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CIRCLE OF WILLIS MORPHOLOGY AND CEREBROVASCULAR COMPLICATIONS IN CAROTID ATHEROSCLEROSIS

PhD thesis

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List of abbreviations

ACA = anterior cerebral artery

ACAS = Asymptomatic Carotid Atherosclerosis Study

ACST-1 = Asymptomatic Carotid Surgery Trial-1

ACT I = Asymptomatic Carotid Trial I

AComA = anterior communicating artery

A1 = precommunicating segment of the anterior cerebral artery

BMT = best medical treatment

CAS = carotid artery stenting

CCA = common carotid artery

CEA = carotid eversion endarterectomy

CoW = Circle of Willis

CREST = Carotid Revascularization Endarterectomy versus Stenting Trial

CTA = computerized tomography angiography

DSA = digital subtraction angiography

DWI = diffusion-weighted imaging

ECA = external carotid artery

ECST = European Carotid Surgery Trial

EVA-3S = Endarterectomy Versus Angioplasty in patients with Symptomatic Severe Carotid Stenosis

FLAIR = fluid-attenuated inversion recovery

HR = hazard ratio

ICA = internal carotid artery

ICST = International Carotid Stenting Trial

iMCA = isolated middle cerebral artery

INE = immediate neurological event

MCA = middle cerebral artery

MD CTA = multidetector computerized tomography angiography

MRI = magnetic resonance imaging

MRA = magnetic resonance angiography

NASCET = North American Symptomatic Carotid Endarterectomy Trial

NNT = number needed to treat

OD = odds ratio

PACS = picture archiving and communication system

PCA = posterior cerebral artery

PComA = posterior communicating artery

PC-MRA = phase contrast magnetic resonance angiography

P1 = precommunicating segment of the posterior cerebral artery

RCT = randomized controlled trial

RR = relative risk

SD = standard deviation

SPACE = Stent-Protected Angioplasty versus Carotid Endarterectomy

TIA = transient ischemic attack

3D-TOF = three dimensional time-of-flight

TCCD = transcranial color coded Doppler

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1. Introduction

1. 1. History of the Circle of Willis

Although the first pathoanatomical description of the intracranial arterial circle by Fallopius and Johann Jakob Wepfer dates back to 1561 and 1658, Thomas Willis is best known for his description and figuration of the circle of Willis (CoW) in his work „The Anatomy of the Brain and Nerves" (1664) demonstrating the whole of the circle. He was also the first to realize the physiologic significance of the anastomosis supporting this with relevant scientific investigations and well-documented case reports. Willis and his colleagues were pioneers in developing a new dissection method of the brain removing it in whole, enabling to study a much less deformed organ and the delicate anatomy of the base of the brain. Another achievement was the use of a new organ preservation technique with pure alcohol (Robert Boyle). Christopher Wren invented intravenous injection, later applied by Willis and his colleagues with dye into arteries. This method, similar in principle, predated radiologic angiography (1).

1. 2. Anatomy and collateral circulation of the CoW

The CoW is fed by four cervical arteries: the two internal carotid arteries (ICA) and the two vertebral arteries. The vertebral arteries later give origin to the basilar artery, which divides into the two posterior cerebral arteries (PCA). The ICA enters the skull base through the carotid canal in the petrous temporal bone. It then proceeds within the cavernous sinus and finally passes medial to the anterior clinoid process. At this point, it divides into the middle and anterior cerebral arteries (MCA and ACA, respectively), and gives off two smaller branches, the anterior choroidal artery and the posterior communicating artery (PComA). The PComA has a length of 17-25 mm linking the ICA and the vertebrobasilar sytem (2).

The CoW is a polygon at the skull base with seven segments. The three anterior elements are the two precommunicating segments (A1) of the ACA and the anterior communicating artery (AComA), which together form the anterior semicicle. The two

posterior segments are the posterior communicating artery (PComA) and the precommunicating segment (P1) of the PCA, both bilateral, composing the two posterior semicircles.

The A1 passes anteriorly and medially from the division of the ICA, extending 10-20 mm in length, and continuing in the postcommunicating segment of the ACA. The AComA has a length of 0.1 to 4 mm. The AcomA is usually single. Sometimes double or triple AComA can be seen, rarely a network of fine arteries can be identified (2).

The precommunicating segment (P1) of the PCA is originating from of the basilar artery and has a lateral and slightly anterior course. Its length ranges from 2 to 15 mm in adults (2).

Reduction of blood flow due to a severe ICA stenosis or an intraoperative cross clamping of the ICA requires compensation via other pathways to maintain sufficient perfusion of the affected vascular territory. The CoW is considered the primary collateral pathway which may allow blood supply from the contralateral ICA by the anterior semicircle with anterograde flow through the contralateral A1, via the patent AComA and retrograde flow through the ipsilateral A1. Collateral flow from the vertebrobasilar system to the obliterated ICA can be provided throught the P1 and with simple reversal of flow (posterior-to-anterior in direction) in the PComA (3, 4). In case of significant ICA stenosis with tight stenosis/occlusion of the contralateral ICA, the perfusion of the ICA territory might rely on the flow from the vertebrobasilar system via the PComA. Blood flow through the contralateral P1, PComA and the whole anterior semicircle can supply the more severely affected, single or clamped ipsilateral ICA. The potential to develop these anterior and posterior collateral pathways depends on the continuity of the anterior and posterior semicircles of the CoW, respectively. Supply from the external carotid artery (ECA) and the leptomeningeal branches are considered secondary collaterals as they need more time to develop.

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1. 3. Imaging of the CoW

1. 3. 1. Digital subtraction angiography

Digital subtraction angiography (DSA) is considered the reference of standard in imaging of the CoW. Apart from anatomical details, selective four-vessel DSA can obtain information about the collateral flow dynamics from the contralateral ICA, the vertebrobasilar system, the ECA and in particular from the leptomeningeal collaterals. However, DSA is not performed under normal physiologic conditions. As the forced injection of contrast material increases the arterial pressure, it can open non-functional collaterals. Conversely it is possible that a non-recruited but patent vessel is not seen with DSA, because compression maneuvers and superselective catheterization are not routinely performed. This technique has further disadvantages including invasiveness, risk, and high cost.

1. 3. 2. Computerized tomography angiography

Multidetector (MD) computerized tomography angiography (CTA) is a fast and minimally invasive examination with a high spatial resolution. It allows for image reformats along any plane and for 3D views to detect normal variants (fenestrations, duplications), persistent carotid-vertebrobasilar anastomoses and abnormalities of the intracranial circulation with a major clinical impact, such as incompleteness or aneurysms (5). CTA is increasingly used for the preoperative assessment of steno-occlusive carotid disease, providing detailed anatomical depiction of the extracranial and intracranial arteries in a single scan. In contradistinction to magnetic resonance angiography (MRA) CTA is not dependent on flow velocity, thereby allowing accurate documentation of vessel diameters. The disadvantages of CTA compared to MRA include lack of information on flow direction, possible venous contamination, radiation exposure, and administration of iodinated contrast material.

1. 3. 3. Transcranial Color Coded Doppler Ultrasound

Transcranial Color Coded Doppler Ultrasound (TCCD) can determine flow patterns suggestive of primary or secondary collateral circulation, for instance presence of retrograde flow in the ipsilateral A1, PComA, from the ophthalmic artery (direct criteria) (6) or higher flow velocity in the P1 segment than the MCA on the symptomatic side or following compression of the ipsilateral ICA (indirect flow criteria for the PComA) (7). TCCD allows continuous noninvasive monitoring of MCA blood velocity (7) and of silent cerebral emboli, thus identifying a group of patients at higher risk of subsequent stroke or transient ischemic attack (TIA) (8). Furthermore, TCCD is helpful in assessing vasomotor reactivity.

TCCD identifies major collateral pathways with a sensitivity of 80-90% and a specificity of 80% when compared with angiography, but the specificity is lower (47-60%) for the identification of PComAs (6, 7). The series of specific compression maneuvers of the ipsilateral, contralateral common carotid arteries (CCA) and vertebral arteries required to identify collaterals might be lengthy and not very well appreciated by the patients. Moreover, the acoustic window is known to become smaller or disappear with increasing age, and this may prevent insonation in up to 30% of cases (6).

1. 3. 4. Phase contrast MR angiography

The advantage of phase contrast MRA (PC-MRA) is, that it contains information about blood flow direction and velocity. This technique allows for producing three direction-sensitive flow images (right/left, anterior/posterior, superior/inferior) for each location. With conventional magnitude images the static anatomy of the CoW can be also determined. However, the AComA most frequently can not be visualized, due its short course between the A1 segments. The vessel detection on PC-MRA depends on two main technical factors: spatial resolution and velocity encoding strength. Small voxel size and therefore high spatial resolution can increase small vessel detection, but this advantage must be weighed against decreased signal-to-noise ratio and increased acquisition time. Regarding velocity encoding, if too high velocity is chosen, it will result in lower signal from low-flow vessels like the PComA, making the PComA more difficult to detect. If

too low velocity is chosen, aliasing occurs and flow can be erroneously portrayed as being in the opposite direction. PC-MRA tends only to delineate the functional collaterals with substantial flow, therefore low-flow collateral filling, that might be seen on DSA, may be missed with MRA (9).

1. 3. 5. Three-dimensional time-of-flight MR angiography

Three-dimensional time-of-flight (3D TOF) MRA is another noninvasive, objective and sensitive MR technique for depicting the anatomy of the CoW without the need of intravenous contrast material. It has its own disadvantages, however. Some of the vessels cannot be seen with 3D TOF MRA because of turbulent flow, the saturation effect of slow flow or long in-plane flow, or slower velocity of the blood adjacent to the vessel wall. In addition, laminar flow-related spin dephasing and partial volume averaging at the vessel wall may result in signal loss and underestimation of vessels (10). The general contraindications of MRI (claustrophobia, metallic implants, pacemakers, high body weight) also limit the application of MRA.

1. 4. Studies of the CoW in relation to carotid atherosclerosis

The CoW has been widely investigated in the 20th-21st centuries and the earliest non-selected post mortem studies showed substantial individual differences (11, 12).

Further autopsy studies found, that the prevalence of absent or hypoplastic segments was increased in stroke patients as compared to normal subjects (13, 14). Discontinuity of the CoW in patients with symptomatic ICA stenosis was associated with higher risk of transient ischemic attack (TIA) and ischemic stroke (3). Subjects with high-grade ICA stenosis or occlusion with nil or one ipsilateral collateral vessel had a higher likelihood of stroke when compared to patients with two functional ipsilateral collaterals (15-17). A single imaging study showed decreased prevalence of CoW variants in patients with TIA or ischemic stroke due to severe carotid disease (18), while all others found higher prevalence of hypoplastic or absent segments (9, 10, 16, 17, 19).

Carotid endarterectomy (CEA) is a frequent vascular surgical procedure with low reported complication rates, postoperative stroke or death beeing its main considerations.

Cross-clamping during CEA may result in cerebral ischemia, which can be prevented by shunt usage. Those CEA patients who have collaterals supplying the operative side are less prone to perioperative stroke (3). The configuration of the primary collateral pathways may be a major risk factor for cerebral ischemia during clamping of the ICA; in particular, the number of non visualized segments correlates with intolerance to cross clamping (20-23). TCCD ultrasound revealed association between undetectable CoW segments and decreased velocities of the MCA as well as ischemic electroencephalographic abnormalities (7).

Several articles addressed the CoW anatomy using DSA, TCCD (6, 7, 15) and MRA both in healthy volunteers (9, 24-26) and in patients with ischemic cerebrovascular diseases (6, 18, 20-22, 27-32). However, few reports have been published with the use of MD-CTA (19, 33-36), and apart from ours, only one of them focused exclusively on patients with ICA stenosis (19).

Similarly the impact of multiple incompleteness of the CoW has not been thoroughly studied either (23).

CTA could be incorporated in an imaging-based prediction model for prevention of unnecessary shunting, while establishing more precise indications of shunting for non-routine shunt-user vascular surgeons.

2. Aims

We aimed for

1) assessing the prevalence of anatomical variants of the CoW which may hamper collateral supply in a cohort of 544 CEA subjects compared to 196 controls, since recent data on the CoW variations in patients with carotid disease are sparse and conflicting

2) correlating these variants with cerebral ischemia proved by cerebral CT or magnetic resonance imaging (MRI)

3) determining the reproducibility of CTA in CoW assessment by estimating the intra- and inter-observer agreement

4) evaluating the impact of an incomplete CoW with an isolated MCA (iMCA) on immediate neurological events (INE) after CEA

5) reviewing the main carotid revascularization studies and comparing our immediate and in-hospital stroke/death rates of CEA with those published in the literature.

Aims 1)-3) were referred as radioanatomical approach, whereas aims 4-5) as clinical approach.

Ad 1) We hypothesized, that hypoplastic and non-visualized CoW segments occur more frequently in our patients with steno-occlusive carotid disease, leading to impeded intracranial collateral capacity.

Ad 2) Furthermore we hypothesized, that the flow reduction through the severely stenotic ICA, in association with an incomplete CoW, could have led to critical drop in the cerebral perfusion of the affected vascular territory and resulted in more frequent cerebral infarcts. Brain CT or MRI allowed us the objective evaluation of these infarcts.

Ad 4) Our final hypothesis was, that in case of incompleteness of the CoW from both the contralateral ICA and the vertebrobasilar system, the reduced brain perfusion on cross clamping of the ICA may cause more immediate neurologic complications following CEA.

3. Methods

3. 1. Study group

After approval from the Institutional Review Board was obtained (approval number *216/2016*) and signed informed consent was received from all subjects, we retrospectively analysed the data of our registry from the Heart and Vascular Center of Semmelweis University. To minimalize bias we recruited all CEA patients from January 2013 to November 2015. Eligibility to CEA was stated as ICA stenosis of >70% (in exceptional cases >50%) for symptomatic or ICA stenosis of >70% for asymptomatic subjects (Class I, Level of Evidence A). (37). Carotid artery stenosis severity was established according to the North American Symptomatic Carotid Endarterectomy (NASCET) method (38). Symptomatic ICA stenosis was defined as history of stroke, amaurosis fugax or TIA involving the ipsilateral ICA territory and in the period of 180 days prior to CEA. Patients with a severe disabling stroke due to large infarcts were generally not subjected to carotid revascularisation (39). Subjects without adequate preoperative CTA to evaluate the CoW and those who had shunting were excluded. Risk factors of atherosclerosis were defined according to the recommendations of the American Heart Association (40).

One patient was removed from the radioanatomical study group on the grounds of suboptimal preoperative imaging quality, but for the important outcome in this particular case the same patient was included in the clinical study, explaining the difference in patient numbers (544 versus 545). The patient's CoW could be assessed on the postoperative CTA, which was performed to check the patency of the operated ICA, since he had a major stroke after CEA.

3. 2. Eversion endarterectomy of the carotid arteries

10 experienced vascular surgeons participated in this study (experience ranging from 7 to 36 years). All CEAs were performed under general anaesthesia (41). Longitudinal incision parallel to the medial border of the sternocleidomastoid muscle was made. The carotid sheath was entered and the medial border of the jugular vein dissected.

After systemic heparin administration the ICA, the CCA and ECA were clamped sequentially. Following oblique transection of the carotid bulb and plaque removal with the eversion technique, the CCA and the proximal part of the ECA were endarterectomised. At the end of the CEA procedure the divided bifurcation was reunited with a simple end-to-end anastomosis. Technical success was considered when the plaque removal and the arterial wall reconstruction was achieved with <30% residual stenosis (42).

