

NKFI K129277

Report

2019.09.01.-2023.08.31.

OVERVIEW

The aim of our studies was to reveal the role of static (CT - CoW, plaque and ischemic lesion analysis, OCT, ect.) and dynamic (TCD, NIRS, intraarterial blood pressure measurement, ect.) parameters in the background of neurological events in patients with carotid stenosis. We also examined functional parameters such as cognitive function, which we compared with the previous ones. In our clinical study, we performed several imaging and hemodynamic measurements pre-, intra- and postoperatively. Examination of the patients, sample collection, and evaluation were performed by a multidisciplinary team. We have co-operated with the Department of Neurology (NK) of Semmelweis University (SE), the Department of Anaesthesiology and Intensive Therapy (AIK) of SE, and the Department of Ophthalmology (SZK) of SE, in order to carry out additional studies for the project. Part of this co-operation included pre-operative TCD measurements that were used for the project. The planned protocol was modified: intra-operative TCD monitoring was removed due to its complexity. Instead, intra-operative neurological monitoring was performed using NIRS monitoring, in cooperation with SE-AIK. The necessary devices were acquired from allocated funds from the grant. Pre- and post-operative TCD measurements were performed in cooperation with the Department of Neurology of SE. The mathematical calculations, 1D and 3D modeling were carried out by staff of Department of Hydrodynamics Systems, Budapest University of Technology and Economics participating in our OTKA/NKFI study.

We have applied for Ethical Approval and received Regional Ethical Approvals SE-RKEB 256/2018 and SE-RKEB 84/2019. The finalised study protocol was approved at clinicaltrials.gov, and registered under no. NCT03840265.

During the period 1/9/2019-31/8/2023, pre-and post-operative examinations and measurements (CTA, MR, TCD, OCT, NIRS, plaque sampling, lab test and CTA plaque analysis) were performed in accordance with the protocol in the case of the enrolled patients.

Due to the COVID-19 pandemic the study period has been prolonged with 1 year. Statistical evaluations were performed. The results have been published in several conference abstracts and 10 original articles and 2 review articles have been published in international Q1 and Q2 journals. Currently, 4 manuscripts are pending and under revision.

DETAILED REPORT OF INDIVIDUAL SUB-PROJECTS

Pre- and post-operative investigations and measurements (CTA, MR, TCD, OCT, NIRS, plaque sampling, laboratory testing and CTA plaque analysis, cognitive tests) were performed

according to the protocol for all included patients between 1 January 2020 and 31 November 2022.

Retrospective studies of the CoW anatomical variation's effects on the clinical outcome of the carotid artery reconstruction were published. Our retrospective study results with the contralateral carotid occlusion with insufficient CoW without intraoperative shunting is under review in Journal of Vascular Surgery.

CoW status of each enrolled patient based on carotid CTA images were evaluated, which were compared with OCT, TCD and NIRS results. OCT measurement results were presented in SIVS International Congress. The manuscript about CoW and OCT results has been published in Journal of Clinical Medicine. The stump pressure measurements and CoW morphology results were analysed and sent for publication, the article has been under review in Scientific Reports yet. The NIRS measurement evaluation needs further and more complex data analysis. The studies with NIRS measurements will be published in 2024.

Based on the CTA images, the 3D flow models created in the Slicer program were compared with the lumen models created in the VascuCap software on Wacom monitor. An article, which shows the outcome of the comparison, was accepted for publication in the Applied Science Special Issue "Applications of Image Processing in Anatomy". A numerical boundary condition (BC) package was developed based on the measurements done by a parallel working group. The BC package is a set of correction procedures to modify the inlet (CCA) and outlet (ICA, ECA) diameters so that Doppler flow measurements obtained in the internal and external carotid artery can be used. A conference abstract was accepted for oral presentation about the method and a manuscript for a journal article is underway. Comparison of intraoperative backflow measurements with CoW status in 3D model is currently under evaluation. Furthermore, a smaller and a larger numerical study is in progress, comparing lesion characteristics with the flow and wall shear stress field of the pre and post operative states.

