascular burden. In patients with severe carotid stenosis undergoing ischemic stroke, the odds ratio of nonfunctioning anterior and nonfunctioning posterior collateral network is OR: 7.33 (95% confidence interval [CI] = 1.19-76.52) and 3.00 (95% CI = 0.77-12.04), respectively, based on the results of a previous study in a similar group of patients.

The condition of the collateral network of the circle of Willis plays an important role in the need for shunt, and therefore the higher shunt rate in our study suggests a more severe condition of the intracranial vessels in patients, resulting in non-functioning collateral vessels at the time of clamping. Consistent with our results, several authors have reported a 50-70% reduction in blood flow velocity at clamp during CEA under general anesthesia. Continuous TCD measurement during CEA under regional anesthesia showed that patients who tolerated well carotid artery clamping had significantly higher cerebral blood flow velocity (MCAV) than those who did not (26. 2 ± 8.5 vs 1.8 ± 1.1 cm/s). Moritz and colleagues have shown in a comparative study that relative changes in cerebral blood flow velocity are a more accurate predictor of cerebral ischaemia than absolute values. They reported that a 50% decrease in arteria cerebri media velocity showed 100% sensitivity and 86% specificity. When they wanted to exclude false positive cases (100% specificity), the corresponding arteria cerebri media velocity reduction was 70%.

Cao and colleagues also found that a decrease in arterial cerebral media flow rate of more than 70% is the best TCD criterion for the need for shunt insertion. In their study, TCD showed 83% sensitivity and 96% specificity, with positive predictive values of 71% and negative predictive values of 98%. These results are in agreement with our results: patients with symptoms after carotid occlusion had a decrease in surgical cerebral blood flow velocity (MCAV) greater than 70%

in 8 of 11 cases (72.7% sensitivity), specificity was 93.1%, and TCD hit rate was 89.23%. When the threshold for post-occlusion decrease in MCAV was set at 50%, sensitivity was 90.1%, specificity 59.6%, and accuracy 64.62%. In the light of these findings, it is worth reconsidering the value and role of TCD in general anaesthesia CEAs. A major advantage of TCD is its ability to non-invasively monitor changes in cerebral blood flow velocity on both sides and embolization during surgery. As we know from previous studies, the sensitivity and specificity of TCD to detect shunt demand in CEAs performed under general anaesthesia is limited. An additional benefit of TCD, in combination with carotid compression, may be the preoperative assessment of the integrity of collateral Willis circle function. This method is in fact a preoperative modelling of carotid clamp during CEA. A recent study has demonstrated that incomplete Willis circle is a risk factor for neurological symptoms after carotid clamping during CEA.99 TCD in combination with carotid compression allows assessment of Willis circle collateral function before CEA under general anaesthesia, thus predicting the need for shunt during surgery. Its use is extremely limited and unethical due to occasional embolizations after compression testing.

We must also discuss the limitations of our present study. We originally planned to include 80 patients, but we had to exclude 14 patients due to the lack of a temporal acoustic window. In these patients it was not possible to perform the TCD study. It should be mentioned that 3 of these 14 patients developed neurological symptoms during carotid clamping. Another limiting factor may be that we selected only patients with unilateral hemodynamically significant carotid stenosis for our study. We chose this approach because the hemodynamically significant carotid stenosis of the contralateral hemodynamic makes the hemodynamic changes during the clamping largely dependent on intracranial collaterals. We examined hemodynamic changes of the surgical side in isolation. Thirdly, we measured cerebral blood flow velocities only in the medial cerebral artery, and we have no information on hemodynamic changes in the anterior and posterior cerebral vessels or on possible steal phenomena during clamp. Our results suggest that neurological symptoms due to cerebral ischemia are more indicative of the need for shunt insertion than changes in cerebral blood flow velocity monitored by TCD.

Regional anaesthesia allows safe monitoring of CEA surgery based on symptoms. In our second prospective observational study, we found that non-functioning collaterals of the circle of Willis should be considered as a risk factor for ischemic brain events after carotid artery clamp in carotid artery surgery.