Intra-arterial shunting was rare and based on the individual decision of the operating surgeon. Shunting was performed when the carotid lesion was too high for eversion, or in case of relatively large acute brain infarct, or with multiple supra-aortic occlusions. In this series, specific neuromonitoring was not applied.

3. 3. Brain CT and carotid CTA Examinations

All examinations were performed on a 256-detector scanner (Brilliance iCT 256, Philips Healthcare, Best, The Netherlands).

Brain CT was obtained using the following parameters (field of view 200-250 mm, collimation 64×0.625, pitch 0.39, gantry rotation time 400 ms, tube voltage 120 kVp, tube current 120-204 mAs, slice thickness 2mm, dose-length product 312-626 mGycm).

All CTA examinations were performed from below the aortic arch to the vertex, with a field of view 180-200 mm. A collimation of 128×0.625 was used and a pitch of 0.758 (gantry rotation time of 330 ms). The tube voltage was 120 kVp and tube load 76–206 mAs, depending on the scanned body volume (average 129 mAs), resulting in a volume CT dose index of 220–608 mGycm (average 451 mGycm). Bolus tracking technique in the aortic arch was applied with 50 ml of iodinated contrast agent (Iomerone 400, Bracco Imaging SpA, Milan, Italy) followed by a 40 ml saline solution bolus, both injected at 5 ml/s through a 18G cannula. Continuous sections were reconstructed with 0.67 mm slice thickness and 512×512 matrix using hybrid iterative reconstruction technique (iDose, Philips Healthcare, Cleveland, USA).

The images were evaluated on a dedicated workstation (IntelliSpace Portal, Philips Healthcare, Best, The Netherlands). The visualization included 3-mm maximum intensity projection slabs parallel and perpendicular to the anterior skull base, providing

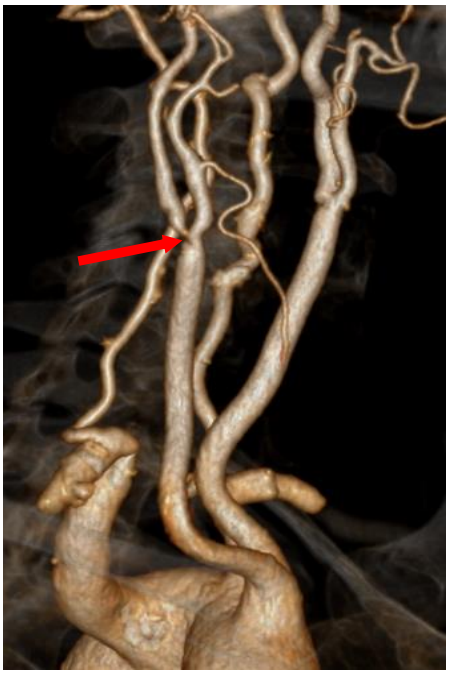
an overview of the CoW. The slab thickness and orientation were adjusted to obtain optimal visualization of vascular details, but final decisions were made on the thin section images.

The CT and CTA assessment was carried out by two skilled radiologists (R1 with 13 years of experience in vascular imaging and neuroradiology; R2, with 8 years of experience in vascular imaging).

3. 4. CTA assessment of the supraaortic arteries

The grade of the ICA stenosis was determined on CTA using a dedicated software provided by the vendor (Advanced Vascular Analysis, Philips Healthcare, Best, The Netherlands). Curved reconstruction of the supraaortic vessels was performed using automatic segmentation followed by manual correction of the centerline, if necessary. The ICA stenosis percentage was calculated according to the following formula (38):

%ICA stenosis = (1-[narrowest ICA diameter/diameter normal distal cervical ICA]) x 100



The vertebral arteries were regarded as normal (diameter of >1 mm), hypoplastic/stenotic (defined as <1 mm or less than one-third of the contralateral vertebral artery; or having a stenosis of >70%) or occluded/absent. In case of proximal subclavian artery occlusion or high-grade stenosis, we considered the vertebral artery absent or stenotic.

For the radioanatomical study individual ICA scores were established for each side (0 if <70%, 1 if 70–89%, 2 if 90–99%, 3 if 100%). We then categorized our subjects based on the sum of the individual ICA scores (range 0–6). **Fig. 1.**

Fig. 1. Oblique coronal volume rendered reconstruction of the supraaortic vessels from a carotid CT angiography showing a 70% right internal carotid artery stenosis (arrow) corresponding to score 1.

From the picture archive of the Heart and Vascular Center of Semmelweis University

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3. 5. Assessment of the CoW

The CoW was evaluated according to different approaches for the radioanatomical and clinical studies.

3. 5. 1. Segmental anatomy

Each individual segment was scored as normal (diameter ≥0.8mm), hypoplastic (<0.8mm) or non-visualized. We considered the AComA as patent if the junctions of A1 and A2 segments were in close contact and, therefore, not separable from each other on the CTA. The communication of the PComA with both the ICA and the posterior cerebral artery had to be visualized for defining the PComA. **Fig. 2.**

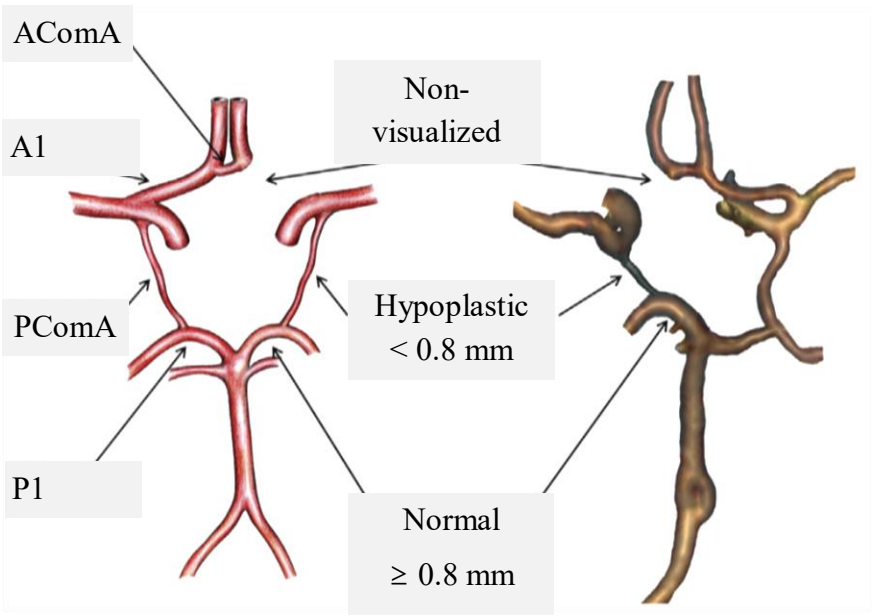

Fig. 2. Definition of the circle of Willis segments: normal diameter ≥0.8mm; hypoplastic <0.8mm; non-visualized/absent. AComA = anterior communicating artery; A1 = precommunicating segment of the anterior cerebral artery; PComA = posterior communicating artery; P1 = precommunicating segment of the posterior cerebral artery. Illustration from reference 23, courtesy of Péter Banga.

3. 5. 2. Anatomy of the anterior and posterior semicircles and the whole of the CoW

The anterior and two posterior semicircles of the CoW were first considered separately and classified as complete (all segments ≥0.8mm), hypoplastic (any of the components hypoplastic) or incomplete (any of the segments non-visualized). For the anterior semicircle, both A1 segments and the AComA were evaluated, since all vessels should be sufficiently developed to allow collateral supply from the contralateral to the ipsilateral ICA. For the posterior semicircles, the P1 segment and the PComA were assessed on either side. Data on the anterior and posterior parts were then crossed in a contingency table showing all observed combinations of the CoW (mirror configurations were not considered as separate entities).

We placed emphasis on the anatomy of the anterior and ipsilateral posterior semicircles of the CoW, which provide collaterals to the cross-clamped ICA on the surgical side. **Fig. 3.** These semicircles were qualified as normal, hypoplastic or incomplete as previously described. The new terminology of isolated middle cerebral artery (iMCA) was initiated. The MCA was considered isolated in case of incompleteness of both the anterior and ipsilateral posterior semicircles.

3. 5. 3. Reclassified CoW groups

Four CoW groups were created based on the number of hypoplastic and non-visualized segments, as follows:

I) not/minimally compromised CoW: complete or only one hypoplasia;

II) ≥2 hypoplastic segments;

III) 1 non-visualized segment;

IV) severely compromised CoW: ≥2 non-visualized segments.

Groups II), III) and IV) together were referred as compromised CoW.

3. 6. Reproducibility of CTA

To estimate the inter-observer agreement in defining CoW morphology on CTA, 100 randomly selected subjects' CTAs were assessed by two independent radiologists,

blinded for the patient characteristics and clinical outcomes. In case of discrepancy, agreement was reached by consensus reading. Intra-observer agreement was evaluated for both observers by comparing two different reading sessions at least 2 months apart.

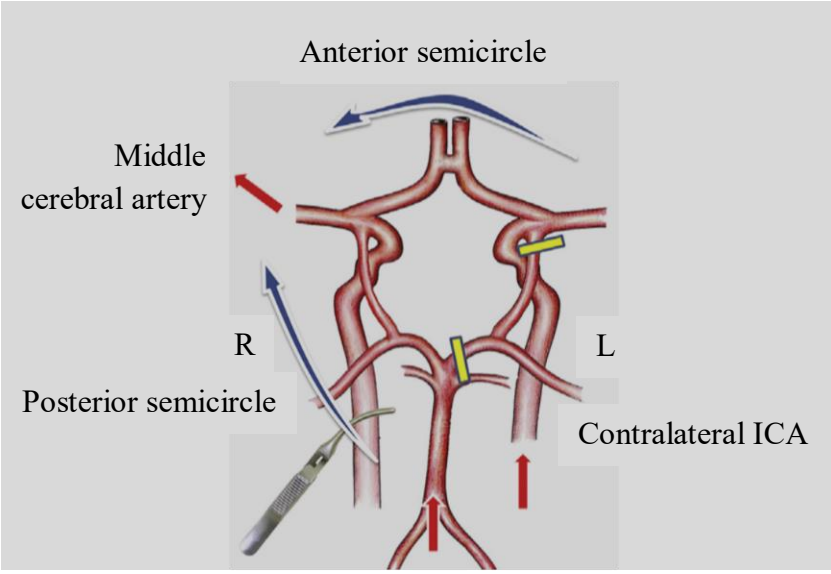

Fig. 3. The primary collateral network of the circle of Willis. The anterior semicircle was defined from the contralateral to the ipsilateral internal carotid artery (ICA): contralateral precommunicating segment of the anterior cerebral artery (A1), anterior communicating artery, ipsilateral A1. As per definition the posterior semicircle consisted of the precommunicating segment of the ipsilateral posterior cerebral artery and the ipsilateral posterior communicating artery connecting the ICA with the basilar artery.
Illustration from reference 23, courtesy of Péter Banga.

3. 7. Radioanatomical approach

3. 7. 1. Control group

Having reviewed all carotid CTAs performed in our institution from January 2014 to November 2017, we identified all subjects with either negative CTA or minor/mild carotid atherosclerosis to provide a sex-matched control group.

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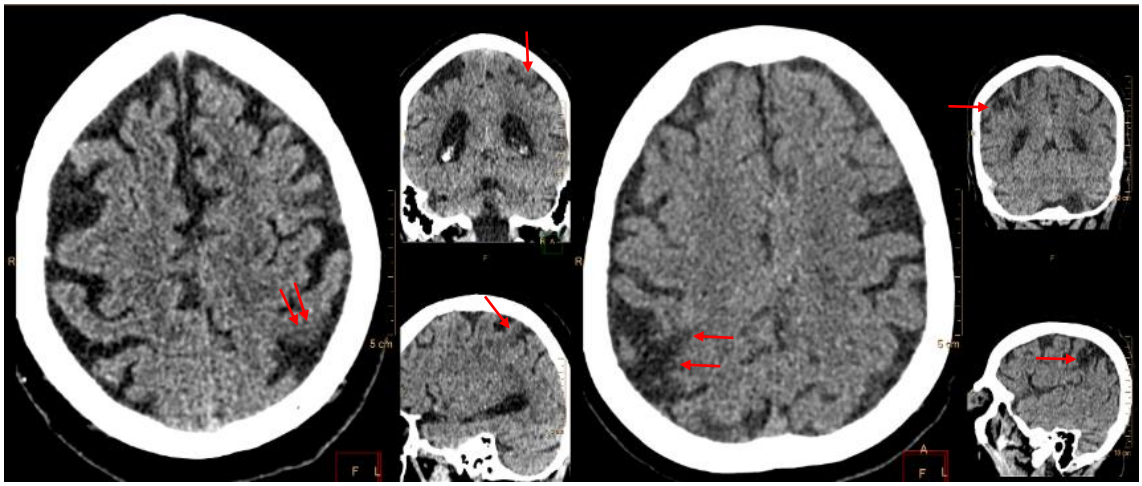
3. 7. 2. Brain CT assessment in the patient group

Any detectable ICA territory infarct on the side of surgery evidenced by CT hypoattenuation was considered as a positive CT regardless of the infarct's features (acute, subacute or chronic; territorial, lacunar or watershed). **Fig. 4.** The lack of infarct in the corresponding ICA territory was classified as a negative CT result.



a) b)

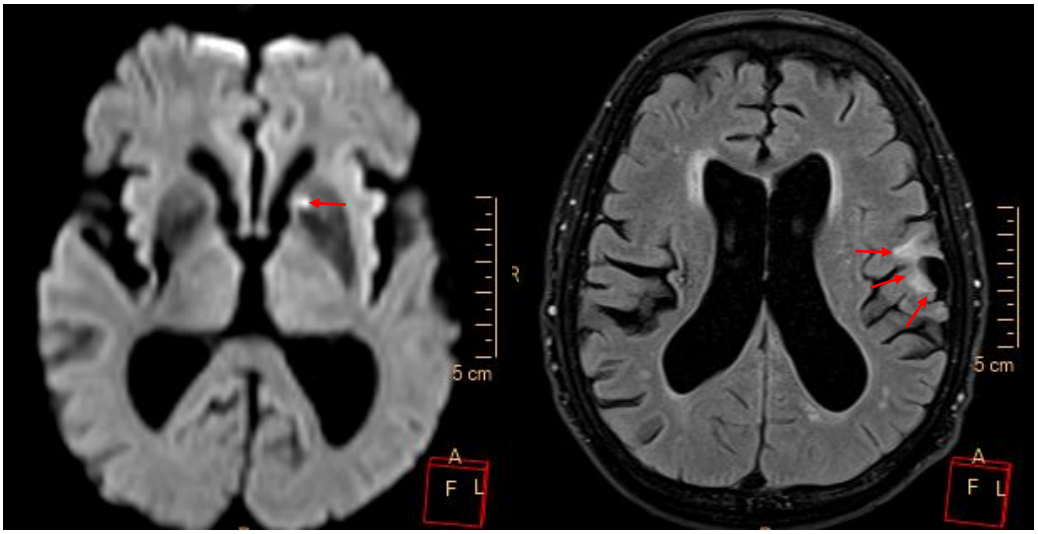
Fig. 4. Multiplanar reformats of unenhanced brain CTs. **a)** Very subtle left postcentral hypodensity with loss of the grey-white matter differentiation, corresponding to a recent left middle cerebral artery (MCA) infarct (arrows). **b)** Marked hypodensity in the right postcentral region, contributable to a chronic right MCA infarct (arrows). Both cases were regarded as postitive in the brain CT assessment.
From the picture archive of the Heart and Vascular Center of Semmelweis University

3. 7. 3. Brain MRI examinations

As part of an ongoing prospective study in the Heart and Vascular Center of Semmelweis University (Institutional Review Board approval number *169/2015*), between January 2016-May 2017, 72 brain MRIs were performed one day before the CEA on a 1.5T MR scanner (Achieva1.5, Philips Healthcare, Best, The Netherlands) using a

8-channel head coil. All of the 72 patients underwent CTA to evaluate plaque morphology and CoW anatomy. The aim of this substudy was to determine the association between i) plaque morphology and cerebral embolization (this subject is beyond the goals of the present thesis) and ii) configuration of the CoW and brain ischemia. The MRI protocol included diffusion weighted imaging (DWI), fluid-attenuated inversion recovery **(**FLAIR**),** T2-weighted, T2*- gradient echo, 3D T1-weighted sequences. The MRI examinations were evaluated on a picture archiving and communication system (PACS) workstation (IMPAX 6.5.2, AGFA Healthcare, Mortsel, Belgium).