Carotid plaque analysis with the VascuCap software was performed for enrolled patients, comparison of this with clinical data is ready. Our propensity matched analysis study of carotid stent implantation vs carotid artery endarterectomy in perioperative new DWI lesions on postoperative MR images was presented in London Charing Cross Congress and published in Journal of Cardiovascular Development and Disease.

In some targeted patients, intraoperative ultrasound measurements were performed. We plan to compare the data of intraoperative backflow measurements with the results measured with US. Postoperative 3D US measurements were taken two patients, whose complex pre-intra and postoperative hemodynamic measurements will be published in technical note in the next year.

The NIRS measurements dataset has been cleaned and ready for statistical evaluation. With NIRS results, the results of these preliminary studies were accepted as abstracts at international conferences. Intraoperative NIRS data and changes in intraoperative entropy measurements and cognitive function tests caused by desaturation were used to supplement the study directions. Both projects' results will be published within a year.

Hematoxylin-eosin stained; digitalised slides of the plaque samples are available for every case. Detailed analysis of the scanned slides is under investigation. For structural analysis of plaques, they had been digitalized with 3DHitech microscope. We have acquired TNFa, IL-6, and IL-10 ELISA kits using funds allocated for the project. These were intended to determine the extent of atherosclerosis-induced inflammatory stress on the body. Categorization of the plaque material components has begun, highlighting the vulnerable components. Evaluation will focus on clinically determined subgroups.

Our review article on the potential role of OCT in the measurement of microcirculatory changes caused by carotid artery stenosis reconstruction was published in 2021. Our original article on comparing OCT and clinical data has been published in Geroscience in 2022 and OCT data compared to CoW status was published in 2013. The proof-of-concept study of OCT and TCD study is under review in Journal of Cerebral Blood Flow and Metabolism. The manuscript of the comparison of OCT and CoW data was published in Journal of Clinical Medicine.

Pre-operative TCD tests were performed on all enrolled patients, but unexpectedly high ration of the patients did not have a proper TCD window present and therefore were excluded from further examination for this sub-project. Cerebrovascular reactivity estimation results according to circle of Willis morphology were submitted to Journal of Cerebral Blood Flow and Metabolism. Our results were presented at SIVS International Congress. Correlation analysis of TCD data and OCTA data were accepted for publication in PlosOne. One manuscript regarding the cerebrovascular reactivity on TCD is pending submission to international journals.

FUTURE PROSPECTIVES

We plan to review clinical protocols and surgical indications for asymptomatic patients based on our multidisciplinary results. The current multidisciplinary prospective clinical study gave some interesting and thought-provoking results due to the interdisciplinary cooperation.

The results are currently being evaluated using MR, NIRS data and intraoperative entropy and desaturation-induced changes in cognitive function. Our aim is to assess diffusion tensor imaging metric and volumetric changes from preoperative to 2-year MRI in the white matter of the index and contralateral sides of the brain. These results will be published in the next year. Our ongoing project's aim is to investigate the intraoperative US measurements and the backflow results, the manuscript is under review. There is plan for further TCD measurements evaluation to compare the CO₂ reactivity with results obtained with other vasoactive stimuli and the CCC results of healthy young individuals in the light of their Willis circle variation.

Immunohistological processing of collected plaques has been performed. The availability of CTA imaging-based lumen segmentation software makes possible to examine the carotid artery plaque morphology. The development of the CFD analysis 3D models gives an opportunity to describe the non-conventional fluid dynamics system's pathological changes in complex lumen geometries. The combination of the two methods opens a new era in examination of the interaction of pathological changes in the stenotic lumen. Our further aim

is a comparison of a predefined subgroup from our previous results based on histopathological features and CFD features to determine hemodynamically prone localization for high-risk plaque features.