The grouping of patients in our present study was based on whether neurological symptoms of ischemic origin, such as impaired consciousness, contralateral limb paresis/paralysis or aphasia develop after carotid artery clamp during surgery. In all patients with neurological symptoms, a deficient or hypoplastic Willis circle collateral system and a decrease in cerebral tissue oxygen saturation at the surgical site following clamp were detected.

Although ischemic stroke is considered to be primarily of thromboembolic origin in the presence of hemodynamically significant carotid artery stenosis, clinical observations support the importance of Willis circle collaterals.

In a follow-up study of a group of patients free of cerebrovascular disease, incomplete anterior and posterior collaterals increased the odds of ischemic stroke by 5.4 to 7 times. In a previous publication, Harrison and colleagues described that ischemic brain lesions seen on CT scans may be associated with missing intracranial collaterals in patients with ACI occlusion. Hoksbergen and colleagues demonstrated in patients with ischemic stroke that incomplete or nonfunctioning circle of Willis is an independent risk factor for stroke and the association is even stronger in the presence of hemodynamically significant co-morbidity in the ICA. The prevalence of Willis circle variants was higher in stroke patients compared with controls in the study by De Caro and colleagues.

A recent study has shown that an incomplete circle of Willis worsens the outcome of ischemic stroke. Preoperative perfusion images such as transcranial Doppler, SPECT (single photon emission computed tomography), PET (positron emission tomography) or arterial spin labeling MRI may help in the preoperative evaluation of CEA surgery. Further studies are needed in the absence of sufficient scientific evidence to demonstrate the benefits of all these.

There are basically two surgical approaches to shunt application in carotid endarterectomy: some insert the shunt in all cases, others selectively apply the shunt, based on the indication of different neuromonitoring techniques (EEG, carotid stump pressure measurement, transcranial Doppler, somatosensory evoked response, NIRS) in general anaesthesia and on the onset of neurological symptoms in regional anaesthesia.

A disadvantage of general anaesthesia is the need for continuous monitoring during the procedure. Several of these monitoring methods have low sensitivity to brain ischemia and intraoperative detection of brain ischemia, their results are influenced by anaesthetics, and vascular surgeons cannot rely on their results to judge the need for a shunt. In addition to the inherent risks of shunt insertion, a recent meta-analysis suggests that there is insufficient data to support either selective or routine shunt use. In a recent study, Banga et al. suggested that angiography should be performed prior to carotid surgery to assess the Willis circle collaterals in cases of vascular surgeons who do not routinely use shunts, because there was a higher incidence of postoperative stroke in patients who were not shunted and had nonfunctioning intracranial collaterals.

This idea was supported by a report by Squizzato and colleagues, who found that when the decision to apply a shunt was made intraoperatively, there was a higher incidence of postoperative stroke.

In the present study, we used clinical symptoms to categorize patients (symptomatic / asymptomatic), but the results of near-infrared spectroscopy on oxygen saturation of brain tissue were consistent with the appearance of symptoms of cerebral ischemia after carotid clamp. Interpreting the results of near-infrared spectroscopy using the recorded neurological symptoms, a 20% ipsilateral rSaO2 decrease with a cut-off value of 76.9% sensitivity, 74.5% specificity, 29.1% positive predictive value, 95.9% negative predictive value. Our results are in agreement with the data published by Moritz and with the results of the Duarte-Gamas meta-analysis, where sensitivity was found to be 72% and specificity 84.1%. The measured sensitivity and the poor positive predictive value reiterate the need for new, more sensitive monitoring methods in carotid endarterectomy. From a clinical point of view, treated with caveats, reduced cerebral tissue oxygen saturation may be a suitable indication for shunt insertion. With regard to the limitations of our study, we must first mention the number of patients included (n=107). In this prospective observational study, the collaboration of at least three specialties was required to collect clinical and radiological data. In addition, the offline, post hoc analysis of CT angiography images by three radiologists also required considerable work. We are confident that even this modest number of patients was suitable as food for thought, which could form the basis for a prospective multicentre or synthesis study with a larger number of cases in the future. The diameter limit used to determine the functionality of the collaterals of the Willis circle may be open to criticism. In fact, previous studies have used a threshold of 1mm or 0.8mm to define hypoplasia of cerebral collateral arteries. However, these diameter values were arbitrarily assigned and likely underestimated the number of non-functional collaterals. Several clinicopathological and modelling studies have suggested that anterior and posterior communicating arteries can be considered nonfunctional if their minimum diameter is less than 0.5-0.6 mm. Finally, in the present study we focused mainly on the morphology of the circle of Willis and did not consider other factors than a positive awake test, such as contralateral stenosis, hypertension and diabetes. Since there was no statistically significant difference between these confounders between symptomatic and asymptomatic patient groups, we can conclude that they are unlikely to have a significant effect on our results.