An experienced neuroradiologist (R1) reviewed all MRIs and recorded the presence of any ipsilateral recent infarcts with diffusion restriction on DWI and that of old ischemic infracts displaying FLAIR hyperintensity. **Fig.5.**



a b

Fig. 5a) Hyperintensity on the „trace" image of diffusion weighted imaging (DWI) of a patient with left sided internal carotid artery stenosis showing a recent ipsilateral basal ganglion (deep middle cerebral artery (MCA) territory) infarct. This focus displayed signal drop on the corresponding apparent diffusion coefficient (ADC) map (not shown). **b)** Axial fluid-attenuated inversion recovery (FLAIR) sequence. A chronic left temporal (cortical MCA territory) infarct evidenced by FLAIR hyperintensity and parenchymal loss is illustrated (arrows).

From the picture archive of the Heart and Vascular Center of Semmelweis University

3. 8. Clinical approach

3. 8. 1. Outcome measures

The primary outcome was an INE, including any TIA or stroke immediately after CEA. Stroke was defined as an acute neurological event with focal symptoms and signs, lasting for 24 hours or more, consistent with focal cerebral ischemia (42), assessed by the modified Rankin scale by an independent neurologist on the first postoperative day. TIA was defined as a brief episode of neurological dysfunction caused by focal brain or retinal ischemia lasting less than 24 hours and without evidence of acute infarction (43). Upon INE urgent Duplex ultrasound imaging was performed to exclude ICA occlusion. In case of a patent ICA, brain CT with carotid CTA was done to exclude embolisation or treatable intracranial bleeding. At 4-6 days, the brain CT was repeated to reveal any new ischemic lesions.

Early secondary outcomes were defined as any significant events during the hospital stay after CEA. Recorded events were in-hospital postoperative stroke, myocardial infarction and death.

3. 8. 2. Literature search to compare outcome measures with eligible publications

We conducted PubMed and Cochrane Central Register searches using the keywords "*carotid artery disease"*, "*carotid atherosclerosis", "carotid endarterectomy"* until 2020. We checked the reference lists of review articles, meta-analyses, and original research studies to find other relevant publications such as i) randomized clinical trials (RCT) of subjects with or without symptomatic carotid artery stenosis reporting early or 30-day or longer term outcomes of CEA, and ii) meta-analyses of these RCTs, iii) observational studies using data registries for quality improvement.

3. 9. Statistical analysis

All statistical analysis was performed using the SPSS software (SPSS v.23; IBM Corp., Armonk, NY) according to the reporting standards of the Society of Vascular Surgery (36).

Continuous variables were expressed as mean ± standard deviation (SD), or median ± range, as appropriate. Categorical variables were expressed as counts and percentages. Distributions were given according to the three different approaches to classify the CoW.

3. 9. 1. Radioanatomical approach

Bivariate association analysis was performed using the ANOVA for continuous variables or $\chi 2$ test for categorical variables. The multiplicity of statistical tests accounts for applying the Bonferroni method. Considering that a statistical test was performed for each of the 11 analysed variables, the threshold for significance was divided by 10 and defined as $p \leq 0.005$. All variables that were significantly different between study patients and controls at bivariate analysis were entered into a multivariate logistic regression analysis for ordinal data. In the χ^2 test used for brain CT and MRI analysis $p \leq 0.05$ was considered statistically significant. Yates correction was applied in the MRI analysis. Intra-observer and inter-observer agreement was estimated using the Cohen κ statistics. Cohen's κ values were interpreted as: 0.81–1.00, excellent; 0.61–0.80, good.

3. 9. 2. Clinical approach

Fisher exact test and Pearson χ^2 test were used for categorical variables, the Mann–Whitney U test for ordinal variables, when appropriate, and two sample t-test was applied for continuous variables. Uni- and multivariate logistic models were used to predict INE. The threshold of significance was $p \leq 0.05$.

4. Results

4. 1. Radioanatomical approach

4. 1. 1. Characteristics of the radioanatomical study group

From 902 consecutive carotid endarterectomy patients in the study period, we initially excluded 4 subjects due to shunt usage plus ICA patching. Further exclusion criteria were i) poor image quality (21/898, 2%), ii) missing or incomplete CTA (302/898, 34%), iii) shunting during CEA (3/898, 0.3%) or the combination of the previous two criteria (28/898, 3%). Altogether 358 patients were excluded (40%) from the radioanatomical study. The remaining 544 study subjects were analysed (331 males, mean age 69±8 years, range 44–90 years). Of them, 205 (38%) had symptomatic ICA stenosis, including 59 patients (11%) with previous minor stroke, 25 (5%) with amaurosis fugax and 121 (22%) with TIA. The three study subjects with stenosis of <70% were all symptomatic. The demographics and co-morbidities of the 544 study subjects, those of the 196 controls, and the internal carotid artery scores of 544 study participants are summarized in **Table 1.**

4. 1. 2. Brain CT analysis in the study group

Of 544 study patients, 398 (73%) patients had a negative brain CT: 61/398 (15%) in Group I); 74/398 (19%) in Group II); 151/398 (38%) in Group III); 112/398 (28%) in Group IV). While the remaining 146 (27%) had a recent or old cerebral infarct in the territory of the operated ICA. 19/146 (13%) in group I); 24/146 (16%) in group II); 42/146 (29%) in group III); 61/146 (42%) in group IV). **Table 2.** The prevalence of brain ischemia was significantly higher in patients in group IV) as compared to groups I)-III) (p=0.002). As according to guidelines, disabling stroke with a large acute brain infarct is a contraindication to CEA, we have not found a major recent infarction in any of our study patients.

Table 1. Demographics, co-morbidities and different configurations of the circle of Willis in 544 study subjects and 196 controls, internal carotid artery scores of 544 study participants

	Study subjects (n=544)	**Controls (n=196)**	**p-value**
Demographics			
Male gender	331 (61%)	117 (60%)	0.777
Mean age ± SD (years)	69 ± 8	66±11	<0.001
Symptomatic	205 (38%)	-	
Cardiovascular risk factors, N (%)		***Data available in 173***	
Hypertension	500 (92%)	110 (64%)	<0.001
Cigarette smoking	175 (32%)	16 (9%)	<0.001
Hyperlipidemia	234 (43%)	49 (28%)	0.001
Coronary artery disease	170 (31%)	30 (17%)	<0.001
Chronic pulmonary disease	53 (10%)	13 (8%)	0.377
Chronic kidney disease (Stage IIIb-V)	16 (3%)	6 (3%)	0.726
Diabetes mellitus	203 (37%)	32 (18%)	<0.001
Internal carotid artery stenosis N (%)			
<70% on both sides (Score 0)	3 (0.6%)	-	
70–89% on side of surgery (Score 1)	128 (24%)	-	
70–89% on both sides (Score 2)	26 (5%)	-	
90–99% on side of surgery (Score 2)	282 (52%)	-	
90–99% on the side of surgery + 70–89% on the contralateral side (Score 3)	54 (10%)	-	
90–99% on both sides (Score 4) OR contralateral occlusion +either 70-89% (Score 4) or 90–99% on side of surgery (Score 5)	51 (9%)	-	

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	Study subjects (n=544)	**Controls (n=196)**	**p-value**
CoW groups N (%)			
Group I)	78 (14%)	55 (28%)	
Group II)	97 (18%)	52 (27%)	<0.001
Group III)	191 (35%)	55 (28%)	
Group IV)	178 (33%)	34 (17%)	

CoW = circle of Willis*; SD* = standard deviation

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Table 2. Association of circle of Willis configurations and demographics, cardiovascular risk factors, internal carotid artery stenosis and prevalence of brain ischemia

Variable	**Group I)** Complete CoW or 1 hypoplasia (n = 78)	**Group II)** ≥2 hypo-plasia (n = 97)	**Group III)** 1 non-visualized segment (n = 191)	**Group IV)** ≥2 non-visualized segments (n = 178)	**p**
Demographics					
Male gender, N (%)	48 (62%)	51 (53%)	121 (63%)	111 (62%)	0.32
Age ± SD (years)	68 ± 9	67 ± 8	69 ± 8	70 ± 8	0.11
Symptomatic, N (%)	21 (27%)	38 (39%)	68 (36%)	78 (44%)	0.07
Cardiovascular risk factors, *N (%)*					
Hypertension	70 (90%)	89 (92%)	175 (92%)	166 (93%)	0.81
Cigarette smoking	26 (33%)	39 (40%)	73 (38%)	37 (21%)	0.001
Hyperlipidemia	41 (48%)	41 (42%)	77 (40%)	75 (44%)	0.32
Coronary artery disease	34 (44%)	31 (32%)	52 (27%)	53 (30%)	0.07
Chr. pulmonary disease	9 (9%)	14 (14%)	19 (10%)	11 (7%)	0.29
Chr. kidney disease (IIIb-V)	2 (2%)	5 (5%)	4 (2%)	5 (3%)	0.47
Diabetes mellitus	26 (32%)	36 (37%)	69 (36%)	72 (42%)	0.71
ICA stenosis, *N (%)*					
<70% on both sides	0	0	0	3 (1%)	
70-89%	13 (21%)	20 (22%)	52 (27%)	43 (23%)	
70-89% both sides	5 (6%)	3 (3%)	8 (4%)	10 (6%)	
90-99%	35 (44%)	59 (61%)	94 (49%)	94 (55%)	0.010
90-99%+contralat. 70-89%	12 (14%)	5 (5%)	14 (7%)	23 (14%)	
90-99% both sides 70-99% + occlusion	13 (15%)	10 (10%)	23 (12%)	5 (2%)	
Brain CT *N (%)*					
Negative 398 (73%)	61 (15%)	74 (19%)	151 (38%)	112 (28%)	0.002*
Positive 146 (27%)	19 (13%)	24 (16%)	42 (29%)	61 (42%)	

chr. = chronic; *contralat.* = contralateral*; ICA* = internal carotid artery; *SD* = standard deviation

*χ^2 test between pooled Groups I-III) versus Group IV)

4. 1. 3. Analysis of the CoW in the study group

4. 1. 3. 1. Analysis of all individual CoW segments

The number and frequency of normal, hypoplastic or non-visualized segments (single variant or combined with other variants) are presented in **Table 3**. Hypoplastic or non-visualized segments were mainly observed together with other variants, either in the anterior and/or posterior parts of the CoW. Non-visualization of PComA (447/1088, 41%), hypoplasia of AComA (154/544, 28%) and hypoplasia of PComA (275/1088, 25%) were the most frequent variants.

The frequencies of non-visualization and hypoplasia of each CoW segment reported in anatomic and imaging studies as well as those found by us are summarized in **Table 4.**

4. 1. 3. 2. Analysis of the anterior and posterior semicircles of the Cow

The variants of the anterior part fell into 5 types, while the posterior part of the CoW demonstrated higher variability and was classified into 16 groups (mirror configurations were not considered as separate entities). **Table 5.** The most common variants in the posterior part of the CoW were bilateral non-visualization of the PComA (118/544, 21%), combined non-visualization of one PComA and hypoplasia of the other PComA (93/544, 17%), unilateral non-visualized PComA (67/544, 12%), and unilateral PComA hypoplasia (64/544, 12%) The most common variant of the anterior CoW was single AComA hypoplasia (143/544, 26%).

Considering the anterior and two posterior semicircles of the CoW (bottom part of **Table 3**, the frequency of normal, hypoplastic, incomplete anterior part was 257/544 (47%), 223/544 (41%), and 64/544 (12%), respectively; 234/1088 (22%), 351/1088 (32%), and 503/1088 (46%) for the posterior parts.

4. 1. 3. 3. Analysis of the entirety of the CoW

Only 19/544 patients (3.5%) had an entirely complete CoW with all segments ≥0.8 mm. The frequency and number of all possible combinations of the anterior and posterior variants are listed in **Table 5.**

Examples of CoW groups I)-IV) are shown in **Fig. 6.a-d)**.

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Table 3. Number (frequency) of normal, hypoplastic, non-visualized/incomplete individual segments, anterior and posterior semicircles of the circle of Willis

Segment/Semicircle		study subjects (n=544)			controls (n=196)			p*
		normal	hypoplasia	non-visualization	normal	hypoplasia	non-visualization	
AComA (n)	All	369 (68%)	154 (28%)	21 (4%)	155 (79 %)	40 (20%)	1 (0.5%)	0.003
	Single variant	NA	9 (2%)	2 (<1%)				
	Combined	NA	145 (27%)	19 (3%)				
A1 (n x 2)	All	964 (89%)	81 (7%)	43 (4%)	380 (97%)	8 (2%)	4 (1%)	<0.001
	Single variant	NA	6 (<1%)	2 (<1%)				
	Combined	NA	75 (7%)	41 (4)				
PComA (n x 2)	All	366 (34%)	275 (25%)	447 (41%)	161 (41%)	121 (31%)	110 (28%)	0.008
	Single variant	NA	36 (3%)	26 (2%)				
	Combined	NA	239 (22%)	421 (39%)				
P1 (n x 2)	All	948 (87%)	81 (7.5%)	59 (5.5%)	354 (90%)	33 (8.5%)	5 (1%)	0.098
	Single variant	NA	6 (<1%)	2 (<1%)				
	Combined	NA	75 (7%)	57 (5%)				
Anterior semicircle (n)	All	257 (47%)	223 (41)	64 (12%)	143 (73%)	48 (24.5%)	5 (2.5%)	<0.001
	Complete pos-terior .semicircle	19 (3.5%)	198 (4.5%)	60 (11%)				
	Posterior variant	238 (44%)	25 (36%)	4 (<1%)				
Posterior semicircle (n x 2)	All	234 (22%)	351 (32%)	503 (46%)	123 (31%)	154 (39%)	115 (29%)	<0.001
	Complete an-terior semicircle	38 (3.5%)	182 (17%)	226 (21%)				
	Anterior variant	196 (18%)	169 (16%)	277 (25%)				

Cont. Table 3.