PUBLICATIONS

Papers

- Péter Vince Banga, MD Andrea Varga, MD Csaba Csobay-Novák, MD, Marton Kolossváry, MD, Emese Szántó, Gustavo S. Oderich, MD, László Entz, MD, Péter Sótónyi, MD: Incomplete circle of Willis is associated with a higher incidence of neurologic events during carotid eversion endarterectomy without shunting, *Journal of Vascular Surgery*, 2018
- Andrea Varga, Giovanni Di Leo, Péter Vince Banga, Csaba Csobay-Novák, Márton Kolossváry, Pál Maurovich-Horváth, Kálmán Hüttl: Multidetector CT angiography of the Circle of Willis: association of its variants with carotid artery disease and brain ischemia, *European Radiology*, 2018
- István L, Czakó C, Élő Á, Mihály Z, Sótónyi P, Varga A, Ungvári Z, Csiszár A, Yabluchanskiy A, Conley S, Csipő T, Lipecz Á, Kovács I, Nagy ZZ: Imaging retinal microvascular manifestations of carotid artery disease in older adults: from diagnosis of ocular complications to understanding microvascular contribution, *Geroscience*, 2021
- István L, Czakó C, Benyó F, Élő Á, Mihály Z, Sótónyi P, Varga A, Nagy ZZ, Kovács I.: The effect of systemic factors on retinal blood flow in patients with carotid stenosis: an optical coherence tomography angiography study, *Geroscience*. 2022 Feb;44(1):389-401, 2022
- B Csippa, Z Mihály, Z Czinege, MB Németh, G Halász, G Paál, P Sótónyi Jr: Comparison of manual versus semi-automatic segmentations of the stenotic carotid artery bifurcation, *Appl Sci*. 2021, 11: 8192., 2021
- Magyar-Stang R, István L, Pál H, Csányi B, Gaál A, Mihály Z, Czinege Z, Sótónyi P, Tamás H, Koller A, Bereczki D, Kovács I, Debreczeni R.: Impaired cerebrovascular reactivity correlates with reduced retinal vessel density in patients with carotid artery stenosis: Cross-sectional, single center study., *PLoS One*. 2023 Sep 14;18(9):e0291521, 2023
- Magyar-Stang R, Pál H, Csányi B, Gaál A, Mihály Z, Czinege Z, Csipo T, Ungvari Z, Sótónyi P, Varga A, Horváth T, Bereczki D, Koller A, Debreczeni R: Assessment of cerebral autoregulatory function and inter-hemispheric blood flow in older adults with internal carotid artery stenosis using transcranial Doppler sonography-based measurement of transient hyperemic response after carotid artery compression, *Geroscience*, 2023
- Mihály Z, István L, Czakó C, Benyó F, Borzsák S, Varga A, Magyar-Stang R, Banga PV, Élő Á, Debreczeni R, Kovács I, Sótónyi P.: The Effect of Circle of Willis Morphology on Retinal Blood Flow in Patients with Carotid Stenosis Measured by Optical Coherence Tomography Angiography, *J Clin Med*. 2023 Aug 16;12(16):5335., 2023
- Mihály Z, Booth S, Nguyen DT, Vecsey-Nagy M, Vértes M, Czinege Z, Péter C, Sótónyi P, Varga A: A Propensity-Matched Comparison of Ischemic Brain Lesions on Postprocedural MRI in

Endovascular versus Open Carotid Artery Reconstruction, J Cardiovasc Dev Dis. 2023 Jun 13;10(6):257, 2023

- Richárd Wéber, Dániel Gyürki, György Paál: First blood: An efficient, hybrid one- and zero-dimensional, modular hemodynamic solver, Int J Numer Meth Biomed Engng.2023;39:e3701, 2023
- Dániel Gyürki, Péter Sótonyi, György Paál: Central arterial pressure estimation based on two peripheral pressure measurements using one-dimensional blood flow simulation, Computer Methods in Biomechanics and Biomedical Engineering, 2023
- Mihály Z; Fontanini DM; Sándor ÁD; Dósa E; Lovas G; Kolossváry E; Kovács I; István L; Entz L; Sótonyi jr, P: A nyaki verőér-szűkületes betegek ellátási irányelveinek különbségei Európa különböző országaiban, ORVOSI HETILAP 161 : 51 pp, 2139-2145., 2020