As a lesson learned, an incomplete or non-functioning circle of Willis may be considered as a risk factor for ischemic brain events occurring during carotid endarterectomy.

Further multicenter studies are needed to confirm whether preoperative assessment of the collateral capacity of the circle of Willis can help guide the decision to use a shunt in carotid endarterectomies.

5.1. Based on results of our investigation, we conclude that

1. We were among the first in the international literature to use complex (clinical signs and symptoms and NIRS and TCD) monitoring in carotid surgery under regional anaesthesia.
2. We found that the TCD test has a sensitivity of 83% and a specificity of 96% for detecting ischaemic symptoms at clamp.
3. We also found that the sensitivity of NIRS in detecting ischemic symptoms is lower compared to TCD: 76.9% and 74.5%.
4. For the first time in the international literature, we studied the relationship between ischaemic symptoms during clamp and the Willis circle collateral network during regional anaesthesia
5. We found that there is a correlation between the onset of ischemic symptoms during clamp and non-functioning Willis circle collaterals. There is a 24-fold increase in risk for non-functional collaterals in the anterior communicating artery and a 7.7-fold increase in risk for the posterior communicating artery.

6. Summary

In symptomatic patients requiring shunt insertion after carotid artery occlusion, the ACM flow velocity at the side of the surgery was reduced by more than 70%, while in asymptomatic patients the reduction was less than 50%. After shunt insertion, this reduction was smaller than in asymptomatic patients who did not receive a shunt. After carotid artery clamp, the reduction in the ipsilateral cerebral blood flow velocity (ACMV) in symptomatic patients was greater than 70% in 8 out of 11 cases, giving a sensitivity of 72.7%, specificity of 93.1% and accuracy of 89.23%. When the threshold for post-clamp decrease in blood flow velocity was set at 50%, the sensitivity was 90.1%, specificity 59.6% and accuracy 64.62%. Our results suggest that neurological symptoms due to cerebral ischemia are better predictors of the need for shunt insertion than changes in cerebral blood flow velocity monitored by TCD.

Non-functional collaterals of the circle of Willis should be considered as a risk factor for cerebral events of ischemic origin after carotid artery clamp.

In all patients with neurological symptoms, a deficient or hypoplastic circle of Willis collateral system and a significant reduction in regional cerebral tissue oxygen saturation at the side of surgery following carotid artery occlusion were detected. In symptomatic patients, there were significantly more circle of Willis with incomplete or non-functional segments. This significant difference was also present separately for ACoA and ACoP between the two groups of patients.

The rSaO2 of symptomatic patients showed a significantly greater decrease immediately after carotid clamp than that of asymptomatic patients.

In the light of the neurological symptoms observed during surgery, choosing a 20% rSaO2 decrease as cut off value, the sensitivity of near-infrared spectroscopy was 76.9%, specificity 74.5%, positive predictive value 29.1% and negative predictive value 95.9%.

Decreased cerebral tissue oxygen saturation and ACMV measured after carotid artery occlusion may be suitable to indicate shunt insertion, subject to caveats.

Patient monitoring under regional anaesthesia provides the most reliable symptom-based monitoring for CEA during surgery.