AComA = anterior communicating artery; *A1* = precommunicating segment of the anterior cerebral artery; *PComA* = posterior communicating artery; *P1* = precommunicating segment of the posterior cerebral artery; *NA* = not applicable

*Comparison between study subjects and controls, pooling hypoplasia and non-visualization versus normal

Table 4. Frequency of non-visualized and hypoplastic individual segments and incomplete and hypoplastic anterior and posterior circles of Willis in autopsy and imaging studies

Segment/ circle		Autopsy studies (2, 11, 12, 14, 44)	Imaging studies		Present Study	
			Controls	Study group	Study group	Controls
AComA	Non-visualization	0–3%	1–19% (19, 24, 25, 35, 36)	4–40% (18-20, 30, 32, 45, 46)	4%	0.5%
	hypoplasia	3–32%	23%(36)	4–11% (45, 47)	28%	20%
A1	Non-visualization	0–0.8%	1–7% (19, 24, 25, 35, 36)	4–15% (18-20, 30, 32, 33, 45, 47)	4%	1%
	hypoplasia	1.5–7.5%	4–10% (19, 35, 36)	8–24% (19, 20, 47)	7.5%	2%
PComA	Non-visualization	0–3.5%	22–38% (9, 19, 24, 25, 35, 36)	21–66% (18-20, 22, 30-34, 45-47)	41%	28%
	hypoplasia	23–70%	38–41% (19, 36)	6–18% (19, 45, 47)	25%	31%

P1	Non-visualization	0–2.4%	0–2% (19, 24, 25, 35, 36)	3–10% (18-20, 45-47)	5.5%	1%
	hypoplasia	12–23%	3–6% (19, 35, 36)	1–8% (18, 19, 30, 45-47)	7.5%	8.5%
Anterior semicircle	incomplete	-	2–12% (10, 19, 25, 35, 36)	12–24% (19, 20, 22, 33)	12%	2.5%
	hypoplastic	-	4–10% (10, 19, 35)	17% (10, 22)	41%	24.5%
Posterior semicircle	incomplete	-	23–39% (25, 35, 36)	37–74% (10, 18, 20, 22, 32, 33)	46%	29%
	hypoplastic	-	29% (35)	15–40% (10, 22)	32%	39%

The numbers in brackets are the references.

AComA = anterior communicating artery, *A1* = precommunicating segment of the anterior cerebral artery, *PComA* = posterior communicating artery, *P1* = precommunicating segment of the posterior cerebral artery

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Table 5. Number (frequency) of the Circle of Willis configurations as a combination of the anterior and posterior variants in 544 study subjects

Anterior semicircle (544)		**complete**	**AComA hypoplasia**	**AComA non-visualization**
Both posterior semicircles (544)				
As a whole	complete	19 (3%)	9 (2%)	2 (<1%)
PComA	unilateral hypoplasia	35 (6%)	12 (2%)	0
	unilateral non-visualization	26 (5%9	20 (4%)	2 (<1%)
	bilateral hypoplasia	25 (5%)	9 (2%)	1 (<1%)
	bilateral non-visualization	44 (8%)	39 (7%)	10 (2%)
	aplasia - contralateral hypoplasia	46 (8%)	27 (5%)	0 (<1%)
PComA-	PComA hypoplasia - contralateral P1 hypoplasia	6 (1%)	4 (1%)	0
	PComA and contralateral P1 non-visualization	13 (2%)	6 (1%)	0
	PcomA hypoplasia-contralateral P1 non-visualization	7 (1%)	1 (<1%)	0
	PcomA non-visualization-contralateral P1 hypoplasia	13 (2%)	5 (1%)	2 (<1%)
P1	unilateral hypoplasia	7 (1%)	5 (1%)	0
	unilateral non-visualization	2 (<1%)	0	1 (<1%)
	bilateral hypoplasia	2 (<1%)	2 (<1%)	0
	bilateral non-visualization	3 (<1%)	0	1 (<1%)
	non-visualization - contralateral hypoplasia	6 (1%)	2 (<1%)	1
other	multiple hypoplasia and/or non-visualization	3 (<1%)	2 (<1%)	1 (<1%)
Total		257 (47%)	143 (26%)	21 (4%)

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Anterior semicircle (544)				Total
	Both posterior semicircle s (544)		A1 hypoplasia	A1 non-visualization	
As a whole	Complete		7 (1%)	2 (<1%)	39 (7)%
PComA	unilateral hypoplasia		12 (2%)	5 (1%)	64 (12%)
	unilateral non-visualization		10 (2%)	9 (2 %)	67 (12%)
	bilateral hypoplasia		8 (2%)	3 (<1%)	46 (8%)
	Bilateral non-visualization		19 (3%)	6 (1%)	118 (21%)
	aplasia - contralateral hypoplasia		11(2%)	8 (2%)	93 (17%)
PComA-P1	PComA hypoplasia - contralateral P1 hypoplasia		2 (<1%)	1 (<1%)	13 (2%)
	PComA and contralateral P1 non-visualization		1 (<1%)	2 (<1%)	22 (4%)
	PcomA hypoplasia-contralateral P1 non-visualization		0	2 (<1%)	10 (2%)
	PcomA non-visualization-contralateral P1 hypoplasia		2 (<1%)	0	22 (4%)
P1	unilateral hypoplasia		7 (1%)	1 (<1%)	20 (4%)
	unilateral non-visualization		1 (<1%)	1 (<1%)	5 (1%)
	bilateral hypoplasia		0	1 (<1%)	5 (1%)
	Bilateral non-visualization		0	1 (<1%)	5 (1%)
	non-visualization - contralateral hypoplasia		0	1 (<1%)	9 (2%)
other	multiple hypoplasia and/or non-visualization		0	1	6 (1%)
Total			80 (15%)	43 (8%)	544 (100%)

AComA = anterior communicating artery; *A1* = precommunicating segment of the anterior cerebral artery; *PComA* = posterior communicating artery; *P1* = precommunicating segment of the posterior cerebral artery

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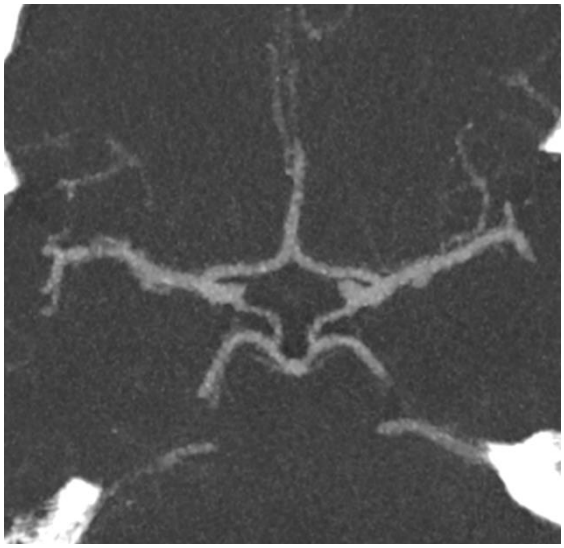
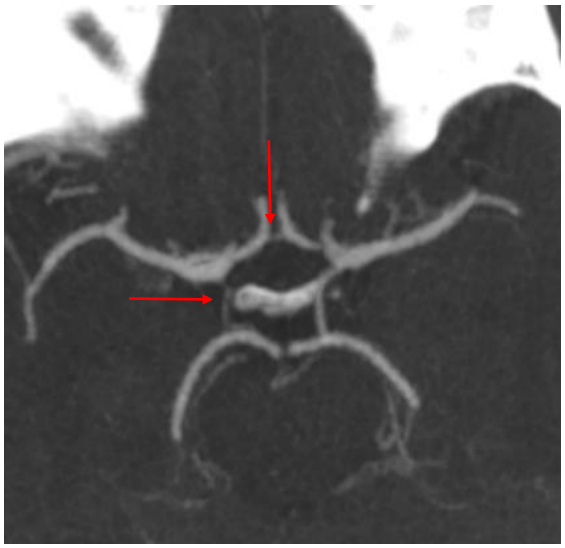
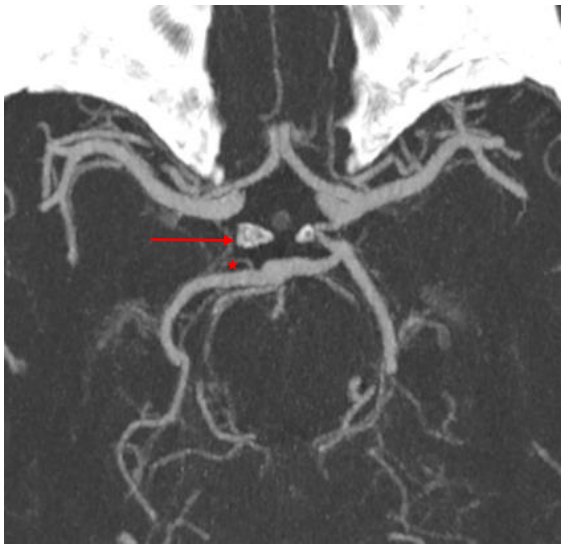


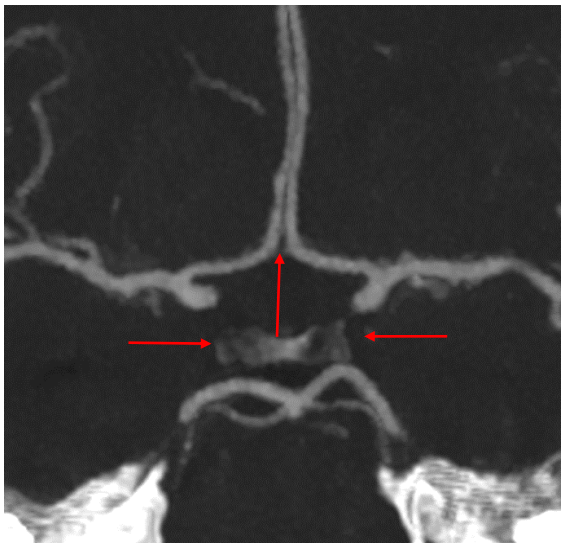
a) Complete CoW (Group I)



b) Hypoplasia of the AComA and right PComA (Group II)



c) Group III). Non-visualized right PComA. The filiform contrast filled structure is the vein of Rosenthal (red star)



d) (Group IV). Non-visualized communicating arteries

Fig. 6a-d). Thick slab maximal intensity projection reformats from CT angiographies illustrating the 4 groups of the circle of Willis. The hypoplastic or non-visualized segments are indicated with arrows. *AComA* = anterior communicating artery; *CoW* = circle of Willis; *PComA* = posterior communicating artery.

From the picture archive of the Heart and Vascular Center of Semmelweis University

4. 1. 3. 4. Correlation analysis in the study group

Association of CoW configurations and demographics, cardiovascular risk factors, degree of ICA stenosis is detailed in **Table 2.** Groups II), III) and IV) together represented 86% (466/544) of our patient population.

After Bonferroni correction, CoW configuration showed a borderline significant association with ICA stenosis (p=0.010). Unilateral stenosis of 90-99% (Score 2 according to Table 1) was the most frequent in all the four CoW configurations, ranging from 44% to 61%. Notably, high carotid stenosis scores (bilateral stenosis of ≥90% - Score 4; stenosis of 70-89% on the side of surgery plus occlusion on the other side - Score 4; stenosis of ≥90% on the side of surgery plus occlusion on the other side - Score 5) were the least frequent in group IV). Considering each single CoW segment, stenosis of the operated ICA was correlated only with ipsilateral A1 segment (p<0.001). Hypoplastic/non-visualized ipsilateral A1 segment was detected in 81/370 (22%) of patients with an ICA stenosis of ≥90% while only in 14/174 (8%) of patients with a stenosis of <90%.

The percentage of smokers was the lowest in patients with severely compromised CoW. The other comparisons showed no significant difference.

4. 1. 4. Reproducibility of the CTA

The inter-observer agreement of CTA in the assessment of AComA was good (κ=0.75) while the intra-observer agreement was excellent (κ=0.84 for R1 and κ=0.96 for R2). The inter-observer (κ=0.82–0.92) and intra-observer (κ=0.84–1.0) agreement for both observers were excellent for all other segments.

We evaluated 3808 (544×7) segments altogether and encountered 212/3808 inter-observer discrepancies (5.5%), 98/212 for the PComA (46%), 60/212 (28%) for the AComA, 27/212 (13%) for the A1 and 27/212 (13%) for the P1 segment. These were mainly one-category discrepancies (hypoplasia versus normal/non-visualization) in 196/212 (92.5%). We had two-category discrepancy (normal versus non-visualization) in only 16/212 (7.5%). Final agreement was reached by consensus reading.

4. 1. 5. Characteristics of the radioanatomical control group

A total of 196 control subjects were analysed (117 males, mean age 66±11 years, range 37–93 years). The indication for CTAs was: (1) positive ultrasound scan with mild-moderate carotid artery stenosis on CTA in 58/196 cases (30%); (2) brachiocephalic/subclavian artery stenosis or aneurysm in 27/196 (14%); diagnostic work-up before cardiac surgery/intervention in 29/196 (14.5%); or (4) vascular intervention/surgery in 15/196 (7.5%); (5) neurology referral in 56/196 (29%) mainly for vertebrobasilar insufficiency; (6) carotid artery dissection in 5/196 (2%); (7) neck tumour in 4/196 (2%); and (8) vascular malformation in 2/196 subjects (1%). Further details are reported in **Table 1.**

4. 1. 6. Analysis of the CoW of the radioanatomical control subjects

4. 1. 6. 1. Analysis of all individual segments

Hypoplasia of PComA (121/392, 31%), non-visualization of PComA (110/392, 28%) and hypoplasia of AComA (40/196, 20%) were the most frequent variants in control subjects. **Table 3**. Non-visualization of the A1 segment and AComA was rare, 4/392 (1%) and 1/196 (0.5%), respectively.

4. 1. 6. 2. Analysis of the anterior and posterior semicircles of the CoW

Amongst controls, the most common variants in the posterior part of the CoW were unilateral hypoplasia of the PComA (43/196, 22%), bilateral hypoplasia of the PComA (41/196, 21%), bilateral non-visualization of the PComA (31/196, 16%), combined non-visualization of one PComA and hypoplasia of the other PComA (29/196, 15%) and unilateral non-visualization of PComA (24/196, 12%). The most common variant of the anterior CoW was hypoplasia of AComA (40/196, 20%).

Considering the anterior and two posterior semicircles of the CoW (bottom part of Table 3), the frequency of normal, hypoplastic, incomplete anterior parts was 143/196 (73%), 48/196 (24.5%), and 5/196 (2.5%), respectively; 123/392 (31%), 154/392 (39%), and 115/392 (29%) for the posterior parts.

4. 1. 6. 3. Analysis of the entirety of the CoW

Of 196 control subjects, 21 (11%) had an entirely complete CoW with all segments being normal.

4. 1. 7. Comparison of the patients and controls

Groups I), II), III) and IV accounted for 28%, 27%, 28% and 17% of control subjects, respectively; whereas in study patients the percentages were 14%, 18%, 35% and 33%, respectively. Table 1. The difference between study patients and controls was statistically significant ($p<0.001$).

The bivariate analysis (**Table 1.**) found, that the study patients and the controls were significantly different in terms of five cardiovascular risk factors and coronary artery disease ($p<0.001$). However, by multivariate logistic regression analysis ICA stenosis was the only independent predictor of CoW morphology ($p<0.001$). The analysis of each CoW segment and the anterior/posterior semicircles proved a significantly higher rate of hypoplasia or non-visualization ($p\leq0.008$) in the study group versus controls except for the P1 (**Table 3**).