Papers/articles under review

- Hanga Pál: Atherosclerosis leads to decreased cerebrovascular reactivity and cardiovascular autonomic nervous system dysfunction simultaneously. - submitted to Scientific Reports
- Zsófia Czinege: Identifying high risk patients for perioperative neurological events during carotid endarterectomy by the analysis of Willis circle and stump pressure. – submitted to Scientific Reports
- Banga Péter: Contralateral carotid occlusion with insufficient circle of Willis is associated with a higher incidence of neurologic events during carotid endarterectomy without shunting. - submitted to Journal of Vascular Surgery
- Ágnes Sándor: The effect of carotid endarterectomy on cognitive function regarding cerebral hypoperfusion submitted to Scientific Reports

Abstracts accepted by domestic and international conferences

- Booth S. Periprocedural Ischemic Brain Lesions in Open vs. Endovascular Carotid Artery Reconstruction, a Propensity Matched Comparison. Semmelweis International Vascular Symposium 2023 Budapest
- Varga A Preliminary results of early carotid endarterectomy following stroke/TIA and analysis of postoperative neurological events related to the anatomy of the circle of Willis. Semmelweis International Vascular Symposium 2023 Budapest
- Czinege Z. Pulse wave analysis in differing Willis-circle variants. Semmelweis International Vascular Symposium 2023 Budapest
- Sándor Á, The effect of carotid endarterectomy on cognitive function regarding cerebral hypoperfusion. Semmelweis International Vascular Symposium 2023 Budapest
- Pál H: Comprehensive analysis of cerebral vasoactive stimuli: Transcranial doppler study. Semmelweis International Vascular Symposium 2023 Budapest

- Csányi B: Estimation of compensation for Circle of Willis anastomoses in patients with significant internal carotid artery stenosis – TCD study. Semmelweis International Vascular Symposium 2023 Budapest
- István L: Measurements of optical coherence tomography angiography in patients with carotid artery stenosis Semmelweis International Vascular Symposium 2023 Budapest
- Gyürki D: Estimation of collateral blood flow rate with one-dimensional mathematical model in the case of patients with isolated middle cerebral artery Semmelweis International Vascular Symposium 2023 Budapest
- Mihaly Z. Propensity matched comparison of ischemic brain lesions on postprocedural MRI in endovascular versus open carotid artery reconstruction. CharingCross Symposium 2023.
- Czinege Zsófia: A Willis-kör anatómiai variánsainak és az intraoperatív regionális agyi oxigéntelítettség változásának együttes értékelése segíti a szelektív shunt alkalmazásának optimalizálását a nyaki verőér nyitott rekonstrukciója során. 2022. Május, Balatonfüred Magyar Angiológiai és Érsebészeti Társaság Kongresszusa.
- István Lilla: A retina érhálózatának OCT angiográfias vizsgálata nyaki érszűkülettel rendelkező betegek esetében. 2022. Május, Balatonfüred Magyar Angiológiai és Érsebészeti Társaság Kongresszusa
- Gyürki Dániel: Willis-kör vizsgálata nyaki verőér szűkület műtete közben, egydimenziós áramlástan segítségével. 2022. Május, Balatonfüred Magyar Angiológiai és Érsebészeti Társaság Kongresszusa
- Csippa Benjamin: Carotis bifurkáció modelljének előállítása orvosi és mérnök szemmel: előkészítés fontossága numerikus áramlástani szimulációkhoz 2022. Május, Balatonfüred Magyar Angiológiai és Érsebészeti Társaság Kongresszusa
- Stang Rita: A cerebrovascularis reaktivitás becslésének új aspektusa szignifikáns carotis interna stenosisban carotis compressios teszt alapján - TCD tanulmány. 2022. Május, Balatonfüred Magyar Angiológiai és Érsebészeti Társaság Kongresszusa
- Stang Rita: Cerebral vasoreactivity examinations by transcranial Doppler sonography in patients with internal carotid artery stenosis. 2022 January, Virtual Network of European Neuroscience Schools, Brain & Mind Cluster online seminar
- Stang Rita: Estimation of compensation for Circle of Willis anastomoses in patients with significant carotid stenosis - TCD study. 2022. Május, Lyon, France European Stroke Organisation Conference (e-Poster)
- Pál Hanga: Comprehensive Analysis of Cerebral Vasoactive Stimuli: Transcranial Doppler Study. 2022. August, Balatonfüred Hungarian Medical Association of America (HMAA) oral presentation
- Gaál Anna: Correlation between cerebral vasoreactivity and retinal blood flow parameters in patients with significant internal carotid artery stenosis. 2022. August, Balatonfüred Hungarian Medical Association of America (HMAA) oral presentation