The measured sensitivity and poor positive predictive value reiterate the need for more sensitive monitoring methods during carotid endarterectomy under general anesthesia.

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Registry number: DEENK/386/2023.PL
Subject: PhD Publication List

Candidate: Zoltán Gyöngyösi
Doctoral School: Doctoral School of Neurosciences
MTMT ID: 10054716

List of publications related to the dissertation

1. **Gyöngyösi, Z.**, Belán, I., Nagy, E., Fülesdi, Z., Farkas, O., Végh, T., Hoksbergen, A. W. J., Fülesdi, B.: Incomplete circle of Willis as a risk factor for intraoperative ischemic events during carotid endarterectomies performed under regional anesthesia: A prospective case-series.
   Transl. Neurosci. 14 (1), 1-8, 2023.
   DOI: http://dx.doi.org/10.1515/tnsci-2022-0293
   IF: 2.1 (2022)
2. **Gyöngyösi, Z.**, Farkas, O., Papp, L., Bodnár, F., Végh, T., Fülesdi, B.: The value of transcranial Doppler monitoring of cerebral blood flow changes during carotid endarterectomy performed under regional anesthesia: A case series.
   Transl. Neurosci. 13 (1), 476-482, 2022.
   DOI: http://dx.doi.org/10.1515/tnsci-2022-0257
   IF: 2.1

List of other publications

3. Orosz, L., **Gyöngyösi, Z.**, Susán, Z., Siró, P., Hoksbergen, A. W. J., Csiba, L., Fülesdi, B.: Assessment of malformations, variations and diameters of vessels forming the circle of Willis: An autopsy study in a non-cerebrovascular cohort.
   Transl. Neurosci. 13 (1), 398-406, 2022.
   DOI: http://dx.doi.org/10.1515/tnsci-2022-0253
   IF: 2.1
4. Fülesdi, B., Farkas, S., **Gyöngyösi, Z.**, Siró, P., Bereczki, D., Bacsó, J., Csiba, L.: Correlation between calcium, water contents and ultrasonographic appearance of atherosclerotic lesions of carotid artery lesions.
   Transl. Neurosci. 11 (1), 269-276, 2020.
   DOI: http://dx.doi.org/10.1515/tnsci-2020-0115
   IF: 1.757

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5. Mitre, C., Mitre, I., **Gyöngyösi, Z.**, Fülesdi, B., Zdrehus, C., Breazu, C., Bíró, P.: Clinical Experiences with the FRONT Formula for Pre-Operative Airway Assessment and Documentation: a Multi-Centre Study.
Turk. J. Anaesth. Reanim. 45 (4), 225-230, 2017.
DOI: http://dx.doi.org/10.5152/TJAR.2017.97992

6. Csiszkó, A., Herr, G., Kiss, S. S., Hallay, J., **Gyöngyösi, Z.**, Szentkereszty, Z.: VATS therapy of chylothorax caused by leiomyomatosis complicated with tuberous sclerosis complex.
J. Minim. Access Surg. 9 (2), 84-86, 2013.
DOI: http://dx.doi.org/10.4103/0972-9941.110970
IF: 1.374

7. Fazekas, B., Mohácsi, A., **Gyöngyösi, Z.**, Vitális, E., Simon, É., Molnár, C., Fülesdi, B.: A maghőmérséklet transoesophagealis mérésének megbízhatósága félig zárt és zárt narkózis rendszerrel végzett anesztéziák során.
Anaesthesiol. Intenziv Ther. 38 (3), 121-126, 2008.

8. **Gyöngyösi, Z.**, Végh, T., László, I., Herr, G., Szentkereszty, Z., Hallay, J.: Video-asszisztált thoracoscopia szerepe chylothorax-szal járó ritka kórkép differenciáldiagnózisában = Video-assisted thoracoscopy for the differential diagnosis of a rare disease with chylothorax.
Aneszt. Int. Ter. 37, 92-94, 2007.

Total IF of journals (all publications): 9,431
Total IF of journals (publications related to the dissertation): 4,2

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

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