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4. 1. 8. Brain MRI study

Brain MRI has been performed in 72 cases (63% males, mean age 66±9 years). 46 out of 72 (64%) had an incomplete CoW (with ≥1 non-visualized segments), only 26/72 (36%) had a complete CoW (with normal or hypoplastic segments).

With incomplete CoW we detected 11 subjects with recent infarcts on DWI, and 16 patients with late subacute/chronic infarcts on FLAIR (11/46, 24% and 16/46, 35%, respectively). With complete CoW the number of subjects with acute and late subacute/chronic infarcts was 2 and 6, respectively (2/26, 8% and 6/26, 23%).

The prevalence of brain ischemia (recent + old) was significantly higher (p=0.04 with Yates correction) in subjects with incomplete CoW (59%) as compared to complete (normal or hypoplastic) CoW (31%). The rate of ipsilateral recent ischemic lesions alone was three times higher in incomplete CoW (24%) relative to complete CoW (8%). Nevertheless, this difference was not significant (p=0.09). **Table 6.**

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Table 6. Demographics, cardiovascular risk factors, carotid stenosis, prevalence and correlation of brain ischemia on MRI with circle of Willis configuration in 72 subjects

Variable	**Overall** n = 72	**Complete CoW** n = 26	**IncompleteCoW** n = 46	**p**
Demographics				
Male gender N (%)	45 (63%)	18 (69%)	27 (59%)	0.38
Age ± SD (years)	66 ± 17	66 ± 12	67 ± 9	0.08
Symptomatic	17 (24%)	4 (15%)	13 (28%)	0.22
Early perioperative ischaemia N (%)	5 (7%)	1 (4%)	4 (9%)	0.44
Cardiovascular risk factors, N (%)				
Hypertension	67 (93%)	25 (96%)	42 (91%)	0.44
Cigarette smoking	3 (4%)	3 (12%)	0 (0%)	-
Hyperlipidemia	27 (38%)	9 (35%)	18 (39%)	0.70
Coronary artery disease	12 (17%)	4 (15%)	8 (17%)	0.83
Chronic pulmonary disease	1 (1%)	1 (4%)	0 (0%)	-
Chronic kidney disease (IIIb-V)	4 (6%)	1 (4%)	3 (7%)	-
Diabetes mellitus	35 (49%)	9 (35%)	26 (57%)	0.07
ICA stenosis, N (%)				
<70% on both sides	1 (1%)	1 (4%)	0 (0%)	
70–99% on the side of surgery	59 (82%)	18 (69%)	41 (89%)	
70–99% on both sides	6 (8%)	3 (12%)	3 (7%)	0.14
70–99% on the side of surgery + contralateral occlusion	6 (8%)	4 (15%)	2 (4%)	
Brain MRI Result N (%)				
DWI positive subjects	13 (18%)	2 (8%)	11 (24%)	0.09
DWI+FLAIR positive subjects	35 (49%)	8 (31%)	27 (59%)	0.04#

CoW = circle of Willis, *DWI* = diffusion weighted imaging*; FLAIR* = fluid-attenuated inversion recovery, *ICA* = internal carotid artery; *SD* = standard deviation

#χ^2 test with Yates correction

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4. 2. Clinical approach

4. 2. 1. Characteristics of the clinical study group

One patient, who had to be removed from the radioanatomical study cohort for suboptimal preoperative imaging quality, was included in the clinical study because of the important postoperative outcome in this particular case. This explains the difference in patient numbers (overall 545 patients in the clinical study, 332 males, mean age 69±8 years, range 44–90 years). The above patient's CEA was unsuccessful (as detailed below) and he suffered a major stroke. His CoW could be assessed on the postoperative CTA performed to check ICA patency.

The excluded and included subjects, the preoperative and postoperative variables (the later including stroke, immediate stroke, immediate TIA and mortality rates) are detailed in **Table 7.** The difference between the radioanatomical and clinical study is highlighted in bold typeset.

Intra-arterial shunting was rare (31 and the primarily excluded 4 cases) and based on the individual decisions of the vascular surgeon. In 8 cases long calcified ICA plaques were found, too high for eversion. 10 patients had a recent stroke with established ischemic infarcts, 4 had a contralateral ICA occlusion. For the remaining cases the cause of shunting was not known. Fifteen patients had a bilateral reconstruction (the second operation 3-82 weeks apart from the first).

Demographics and cardiovascular risk factors of study subjects with and without INE are presented in **Table 8**.

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Table 7. Excluded and included study subjects with preoperative variables and early outcomes (stroke, immediate stroke, immediate transient ischemic attack and mortality) of the clinical study

Preoperative variables	missing imaging n=302	poor image quality **n=20** ***n=21***[¥]	shunting± poor quality n=35	excluded total **n=357** ***n=358***[¥]	included **n=545** ***n=544***[¥]	p
Symptomatic	103 (34%)	2 (10%)	16 (46%)	121 (34%)	205 (38%)	0.28
Contralateral occlusion	20 (7%)	0	4 (11%)	24 (7%)	35 (6%)	0.86
Early outcomes						
All stroke	4 (1%)	0	1 (3%)	5 (1.5%)	12 (2%)	0.46
Immediate stroke	1(<1%)	0	1 (3%)	2 (<1%)	8 (1.5%)	0.33
Immediate TIA	6 (2%)	0	0	6 (2%)	12 (2%)	0.63
Death	0	0	0	0	1(<1%)	1.0

TIA = Transient Ischemic Attack

The differences between the clinical and radioanatomical studies are in bold italic typeset. For details refer to text.

[¥]Exclusions and final study cohort of the radioanatomical study.

Table 8. Demographics, cardiovascular risk factors, anatomic and procedural characteristics in 545 patients without or with immediate neurologic event following carotid endarterectomy

Variable	no INE n=525	INE n=20	p
Male gender N (%)	322 (61%)	9 (45%)	0.22
Age ± SD (years)	69 ± 8	72 ± 8	0.14
Symptomatic N (%)	192 (37%)	13 (65%)	0.02
Cardiovascular risk factors N (%)			
Hypertension	482 (92%)	19 (95%)	1.0
Cigarette smoking	171 (33%)	5 (25%)	0.64
Hyperlipidemia	224 (43%)	10 (50%)	0.67
Coronary artery disease	167 (32%)	3 (15%)	0.14
Chronic pulmonary disease	52 (10%)	1 (5%)	0.71
Chronic kidney disease (stage IIIB to V)	16 (3%)	0	1.0
Diabetes mellitus	197 (38%)	6 (30%)	0.65
Anatomic and procedural characteristics			
Cross-clamping time (min), median (range)	24 (11-90)	25 (13-98)	0.85
Ipsilateral vertebral artery occlusion N (%)	27 (5%)	1 (5%)	1.0
Contralateral vertebral occlusion N (%)	32 (6%)	1 (5%)	1.0
Bilateral vertebral artery occlusion N (%)	2 (0.4%)	1 (5%)	0.10
Basilar occlusion/aplasia N (%)	0	0	-
Basilar hypoplasia N (%)	10 (2%)	0	1.0
Ipsilateral ICA stenosis N (%)			
<90%	165 (31%)	10 (50%)	0.13
90-100%	360 (69%)	10 (50%)	
Contralateral ICA stenosis N (%)			
<90%	474 (90%)	19 (95%)	0.71
90-100%	51 (10%)	1 (5%)	

Mann-Whitney test

ICA = internal carotid artery; *INE* = immediate neurologic event; *SD* = standard deviation

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4. 2. 2. Surgical procedural details

The CEA was technically successful in 99%. The average carotid clamping time was 25±9 minutes. The plaque removal with the eversion technique was unsuccessful in one case. Polytetrafluoroethylene interposition between the CCA and the distal part of the endarterecomized ICA was performed, which occluded immediately. Several thrombectomies were attempted with a Fogarty balloon catheter, unsuccessfully. The patient suffered an immediate stroke, remained unconscious and later passed away. Three further CEA subjects had a successful primary reconstruction and were asymptomatic after the operation, but later (within the first 24 hours) their ICA occluded resulting in a neurologic event.

4. 2. 3. Mortality and major adverse events

Only the patient with unsuccessful CEA discussed above, died in the early postoperative period (0.2%). Two patients suffered myocardial infarction (0.4%), both of whom were treated with successful coronary intervention without further complications. Reoperation was needed in 20 cases (3.7%), haematoma evacuation in 17 (3.1%), thrombectomy in one (0.2%), and reocclusion followed by polytetrafluoroethylene interposition in two (0.4%). **Table 9.**

The ischemic events are detailed further below.

Table 9. Early postoperative complications in 545 patients following carotid endarterectomy

Variable	Number	%
Stroke	**12**	**2.2**
Immediate neurologic event after CEA	8	1.5
Early reocclusion	3	0.6
Embolisation	1	0.2
Myocardial infarction	**2**	**0.4**
Death	**1**	**0.2**
Reoperation	**20**	**3.7**
Cervical bleeding, haematoma evacuation	17	3.1
Thrombectomy	1	0.2
Reocclusion – PTFE carotid interposition	2	0.4

CEA = carotid endarterectomy, *PTFE* = polytetrafluoroethylene

4. 2. 4. Immediate postoperative neurologic events

Of the 545 cases, eight immediate strokes and 12 TIAs were diagnosed immediately after CEA (overall 20 INEs).

To determine which factors were independent predictors of INE we entered our data in a binary logistic regression model including hypertension, smoking, diabetes mellitus, hyperlipidemia, carotid clamping time (minutes), ipsilateral significant ICA stenosis of ≥90%, contralateral significant ICA stenosis of ≥90%, symptoms 180 days before surgery, and iMCA. The model revealed a significant difference (p=0.001; -2LL=137.56; Nagelkerke R^2=0.18), iMCA being an independent predictor of INE (odds ratio (OR): 11.12; 95% confidence interval (CI): 3.57-35.87; p<0.001). Apart from iMCA, only symptomatic ICA stenosis showed a significant association with INE (OR: 3.34; 95% CI: 1.19-9.73; p=0.02). The other parameters were non-significant. **Table 10.**

Table 10. Logistic regression model to test demographic data, anatomic and procedural variables for immediate neurologic events

Variable	OR	95% CI	p
Age	1.03	0.98-1.11	0.35
Symptomatic	3.34	1.19-9.73	0.02
Cardiovascular risk factors			
Hypertension	1.20	0.14-10.76	0.89
Cigarette smoking	0.87	0.27-2.94	0.82
Hyperlipidemia	2.28	0.81-6.40	0.12
Coronary artery disease	0.41	0.10-1.62	0.19
Diabetes mellitus	1.29	0.42-3.70	0.68
Anatomic and procedural characteristics			
Cross-clamping time	0.95	0.86-1.03	0.67
Ipsilateral internal carotid artery stenosis ≥90%	0.52	0.05-4.81	0.60
Contralateral internal carotid artery stenosis ≥90%	0.59	0.20-1.52	0.26
iMCA	11.12	3.57-35.87	<0.001

CI = Confidence interval*; iMCA* = isolated middle cerebral artery*; OR* = odds ratio

4. 2. 5. Relation of CoW configuration and neurologic events

The anterior and ipsilateral posterior semicircles of the CoW were qualified as normal, hypoplastic or incomplete as previously described. If both were incomplete iMCA was recorded.

62 subjects out of 545 (12%) had a normal anterior semicircle and a normal ipsilateral posterior semicircle, including 19 subjects with a fully normal CoW (3.5%). Among these patients only one INE (stroke) was detected (1.5%).

268 patients had a hypoplastic or non-visualized segment either in the anterior (72) or the posterior semicircle (196), whereas the other semicircle was complete. Out of

these 268 subjects with one affected semicircle, only three suffered INE (two strokes, one TIA); the posterior semicircle was incomplete in all these cases. The statistical analysis showed no significant difference ($p=0.57$) in INE between the patients with complete ipsilateral semicircles (1/62) versus those with one affected semicircle (3/268).

The difference became significant ($p<0.001$) when both the anterior and the ipsilateral posterior semicircles were affected having hypoplastic and/or non-visualized segments at the same time (215 subjects). Among these 215 patients we encountered 16 INEs (5 strokes and 11 TIAs). Out of those 34 patients with an iMCA (incompleteness of both semicircles) two had a stroke and six suffered TIA (8 INEs in total; 23.5%), which is a significantly higher rate ($p<0.001$), when compared with the 8 INEs (3 strokes, 5 TIAs) in the remainder of patients with two affected semicircles (8/181; 4.4%).

Out of the three patients with early postoperative stroke due to ICA reocclusion, two had a normal anterior semicircle with a hypoplastic posterior semicircle. The third patient had hypoplasia both in the anterior and posterior semicircles.

The CoW configurations of the detailed subgroups are presented in **Table 11**.

4. 2. 6. Configurations of the isolated middle cerebral artery

Seven types of iMCA configurations were found as shown in **Table 12**. The most frequent iMCA type was combined non-visualization of the AComA and that of the ipsilateral PComA (12/34, 35%), followed by non-visualized ipsilateral A1 and PComA (11/34, 32%), non-visualized contralateral A1 and ipsilateral PComA (4/34, 12%), finally non-visualized ipsilateral A1 and P1 segments (4/34, 12%). **Figs. 7, 8** show the graphical and CTA illustrations of these configurations.

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Table 11. Circle of Willis anatomy in patients with or without immediate neurologic event after carotid endarterectomy

Variable	No INE N=525	INE N=20	p
Complete anterior and ipsilateral posterior semicircles	61 (12%)	1 (5%)	0.72
Entirely complete CoW (all segments normal)	18 (3%)	1 (5%)	0.51
Single semicircle affected			
Hypoplasia in the anterior semicircle	60 (11%)	0	0.15
Incomplete anterior semicircle	12 (2%)	0	1.0
Hypoplasia in the ipsilateral posterior semicircle	89 (17%)	0	0.06
Incomplete ipsilateral posterior semicircle	104 (20%)	3 (10%)	0.39
Both semicircles affected			
Hypoplasia of the anterior and ipsilateral posterior semicircles	65 (12%)	2 (10%)	1.0
Hypoplastia of the anterior and incomplete ipsilateral posterior semicircles	91 (17%)	5 (25%)	0.37
Incomplete anterior and hypoplastic ipsilateral posterior semicircles	17 (3%)	1 (5%)	0.50
Incomplete anterior and incomplete ipsilateral posterior semicircles (iMCA)	26 (5%)	8 (40%)	<0.001
Preoperatively symptomatic	14 (54%)	5 (63%)	1.0

CoW = circle of Willis; INE = immediate neurologic event, *iMCA* = isolated middle cerebral artery

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Table 12. Distribution of isolated middle cerebral artery types as a composite of non-visualized segments in the anterior and posterior semicircles

Non-visualized segment in anterior semicircle	Non-visualized segment in posterior semicircle	N	%
AComA	PComA	12	35
Ipsilateral A1	PComA	11	32
Contralateral A1	PComA	4	12
Ipsilateral A1	ipsilateral P1	4	12
AComA	PComA, ipsilateral P1	1	3
AComA	ipsilateral P1	1	3
Contralateral A1	ipsilateral P1	1	3

AComA = anterior communicating artery; *A1* = precommunicating segment of the anterior cerebral artery; *PComA* = posterior communicating artery; *P1* = precommunicating segment of the posterior cerebral artery

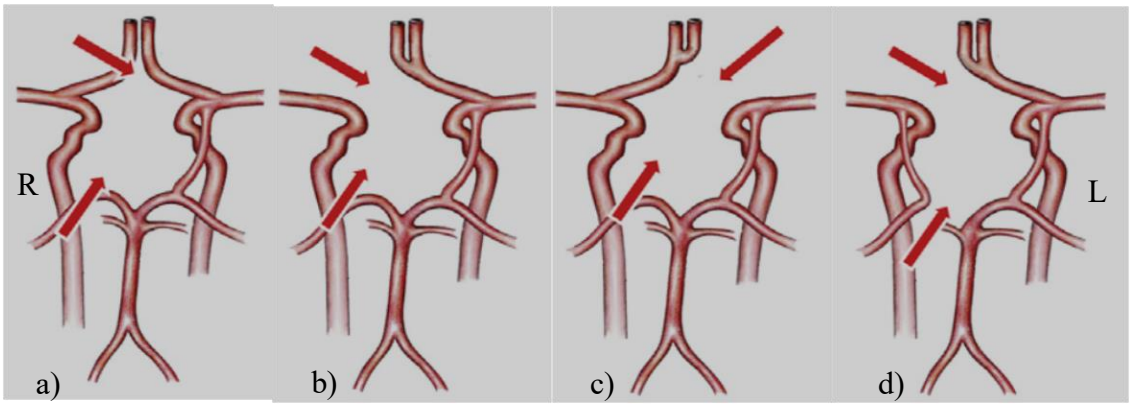

Fig. 7a-d). The four most frequent configurations of the isolated middle cerebral artery (iMCA) are shown here (for all illustrations we assumed right sided internal carotid artery stenosis and cross clamping). The arrows indicate the non-visualized segments. The iMCA is considered isolated if there is non-continuity of collaterals both from the contralateral internal carotid artery (anterior semicircle) and the basilar artery (posterior semicircle). Percentages expressed from the total number of patients with iMCA (n= 34). Illustration from reference 23, courtesy of Péter Banga.