- Csányi Borbála: Estimation of compensation for Circle of Willis anastomoses in patients with significant internal carotid artery stenosis - TCD study. 2022. August, Balatonfüred Hungarian Medical Association of America (HMAA) Poster presentation
- Márton Bence Németh: Boundary condition options for Carotid bifurcation analysis using Doppler velocity measurements. Conference on modelling fluid flow (CMFF 2022).
- Richárd Wéber: One-dimensional modelling of the artery network using the method of characteristics with a lumped heart. Conference on modelling fluid flow (CMFF 2022).
- R Stang, S Darasteh, B Csányi, Z Mihály, P Osztrogonác, Z Czinege, T Horváth, P Sótónyi, D Bereczki, R Debreczeni. Delayed transient hyperemic response recorded by transcranial doppler Sonography. Recommendation of a new common carotid artery compression index. (Simmelweis 250 Klinikai Konferencia)
- Zsuzsanna Mihály, Lilla István, Fruzsina Benyó, Cecília Czakó, Illés Kovács, Andrea Varga, Péter Banga, Péter Sótónyi. The effect of Circle of Willis (CoW) morphology and carotid endarterectomy (CEA) on retinal blood flow in patients with carotid stenosis measured by optical coherence tomography angiography (OCTA). (ESVS 35th congress, e-poster)
- Rita Stang: Estimation of cerebrovascular reactivity in patients with significant carotid stenosis by Transcranial Doppler during Valsalva maneuver (ESVS 35th congress, e-poster)
- Rita Stang: Comparative analysis of functional transcranial doppler studies in patients with significant carotid stenosis. (ESOC 2021, e-poster)
- Z Czinege: The joint evaluation of compromised Circle of Willis status and intraoperative regional cerebral oxygen saturation drop helps selective shunting in carotid artery open reconstruction. (ESVS 35th congress, Fast track presentation)
- Stang, Rita: Funkcionális transcranialis Doppler vizsgálatok összehasonlító elemzése szignifikáns carotis interna szűkületben szenvedő betegekben. (Magyar Stroke Társaság konferenciája)
- Measurement of optical coherence tomography angiography in patients with carotid artery stenosis (XLI. International Vascular Workshop 2020)
- Preliminary results to define NIRS Regional Cerebral Oxygen Saturation (rSO₂) threshold for intraoperative shunting in patients undergoing ICA reconstruction (XLI. International Vascular Workshop 2020)
- More selective shunting based on the intraoperativ NIRS and CoW status in carotid artery open reconstruction (ESVS 34th Annual Meeting 2020)
- The late transient hyperemic response recorded with transcranial doppler sonography. recommendation of a new parameter according to the common carotid artery compression test (ESO-WSO 2020 Conference)

Student Conferences presentation and rewards:

- Gaál Anna, Csányi Borbála A cerebrális vazoreaktivitás és a retinális érsűrűség atherosclerosisba 2023 Korányi Frigyes Tudományos Fóruma Dr Stang Rita- Dr István Lilla Külön Díj
- Ágoston Dóra, Heller Áron: Nyaki verőérszűkület rekonstrukciójának intraoperatív rizikó csökkentése a NIRS és CoW együttes értékelésével. 2022. Országos Diákköri Konferencia Témavezetők: Dr Mihály Zsuzsanna, Prof. Dr. Sótonyi Péter Első helyezés
- Samuel Booth Periprocedural Ischemic Brain Lesions in Open vs. Endovascular Carotid Artery Reconstruction, a Propensity Matched Comparison. 2022. Február, Budapest Tudományos Diákköri Konferencia Témavezetők: Dr Mihály Zsuzsanna, Prof. Dr. Sótonyi Péter
- Csányi Borbála: A Willis-köri anastomosisok jelentőségének vizsgálata szignifikáns carotis stenosisban szenvedő betegekben 2022. Február, Budapest Tudományos Diákköri Konferencia Témavezetők: Debreczeni Róbert, Stang Rita
- Ágoston Dóra, Heller Áron: Nyaki verőérszűkület rekonstrukciójának intraoperatív rizikó csökkentése a NIRS és CoW együttes értékelésével. 2022. Február, Budapest Tudományos Diákköri Konferencia Témavezetők: Dr Mihály Zsuzsanna, Prof. Dr. Sótonyi Péter
- Ágoston Dóra, Preoperatív CoW státusz és intraoperatív NIRS alkalmazása cerebrovaszkuláris rizikó becslésére nyaki verőér szűkületes betegek esetén (TDK Konferencia 2020 2. helyezés; témavezető: Dr. Sótonyi Péter, konzulens: dr. Mihály Zsuzsanna)
- Darasteh, Examination of Transient Hyperaemic response in MCA by Transcranial Doppler 2020. Február, Budapest Tudományos Diákköri Konferencia Témavezetők: Debreczeni Róbert, Stang Rita
- David Hsin-Kuang Chen Preliminary results to define NIRS Regional Cerebral Oxygen Saturation (rSO₂) threshold for intraoperative shunting in patients undergoing ICA reconstruction 2019. Február, Budapest Tudományos Diákköri Konferencia Témavezetők: Dr Mihály Zsuzsanna, Prof. Dr. Sótonyi Péter
- Darasteh, B.: Examination of Transient Hyperaemic response in MCA by Transcranial Doppler, TDK conference SE 2020, 2020
- Chen, D.: Preliminary results to define NIRS Regional Cerebral Oxygen Saturation (rSO₂) threshold for intraoperative shunting in patients undergoing ICA reconstruction, TDK conference SE 2020, 2020
- Ágoston Dóra: Preoperatív CoW státusz és intraoperatív NIRS alkalmazása cerebrovaszkuláris rizikó becslésére nyaki verőér szűkületes betegek esetén, TDK Konferencia SE 2020, 2020
- Ágoston Dóra, Heller Áron: Nyaki verőérszűkület rekonstrukciójának intraoperatív rizikó csökkentése a NIRS és CoW együttes értékelésével, TDK Konferencia SE 2022, 2022
- Csányi Borbála: A Willis-köri anastomosisok jelentőségének vizsgálata szignifikáns carotis stenosisban szenvedő betegekben, TDK Konferencia SE 2022, 2022
- Samuel Booth: Periprocedural Ischemic Brain Lesions in Open vs. Endovascular Carotid Artery Reconstruction, a Propensity Matched Comparison, TDK Konferencia SE 2022, 2022

- Ágoston Dóra, Heller Áron: Nyaki verőérszűkület rekonstrukciójának intraoperatív rizikó csökkentése a NIRS és CoW együttes értékelésével, TDK Konferencia SE 2022, 2022

Theses, PhD dissertations

- dr Mihály Zsuzsanna A nyaki verőér szűkület áramlási modellezése és az in-sztent resztenózis vizsgálata PhD disszertáció 2022
- Az idegrendszer monitorizálása carotis műtét alatt (témavezető: dr. Sándor Ágnes)
- Fredrik Gran Correlation of hemodynamics with NIRS and entropy during X-clamping of carotid artery (témavezető: dr. Sándor Ágnes)
- Pál Hanga A cerebrovaszkuláris rezervkapacitás mérése transcranialis Dopplerrel szignifikáns carotis internastenosiban szenvedőkben Valsalva manőver során 2021 diplomamunka (témavezető: dr. Stang Rita- Debreczeni Róbert)
- Gaál Anna Funkcionális transcranialis Doppler vizsgálatok összehasonlító elemzése 2021 diplomamunka (témavezető: dr. Stang Rita – dr Debreczeni Róbert)
- David Hsin-Kuang Chen Hemodynamic Changes in Patients Undergoing Carotid Artery Reconstruction Based on the Anatomy of Circle of Willis and Near-Infrared Spectroscopy (NIRS) (2021 diplomamunka; témavezető: Dr. Sótóyi Péter)