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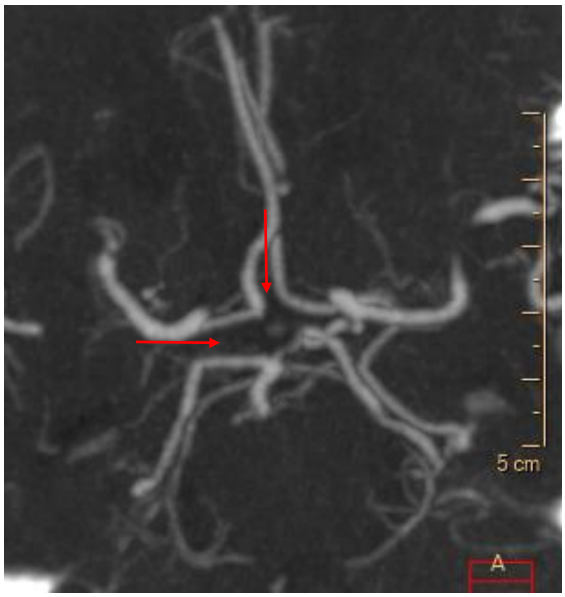
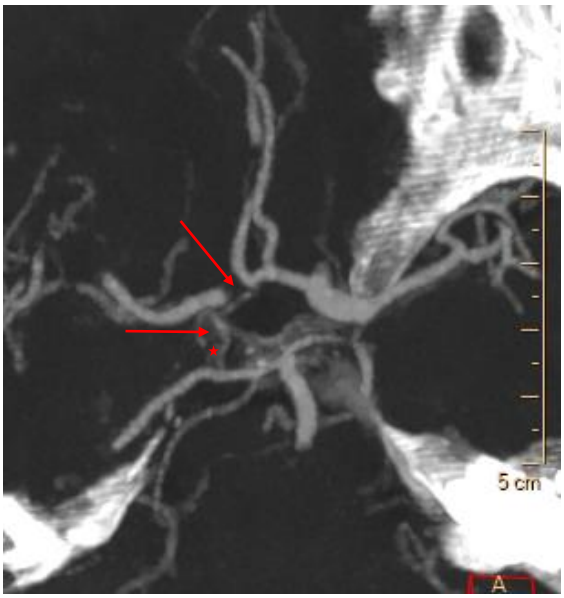
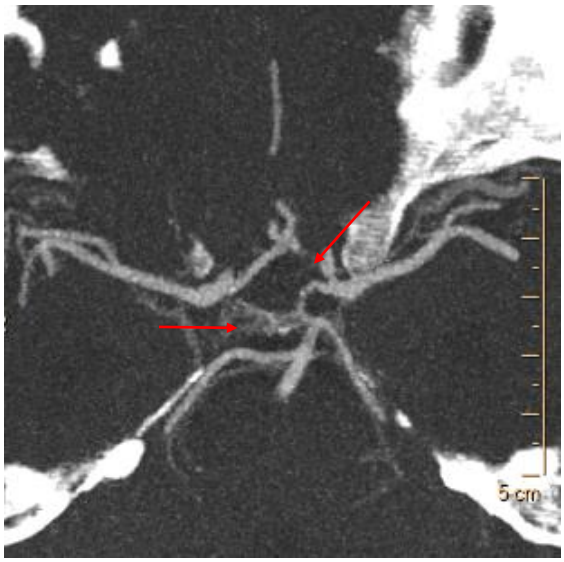


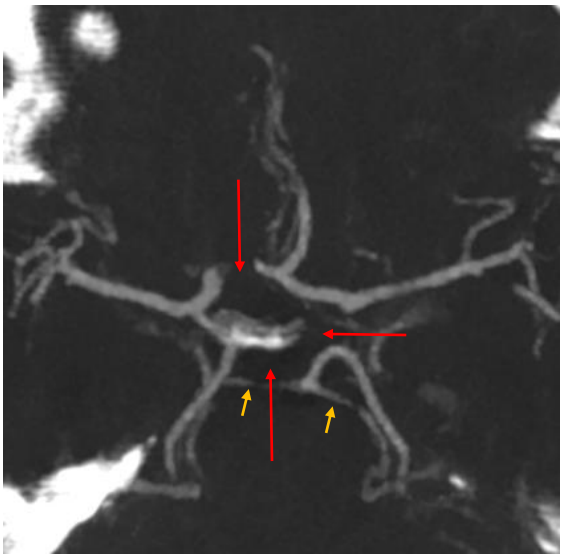
a) Missing AComA +ipsilateral PComA



b) Missing ipsilateral A1, PComA. The contrast filled structure is part of the venous circle of Willis (red star)



c) Non-visualized contralateral A1 and ipsilateral PComA.



d) Non-visualized right A1, P1, left PComA (short arrows: superior cerebellar arteries).

Figs. 8a-d) Thick slab maximal intensity projections from CT angiographies of the circle of Willis corresponding to Fig. **7a-d)**. The non-visualized segments are indicated with long arrows. *AComA* = anterior communicating artery; *A1* = precommunicating segment

of the anterior cerebral artery; *CoW* = circle of Willis; *PComA* = posterior communicating artery; *P1* = precommunicating segment of the posterior cerebral artery.
From the picture archive of the Heart and Vascular Center of Semmelweis University

4. 2. 7. Risk factors associated with iMCA

Similar to the severely compromised CoW in the radioanatomical study, the statistical analysis showed fewer iMCA cases in smokers (p=0.01). Fewer iMCA was found among patients with diabetes mellitus (p=0.02) and in coronary artery disease (p=0.04). The prevalence of iMCA was higher among the preoperatively symptomatic subjects (p=0.03). For details, refer to **Table 13**.

4. 2. 8. Early postoperative strokes among symptomatic and asymptomatic patients

In the cohort of 545 CEA patients, the overall in-hospital ischemic stroke rate was 2.2% (12/545); 3.9% (8/205) for the preoperatively symptomatic and 1.2% (4/340) for the asymptomatic patients. Of the 12 stroke cases, eight were diagnosed immediately after surgery. Early ICA reocclusion resulted in three strokes 1 to 3 hours following surgery. Two of the three patients had a major stroke, one had only minor symptoms (hand weakness). Another patient had a major stroke 6 hours after the procedure with patent ICA and the CT confirmed MCA territory embolisation.

One intracranial haemorrhage occurred in a preoperatively symptomatic patient secondary to hypertensive crisis resulting in minor symptoms.

The 6-day in-hospital rate of major stroke was 1.9% (4/205) among the preoperatively symptomatic patients and 0.3% (1/340) in our asymptomatic group.

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Table 13. Demographics, cardiovascular risk factors and internal carotid artery stenosis in study subjects with or without isolated middle cerebral artery

Variable	**No iMCA n=511**	**iMCA n=34**	**p**
Male gender N (%)	310 (61%)	22 (65%)	0.72
Age ± SD (years)	69 ± 8	70 ± 7	0.33
Symptomatic N (%)	186 (37%)	19 (56%)	0.03
Cardiovascular risk factors N (%)			
Hypertension	469 (92%)	32 (94%)	1.0
Cigarette smoking	171 (34%)	4 (12%)	0.01
Hyperlipidemia	222 (44%)	12 (35%)	0.38
Coronary artery disease	165 (32%)	5 (15%)	0.04
Chronic pulmonary disease	52 (10%)	1 (3%)	0.24
Chronic kidney disease (stage IIIB to V)	16 (3%)	0	0.62
Diabetes mellitus	197 (39%)	6 (18%)	0.02
Anatomic characteristics			
Ipsilateral ICA stenosis N (%)			
<90%	160 (31%)	15 (44%)	0.13
90-100%	351 (69%)	19 (56%)	
Contralateral ICA stenosis N (%)			
<90%	459 (90%)	33 (97%)	0.24
90-100%	52 (10%)	1 (3%)	

SD = standard deviation, *ICA* = internal carotid artery; *iMCA* = isolated middle cerebral artery

5. Discussion

To our knowledge ours is one of the most comprehensive studies on CoW morphology using a 256-detector row CT in a large cohort of CEA subjects. Our major findings are the high prevalence of compromised circles (86%), the significant difference in CoW morphology between the study and control groups, as well as the significant association of CoW configuration with brain infarcts and immediate postoperative ischemic neurologic complications in the study group.

Some of the CoW variations may predispose to the development of ischemic events. With preoperative CTA assessment of the CoW these patients with a high risk for cross clamping ischemia can be identified. We found statistically higher odds for neurologic complications when both the anterior and ipsilateral posterior semicircles of the CoW were incomplete impeding collateral recruitment towards the MCA on the side of the clamped ICA.

With contrast to MRA, CTA has a higher spatial resolution and is not dependent on flow velocity, thereby allowing accurate documentation of vessel diameters. Although compared with DSA, TCCD and phase contrast MRA, first pass CTA does not provide information about flow dynamics, we hypothesized that competent component vessels are potentially capable of supplying collateral flow.

5. 1. Radioanatomical approach

Based on unselected post-mortem studies the prevalence of the “normal” textbook polygon ranges from 15% to 59%, and several configurations have been extensively described (2, 11-14).

In MRA and CTA studies completeness of the entire CoW was reported in a range of 26-90% in healthy individuals (18, 19, 26, 35, 36) and 18-55% in patients with cerebrovascular diseases (18, 32, 33). The prevalence of a complete anterior semicircle was 68-95% in healthy subjects (10, 18, 24-26), while in patients with cerebrovascular diseases it varied from 60% to 88% (10, 18, 19, 22, 30, 32, 33). Completeness of the posterior CoW was reported in healthy volunteers in a wide range of 28-95% (9, 10, 18, 19, 24, 26, 35), versus 11-74% in the cerebrovascular group (10, 18, 19, 22, 30, 32, 33).

We may conclude that despite of considerable overlap, complete CoW, intact anterior and posterior semicircles are in general less frequent in patients as compared to healthy controls and their prevalence is even lower in our study group (entirely complete CoW: 3.5%, complete anterior semicircle: 47%, complete posterior semicircle: 22%).

5. 1. 1. Differences in CoW analysis in literature

The different study populations, methods and techniques and the different criteria to define a "normal" or incomplete CoW can account for the variation in the published results.

5. 1. 1. 1. Population and specimen selection

Autopsy studies performed in stroke patients often reported lower percentages of complete circles than those performed in non-stroke populations: 33-38% versus 52-59% (13, 14). In contrast, in an MRA study comparing study subjects with ICA stenosis or occlusion with controls, a significantly higher percentage of entirely complete CoW (55% versus 36%), complete anterior (88% versus 68%), and complete posterior CoW configurations (63% versus 47%) was demonstrated in patients (18). It was presumed that collateral flow through the CoW was fully developed to maintain adequate cerebral blood flow in this particular study population. Meanwhile other radiology studies found higher prevalence of hypoplastic or absent CoW segments in patients with carotid stenosis (9, 10, 19).

5. 1. 1. 2. Method of investigation

The different sensitivity and specificity of the applied imaging modalities may contribute to the variation of the reported results. Previous MRA studies (6, 25, 27, 45) demonstrated acceptable overall sensitivity (higher than 80%) in depicting the presence or absence of CoW segments, however, the specificity of MRA (50-67%) varied according to the MRA techniques and analysis methods used. The sensitivity of MRA was very low for the PComA: 33% (25) or moderate (65%) for all the communicating arteries (45), which may be explained by the detection limits of MRA for slow flow.

The sensitivity and specificity of CTA in the detection of non-visualized and normal-sized segments were more than 90% as compared to DSA. In contrast, subgroup analysis of the hypoplastic segments revealed a sensitivity of 53% and a specificity of 98%. The agreement rate was poorer for the PComA (84% versus the overall agreement of 92%). CTA showed a trend to underestimate the arterial segments compared to DSA (47). Nontheless, the sensitivity of CTA in the identification of missing or occluded CoW elements was 100% relative to DSA (48).

TCCD against DSA identified the major collateral pathways with a sensitivity of 80-90% and a specificity of 80%, but for the identification of PComAs the specificity dropped dramatically (47% and 60%) (6, 7), while the sensitivity remained good (76%) (7).

5. 1. 1. 3. Varying definitions

The specific criteria used to define a normal CoW vary in the literature. Our classification of the circle's configuration as complete (all components ≥0.8 mm) emphasizes the continuity of the circular structure as a prerequisite for development of collateral flow, which was our primary interest.

Consensus in defining hypoplasia in the scientific literature has not been reached yet. Most of the studies used a threshold diameter, others defined hypoplasia as diameter less than half of the contralateral segment (22, 46, 47). The lower limit of normal diameters is arbitrary and affects the number of segments classified as hypoplastic and the prevalence of circles defined as complete. Threshold of 1 mm has been widely used in anatomic (11, 12, 14, 44) and imaging studies (19, 22, 29, 35, 36). However, a 3D TOF MRA study revealed that a considerable proportion of the communicating vessels had diameters of 0.8-1.0 mm (24). 0.8 mm as a cut-off value to define hypoplasia was rarely used (18, 20, 32). We also set a lower threshold for hypoplasia (<0.8 mm) assuming the improved spatial resolution of modern MD CT scanners.

Nonetheless, the comparison remains difficult as in some studies the investigators used a visible versus non-visible dichotomy for rating the segments of the CoW (21, 25, 30), while normal or hypoplastic versus absent dichotomy (18, 32, 33) was used in others. Clear distinction between normal, hypoplastic and incomplete anterior and posterior

semicircles based on the presence of normal, hypoplastic and non-visualized segments can be found in a minority of radiology studies (19, 35, 47) apart from our study.

5. 1. 2. Segmental analysis of the CoW

5. 1. 2. 1. Non-visualization of the invidiual CoW segments

The non-visualization of any segment was more frequently reported in the cerebrovascular patients as compared to healthy subjects, with some overlap between the two groups. **Table 4.** In our investigation non-visualization of each CoW segment was 1.5–8 times as frequent in patients as in controls (the smallest difference was found for the PComA, the largest for the AComA).

Correlating our patients' data with the results of radiology studies from cerebrovascular patients we found lower prevalence of AComA non-visualization: 7-40% (18, 20, 30, 32, 45, 46) versus 4%, except for the CTA study of Waaijer et al. reporting non-visualized AComA also in 4% (19). The prevalence of absent A1 segments in this study was 4%, at the lower limit of the reported range, and in particular lower as compared to the other CTA studies of patients with cerebrovascular disorders: 5.5-15% (19, 32, 45, 47). In our analysis the most commonly involved vessel was the PComA, however non-visualization of the PComA was reported more frequent in most of the CTA studies in patients with cerebrovascular diseases as compared to ours: 41% versus 47-66% (19, 32, 45, 47). The absence of the P1 segment was 5.5% in or study, which is in line with the previously published data.

The fact that CTA is not dependent of flow velocity as opposed to MRA and the better spatial resolution achieved by MD CTA might have contributed to the lower prevalence of non visualized AComA, A1 and PComA. However, a certain percentage of the absent segments in this study may be hypoplastic vessels, bellow the resolution of CTA, as in autopsy studies absence was found only rarely (0-3.5%) (2, 11, 12, 14, 44), AComP aplasia being the most common.

5. 1. 2. 2. Hypoplasia of the individual CoW segments

Fewer data were published on hypoplasia of the CoW components, mostly from CTA studies.

Comparing patients with control subjects lower percentage of AComA hypoplasia (4-11% versus 23%) and PComA hypoplasia (6-18% versus 38-41%) was demonstrated by the literature. In contrast, A1 hypoplasia showed a tendency towards higher percentages in the cerebrovascular group relative to healthy controls (8-24% versus 4-10%). Regarding P1 hypoplasia there was considerable overlap between the two groups. **Table 4.** In our investigation PcomA hypoplasia was more frequent among controls relative to the study group (31% versus 25%). Although with a little difference only, the same applied to P1 hypoplasia (8.5% versus 7.5%). We might assume that in absence of significant ICA stenosis these segments, in particular the PComA, are not recuired as collaterals and remain small in calibre.

Comparing our study subjects with radiology studies from cerebrovascular patients, we found higher prevalence of AComA and PComA hypoplasia (28 and 25%, respectively). The frequency of A1 hypoplasia was below the lower limit of the reported range (7.5%). The prevalence of P1 hypoplasia was in the reported range (7.5%).

The higher detection rate of hypoplastic communicating arteries due to the better spatial resolution of a modern MD CT equipment relative to the 16-40 row scanners or the MRA techniques used by other investigators might partly account for this difference.

5. 1. 2. 3. Analysis of the anterior and posterior semicircles of the CoW

The prevalence of incomplete or hypoplastic anterior and posterior semicircles reported in the literature is again lower in healthy individuals as compared to patients with cerebrovascular diseases with overlapping results regarding the posterior collateral system. The only major difference between the published data and ours is the high frequency of hypoplasic anterior semicircles (17% versus 41%). **Table 4.** Our analysis of both the anterior and posterior semicircles showed a significantly higher rate of hypoplasia or non-visualization ($p<0.001$) in the study group versus the controls.

5. 1. 3. Clinical aspects of the radioanatomical approach

Discontinuity of the CoW in patients with symptomatic ICA stenosis was associated with higher risk of TIA and ischemic stroke (3). Subjects with high-grade ICA stenosis or occlusion with nil or only one ipsilateral collateral vessel (A1, PComA) had a

higher likelihood of stroke when compared to patients with two functional ipsilateral collaterals (15). This is in agreement with the higher prevalence of brain ischemia found in our patients with severely compromised CoW (p=0.002). We must acknowledge however that CT has low sensitivity in the detection of recent ischemia relative to MR-DWI but our MRI substudy of 72 CEA subjects also showed significantly higher percentage in the composite of old and recent brain ischemia in subjects with incomplete CoW versus those with complete CoW (p=0.04). Recent ischemia of the index side in incomplete CoW was three times as high as in complete CoW, however below the thershold of significance (p=0.09).

A single imaging study showed decreased prevalence of CoW variants in patients with carotid disease as compared to controls (18), while other studies found higher prevalence of hypoplastic or absent segments in patients versus normal individuals (9, 10, 16, 19) or in selected cases of symptomatic carotid stenosis or occlusion (15). The contrasting results of Hartkamp et al. are probably due to the fact that their study included a subgroup of survivors of uni- or bilateral ICA occlusion with minor neurologic deficits (18). Compromised anterior and a combination of compromised anterior and posterior pathways occurred significantly more frequently in the patient group as compared to controls (9% versus 1%, and 26% versus 4%) in the study of Waaijer et al. (19). The anterior pathway is generally considered the most important route for collateral flow in cases of severe carotid steno-occlusive disease (15, 18, 19, 30, 49), but collateral flow via the PComA has also been shown to be of clinical importance (9, 22, 29). Contrary to the study that reported absence of flow through the PComA as the only significant risk factor for watershed infarcts (29), Kluytman et al. found that the PComA alone had little compensating capacity in patients with either uni- or bilateral ICA occlusion. Best-preserved hemodynamics was reported if both anterior and posterior pathways were recruited (49).

In our investigation the high frequency of hypoplastic and incomplete anterior semicircles (53%), posterior semicircles (78%), and compromised circles with 2≥hypoplasic or 1≥absent segments (86%) suggests that our cohort of patients have fewer functional segments in general, and especially fewer functional posterior segments, which might hinder hemodynamic adaptation. Although the study group and controls were

significantly different in terms of 5 cardiovascular risk factors and coronary artery disease, the multivariate regression logistic analysis showed that ICA stenosis was the only independent predictor of CoW morphology ($p<0.001$). The higher frequency of ipsilateral A1 hypoplasia/non-visualization was positively associated to ipsilateral ICA stenosis of ≥90% ($p<0.001$), also implying a correlation between carotid artery disease and hindered collateral recruitment.

Interestingly high grade carotid stenosis scores were the least frequent in patients with severely compromised CoW, with the highest -nevertheless non significantly different- rate of symptomatic cases in the study cohort. We hypothesized that lower grade carotid stenosis in subjects with a severely compromised CoW might have led to earlier symptoms. None of the cardiovascular risk factors correlated to CoW morphology showed significant difference within our study group. In the literature only hypertension was shown to have impaired the development of intracranial collaterals in patients with >75% stenosis or occlusion (15).

5. 2. Clinical approach (correlation of immediate neurologic events and CoW morphology)

In our study cohort entirely complete CoW (3.5 %) was surprisingly rare and only one INE occurred in this subgroup. In subjects with at least one adequate collateral pathway, the odds to suffer a complication were not different from those with two complete ipsilateral semicircles.

Of the 268 patients with at least one sufficient collateral pathway, only two had stroke and another had TIA. In all three of these cases the ispilateral posterior semicircle was incomplete. As opposed to Kluytmans et al., who found that the anterior semicircle was more important than the posterior (49), our data suggests, that the anterior and posterior semicircles are of equal importance in the overall collateral network.

In 215 cases both collateral pathways proved to be insufficient and we encountered 5 strokes and 11 TIAs, wich is a significantly higher complication rate as compared to those with at least one adequate collateral network.

Isolated MCA was an independent risk factor for INE, with odds three times as high as the other significant risk factor of INE, ie. preoperatively symptomatic ICA

stenosis. The higher prevalence of iMCA among symptomatic subjects supports the findings of a previous study (19). Our results are also concordant with another investigation, in which ≥2 non-visualized segments versus complete CoW were shown to have a statistically significant risk to develop carotid clamping intolerance (21). In a further study, in case of contralateral ICA occlusion, the risk of intraoperative TIA was significantly increased when both parts of the CoW (in particular the posterior part) were incomplete (22).

Surprisingly iMCA showed negative association with smoking, diabetes mellitus and coronary artery disease. We might explain this difference with higher compliance in smoking cessation and more aggressive secondary prevention in this group, where the symptomatic rate was the highest (53% versus 37% in those with no iMCA).

Cerebral blood flow can be maintained by the placement of a shunt to make CEA safer, but routine or selective shunting can have drawbacks, so can routine non-shunting. A meta-analysis (50) showed a small difference in perioperative stroke rate between routine shunt (1.4%) and nonshunt use (2%). The updated Cochrane Review published in 2014 cannot definitely support or refute routine or selective shunting, nor the use of one form of neuromonitoring over another in selective shunting has been shown to produce better outcomes (51). Regarding selective shunt usage, detection of ischemia on test clamping may lead to prompt declamping with subsequent reclamping, increasing embolic risk, or to a delay in ischemia management with the test clamp left in place while the shunt is readied. Routine shunt use may be hazardous for patients not requiring a shunt, potentially resulting in thromboembolic complications or arterial injury (50). More new postoperative ischemic lesions were reported when a shunt was used; however eversion CEA seemed to be a protective factor (52). Eversion endarterectomy may have the advantage of a lower restenosis rate found by a large meta-analysis and lower embolization rate due to the absence of any nonautologous material. Shunt usage affects the surgical technique, as a shunt can only be inserted when the eversion is completed. Most surgeons in favour of the eversion technique, do not routinely use a shunt (51-53).

Of the 34 patients without adequate CoW collaterals either from the contralateral ICA or from the vertebrobasilar system (iMCA), eight had neurologic complications. The complication-free 26 subjects might have had sufficient extracranial - intracranial or pial collaterals. Future research of the complex collateral network may provide a better

understanding of stroke development and more personalized carotid revascularization strategies.

5. 3. Carotid Revascularisation Studies

5. 3. 1. Symptomatic carotid stenosis

In the 1990s, three major RCTs comparing CEA to best medical therapy (BMT) in average risk symptomatic patients were conducted (54-56), than their results were pooled (57, 58). In these analyses of >6,000 CEA patients with ≥70% ICA stenosis the absolute risk reduction of stroke/death was 16% at 5 years ($p<0.001$) and the number needed to treat (NNT) was 6 to prevent 1 event at 5 years. This benefit was evident within 1 one year of follow-up and persisted through 8 years. Modest benefit was also seen for patients with 50-69% stenosis with a stroke/death absolute risk reduction of 5% at 5 years ($p=0.04$) and NNT of 14 (55).

At the conclusion of NASCET in 1415 and European Carotid Surgery Trial (ECST) in 1745 patients, the overall rate of perioperative (as per definition 30-day) stroke and death was 6.5-7% (54, 55). Five variables were associated with a statistically significant increase in the risk of perioperative stroke and death: a hemispheric TIA against amaurosis as the qualifying event (odds ratio (OR): 2.3), a left-sided procedure (OR: 2.3), the presence of contralateral carotid occlusion (OR: 2.2), irregular or ulcerated plaque on the angiography on the surgical side (OR: 1.5), and an ipsilateral ischemic lesion on the initial CT scan (OR:1.8) (54).

In contrast to these milestone RCTs, results for CEA in more recent RCTs reported lower 30-day perioperative stroke/death rates for average-risk symptomatic patients: 3.2% in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) (59, 60) and 3.4% in the International Carotid Stenting Trial (ICSS) (61).

As carotid artery stenting (CAS) evolved, studies comparing CEA to CAS in average risk patients proliferated to potentially expand indication of CAS. The three most prominent trials in symptomatic patients reported that CAS was associated with higher rates of perioperative stroke/death as compared to CEA (61-63). However, there was

significant heterogeneity in study design, type of stents, application of protection devices, and experience of the interventionist.

In the ICSS the risk of stroke, death or MI between randomisation and 120 days was significantly higher in the CAS group than in the CEA group (8.5% versus 5.1%, p=0.006). However, there was no significant difference in the 30-day disabling stroke/death rates between groups (CAS 4.0% versus. CEA 3.2%, p=0.34), nor in the cumulative 5-year risk of stroke/death (CAS 6.4% versus CEA 6.5%; p=0.76). The observed effect was largely driven by the higher number of non-disabling strokes in the CAS group (61).

The results of Endarterectomy Versus Angioplasty in patients with Symptomatic Severe Carotid Stenosis (EVA-3S) study suggested that CAS was non inferior to CEA for middle-term prevention of ipsilateral stroke. The HR for fatal/disabling stroke at 120 days was 2 (p=0.17). However, the cumulative 4-year risk of operative stroke/death and non-procedural ipsilateral stroke was higher with CAS than with CEA (11.1 versus 6.2%, HR: 1.97, p=0.03) (62).

In the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial the 2-year risk of ipsilateral ischemic stroke, and that of any periprocedural stroke/death did not differ between the CAS and the CEA groups (9.4% versus 7.8%; HR: 1.23, p=0.31) (63).

Advanced age was also evaluated as an important modifier of operative risk in carotid revascularization. The benefit of CEA for subjects of ≥70 years was confirmed with a pooled analysis of ICSS, EVA-3S, SPACE and the symptomatic CREST cohort analyzing the data of >4700 patients. In CAS, the 120-day HR for stroke/death in patients aged 65–69 years compared with patients of 60> years was 2.16, with HR of roughly 4.0 for patients of ≥70 years. No evidence of an increased periprocedural risk by age group was found in the CEA group (p=0.34) (64). The difference in older patients was almost entirely attributable to increasing periprocedural stroke risk with CAS.

In the results of a large meta-analysis of 13 RCTs with 7477 mainly symptomatic patients, CAS compared with CEA was associated with a 65% increase in 30-day periprocedural death or stroke risk (5.5% versus 3.8%, respectively). However, CEA relative to CAS was associated with a 122% increase in the risk of periprocedural MI (1.2% versus 0.3%, respectively). Regarding the long-term outcomes (during a follow up

of 12-65 months), CAS as compared with CEA was associated with a 24% increase in the risk for death or ipsilateral stroke and 48% increase in the risk of any stroke. The results were similar for both symptomatic and asymptomatic cohorts regarding these outcomes (65).

From a large database (over 29000 CEA and 4415 CAS patients) 4261 matched pairs of a CEA subject and a CAS patient were generated and their mortality rates were compared by the Vascular Study Group of New England (VSGNE). The unadjusted 5-year mortality was 14.0% for CEA versus 18.3% for CAS (log rank $p<0.001$). The HR of overall mortality for CEA versus CAS was 0.75, indicating that patients who underwent CEA were 25% less likely to die than who had CAS. This advantage persisted after adjustment for age, sex, and co-morbidities and was confirmed on a propensity-matched analysis, with a HR of 0.76. Moreover this advantage were more pronounced in symptomatic patients (adjusted HR: 0.69) (66).

In another retrospective observational study of VSGNE based on a quality improvement registry, Nolan at al. reported that symptomatic patients treated with CAS are at a significantly higher risk for in-hospital stroke/death (1.6% for CEA, 5.1% for CAS, $p=0.001$) (67), contrasting the results of some RCTs.

5. 4. 2. Asymptomatic carotid stenosis

Although several trials on symptomatic carotid stenosis have been published, allowing for consensus and specific guidelines concerning treatment options (68), current management guidelines for the asymptomatic carotid stenosis remain the subject of debate. There is an uncertainty whether or not to revascularize asymptomatic patients, and also on which revascularization procedure should be performed. The UK National Institute for Health and Clinical Excellence mostly recommends CEA for revascularisation of asymptomatic patients (69). The US Society of Vascular Surgery guideline reported, that CAS was associated with a significantly higher rate of major complications than CEA in asymptomatic patients (37), and in conjuction with the Canadian guidelines recommends CAS only in those asymptomatic patients, who are not surgical candidates for technical, anatomic or medical reasons (70).

The Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial-1 (ACST-1) were the two landmark trials in asymptomatic carotid disease.

In ACAS, 1662 patients with asymptomatic carotid stenosis of ≥60% were randomized, 834 to best medical treatment (BMT), 825 to CEA and BMT. Patients undergoing CEA had a lower 5-year risk of operative stroke/death + postoperative ipsilateral stroke (5.1% versus 11.0%, p=0.004). CEA was associated with an absolute risk reduction of 5-year ipsilateral stroke of 6.0% (71).

In ACST-1 3120 subjects with asymptomatic carotid stenosis of ≥70% were randomized to BMT or CEA with BMT. Unlike the prior studies, in ACST, BMT consisted of antiplatelet therapy, antihypertensive treatment, and, in the later years of the study, lipid-lowering therapy. Patients undergoing CEA again exhibited decreased rates of operative stroke/death + any postoperative stroke at 5 years (6.9% versus 10.9% p=0.0001) and 10 years (13.4% versus 17.9%, p=0.009) (72).

In the asymptomatic arm of CREST, the perioperative stroke/death rate of CEA was among the lowest reported at 1.4% and was not significantly different than the stroke/death rates associated with CAS (2.5%, p=0.15) (73, 74). Similarly, at 10-year follow-up the rates were no different (CEA 7.9% versus CAS 8.6%, p=0.41) (73). The results were not demonstrably different when utilizing composite endpoints that included MI either.

ACT I was designed to test non-inferiority of CAS (1089 patients) to CEA (364) in average-risk patients with asymptomatic carotid stenosis of ≥70%, and younger than 79 years old. Low perioperative stroke/death rates were again observed (1.7% CEA versus 2.9% CAS, p=0.33). Overall 5-year stroke-free survival was not different (94.7% CEA versus 93.1% CAS, p=0.44). Similarly, the primary composite endpoint (which included myocardial infarction) was not different between groups. The authors concluded that CAS is non-inferior to CEA in the treatment of asymptomatic carotid stenosis (75).

In contrast to ACT-I a systematic review and meta analysis of 3019 asymptomatic patients found an increased risk after CAS with pooled incidences of any periprocedural stroke (relative risk (RR): 1.84), and any periprocedural stroke or death (RR: 1.72), providing evidence that CEA may be a safer treatment option than CAS for asymptomatic carotid stenosis (76).

The VSGNE conducted a large observational study and reported, that the adjusted hazard ratio (HR) of 5-year overall mortality for CEA versus CAS in asymptomatic patients was 0.80, indicating that those patiens treated with surgery are 20% less likely to die than their CAS counterparts. These outcomes are in contrast to some RCTs, which demonstrated no difference in survival between the two procedures, possibly due to the careful patient selection (66).

In another study from the VSGNE the overall early in-hospital stroke/death rate was found higher for CAS (2.3%) versus CEA (1.1%, p=0.03). The composite of stroke, death, or MI rates (2.8% CAS versus 2.1% CEA; p=0.32) were not different, however. Asymptomatic patients had similar in-hospital stroke/death rates (CAS 0.8% versus CEA 0.9%; p=0.78) (67).

5. 4. 4. Comparison of stroke/death rates of carotid revascularization studies and ours

There is substantial heterogeneity in the methodology and outcome measures in different studies, which render the comparison difficult. Large CEA studies provided 30-day perioperative stroke/death risk rates, some of them underpinning the risk for 30-day major stroke and death. **Table 14.** Considering the possible errors of our 30-day data due to the retrospective study design, we only compared our results with those studies detailing the immediate postoperative and in-hospital complications.

In our study the risk for any in-hospital ischemic stroke among symptomatic patients was a bit lower (3.9%) than that reported by NASCET (4.1%), but higher than the 1.6% found by the VSGNE. The rate of in-hospital major stroke in symptomatic carotid stenosis (1.9%) equals with NASCET (1.9%) (54) but higher than that of the VSGNE (0.6%) (67). No death occurred in our symptomatic group, while 0.6% in-hospital death rate was reported by NASCET and 0.2% by VSGNE. It has to be noted that our complication rates were well within the recommended safety threshold of 6% for symptomatic patients (77).

The Vascular Study Group of Northern New England reported that the overall in-hospital stroke/death rate after CEA was 1.0% including TIA in 0.4%, minor stroke in 0.5%, and major stroke in 0.2%. No separate complication rates for symptomatic or

asymptomatic cases were communicated, but the provided data reflect surprisingly low overall stroke/death risk as compared with ours (0.7% versus 2.2%) (78).

In our asymptomatic group the risk for any immediate postoperative stroke was 1.0%. Our 6-day any stroke rate was 1.2% and the major stroke/death rate was 0.3% including one fatal case (0.3%), comparable with the data provided by the VSGNE (0.9%, 0.5%, and 0.2% respectively) (67).

The ACT I study only published the rate of intraoperative deaths and stroke associated with CEA at 1.1%, which is slightly higher than ours. Data regarding in-hospital complication rates were not included (75).

The recommended safety threshold of 3% for asymptomatic patiens (77) was achieved by our study or even the lower thresholds suggested by CREST (59, 60) or ACT-I (75). **Table 15.** Further comparable data are lacking from the literature by date.

5. 4. Limitations

Some of the limitations of our study are the lack of comparison with DSA as reference of standard, the possible bias between the study and control groups (radioanatomical approach) and the fact that the study group was limited to patients eligible for CEA with either asymptomatic ICA stenosis or symptomatic stenosis with TIA or minor ischemic stroke (both studies). In our center, patients with a severe disabling stroke are generally not subjected to carotid revascularisation. This may have resulted in an underestimation of the number of patients with compromised collateral capacity. Futher investigation with an age- and sex-matched control group would be useful to confirm our findings of significantly different CoW anatomy between the study subjects and controls.

We acknowledge the general limitiations of a retrospective study design as well.

The CTA can not provide information on flow dynamics, nor on secondary collaterals, which is a further technical limitation. Moreover we need be aware that in some cases the non-visualization of a CoW segment is in fact hypoplasia beyond the spatial resolution of CTA. The overall small caliber of the CoW elements together with

the finite spatial resolution of the CTA precludes the direct assessment of intracranial atherosclerotic plaques either. Brain CT has lower sensitivity in the detection of little cerebral infarcts, therefore a larger MRI cohort would have provided more statistical power in determining association between brain ischemia and CoW morphology.

Further limitation is the external validity of the anatomic variances of the CoW (both studies). We plan to correlate our findings with the results of the ongoing prospective CoW study in carotid atherosclerosis carried out in our institution. The main limitation of the clinical approach of our study is that we cannot entirely exclude embolisation as a background cause of INEs, as TCCD monitoring or postoperative MRI is not routinely performed. In addition the possible lack of documentation of the 30-day outcomes following CEA limits the comparison with other studies.

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6. Conclusions

CTA is a highly reproducible imaging method to evaluate CoW anatomy. It helps to detect those variants which predispose to cerebral ischemia and thus to tailor surgical or endovascular management of patients with significant extracranial atherosclerotic disease.

Distribution of CoW variants significantly differed between the study and control groups. CoW variants were frequent in or study group and significantly associated with cerebral ischemia proven by CT or MRI, or clinically by immediate neurologic complications following CEA.

Multiple incompleteness of the CoW on the surgical side carries an 11-fold risk of INEs after CEA with cross-clamping and no shunt protection. If iMCA is detected on preoperative CTA, routine shunting is recommended to prevent INEs.

Table 14. 30-day stroke/death rates in major randomized controlled trials

Study Symptomatic	**Year of publication**	**CEA***	**CAS***	**CEA****	**CAS****
NASCET	1991, 1998	6.7	-	2.9	-
ECST	2003	7.0	-	3.5	-
EVA-3S	2008	3.9#	9.6#	1.5	3.4
SPACE	2008	6.6	7.4		
ICSS	2010	3.4#	7.4#	2.2	3.1
CREST	2010, 2016	3.2#	6.0#	0.9	1.6
Asymptomatic					
ACAS	1995	2.3	-	-	-
ACST-1	2010	3.0	-	1.7	-
CREST	2010, 2016	1.4	2.5	0.3	0.5
ACT1	2016	1.7	2.9	0.6	0.6

*30-day any operative stroke/death (%)

** 30-day disabling stroke/death (%)

significant difference

NASCET= North American Symptomatic Carotid Endarterectomy Trial (38)

ECST = European Carotid Surgery Trial (55)

EVA-3S = Endarterectomy Versus Angioplasty in patients with Symptomatic Severe Carotid Stenosis (62)

SPACE = Stent-Protected Angioplasty versus Carotid Endarterectomy (63)

ICSS = International Carotid Stenting Study (61)

CREST = Carotid Revascularization Endarterectomy versus Stenting Trial (59, 73)

ACAS = Asymptomatic Carotid Atherosclerosis Study (71)

ACST-1 = Asymptomatic Carotid Surgery Trial (72)

ACT I = Asymptomatic Carotid Trial I (75)

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Table 15. Immediate postoperative and in-hospital stroke/death rates in randomized trials, observational studies and in our study.

Study	**Year of publication**	**CEA***	**CAS***	**CEA****	**CAS****
Symptomatic					
our study	2018	3.9	-	1.9	-
NASCET	1991, 1998	4.1	-	1.9	-
VSGNE	2012	1.6[#]	5.1[#]	0.8	3.9
Asymptomatic					
our study	2018	1.2 (1.0[†])	-	0.3	-
ACT1	2016	1.1[†]	1.4[†]	-	-
VSGNE	2012	0.9	0.8	0.5	0.8

*Any immediate and in-hospital stroke/death rate (%)

** Immediate and in-hospital disabling stroke/death rate (%)

significant difference

[†]Immediate postoperative stroke/death rates were reported by ACT I only; the percentage in brackets refers to our major immediate neurologic events corresponding to that of ACT I.

NASCET= North American Symptomatic Carotid Endarterectomy Trial (38)

CREST = Carotid Revascularization Endarterectomy versus Stenting Trial (59, 73)

ACT I = Asymptomatic Carotid Trial I (75)

VSGNE = Vascular Surgery Group of New England, regional quality improvement registry (67)

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Summary

Objectives: We hypothesized correlation between circle of Willis (CoW) incompleteness and cerebral ischemia in carotid endarterectomy (CEA) patients evidenced by either preexisting brain infarcts on computed tomography (CT), magnetic resonance imaging (MRI) or immediate neurologic events (INE) following CEA.

Methods: Data of 544 CEA subjects (61% males, mean age 69±8) and 196 controls (60% males, mean age 66±11) who underwent preoperative CT angiography (CTA), and of 72 patients (63% males, mean age 66±9) who had CTA and brain MRI, were retrospectively analysed. Each CoW segments were classified as normal, hypoplastic or non-visualized. 4 groups of CoW variants based on the number of hypoplastic/non-visualized segments were correlated with clinical data. Intra- and inter-observer agreement was estimated.

We considered the ipsilateral middle cerebral artery isolated (iMCA) in case of absent collaterals both from the contralateral internal carotid (ICA) and basilar arteries. INE was defined as transient ischemic attack (TIA) and stroke immediately after CEA. Logistic regression model was used including atherosclerotic risk factors, cross-clamping time, ICA stenosis, and preoperative symptomatic status.

Results: High prevalence of CoW variants (97%) in the study group and significant difference in the distribution of CoW variants compared to controls ($p<0.001$) were found, ICA stenosis being the only independent predictor in CoW morphology ($p<0.001$). Significant correlation was found between CoW configuration and brain ischemia by CT ($p=0.002$) and likewise by MRI ($p=0.04$). Intra- and inter-observer agreement of CTA was good for one CoW segment and almost perfect for all the others (Cohen $\kappa=0.75–1.0$). 12 subjects (2.2%) had a postoperative stroke. There were 20 INEs (8 strokes, 12 TIAs), and 34 iMCA cases (6.3%). Out of these 34 subjects 8 (24%) had INE (2 strokes, 6 TIAs). Overall, iMCA was an independent predictor of INEs (odds ratio: 11.1; 95% confidence interval (CI): 3.6-35.9; $p<0.001$). Symptomatic patients also had significant risk of INE (odds ratio: 3.3; 95% CI: 1.2-9.7; $p=0.02$).

Conclusion: Highly variable CoW morphology was demonstrated in CEA patients compared to controls, with likely compromised CoW in relation to cerebral ischemia.

An iMCA carried a >10-fold risk of INEs after CEA with cross-clamping and without shunt protection. Preoperative imaging of the CoW is of great importance, and if iMCA is proven, routine shunting is recommended to prevent INEs.

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Összefoglalás

Bevezetés: Irodalmi adatok alapján a nyaki verőér műtétes (CEA) betegeken összefüggést feltételeztünk az agyi iszkémia előfordulása és a hiányos Willis-kör (CoW) között. Az iszkémiát a preoperatív komputer tomográfiás (CT) vagy mágneses rezonanciás (MRI) vizsgálat, ill. a közvetlen posztoperatív neurológiai tünetek (INE) bizonyították.

Módszerek: 544 betegnél (61% férfi, átlag életkor 69±8) és 196 kontrollnál (60% férfi, átlag életkor 66±11) történt CT angiográfia (CTA), ill. 72 betegnél (63% férfi, átlag életkor 66±9) CTA és agyi MRI. A képalkotó és klinikai adatok korrelációja retrospektíven történt. A CoW szegmentumokat a következőként értékeltük: normális, hipopláziás, hiányzó. A hipopláziás, ill. hiányzó szegmentumok száma alapján létrehozott 4 betegcsoport klinikai adatait vetettük össze. Meghatároztuk a CTA reprodukálhatóságát (inter- és intraobszerver egyezés).

Amennyiben a CoW az ellenoldali nyaki verőér és a műtéti oldali vertebrobaziláris rendszer felől is hiányosnak bizonyult, izolált artéria cerebri médiáról beszéltünk (iMCA). INÉ-nek tekintettük a közvetlenül műtét utáni stroke-okat vagy átmeneti iszkémiás rohamokat (TIA). Az ateroszklerózis rizikófaktorait, a nyaki verőér leszorítás időtartamát, ill. szűkület mértékét és a preoperatív tüneteket tartalmazó logisztikus regressziós modellt alkalmaztunk.

Eredmények: A CoW variánsok magas aránya (97%) jellemezte a betegcsoportot, a betegek és kontrollok között anatómiai eloszlás szignifikáns különbségével (p<0.001). A nyaki verőér szűkület a CoW morfológia független prediktorának bizonyult (p<0.001). Szignifikáns összefüggés mutatkozott a CoW anatómia és a CT-vel (p=0.002), ill. MRI-vel igazolt p=(0.04) agyi iszkémia között. Az intra- és interobszerver egyetértés egy szegmentum esetén jónak, a többinél kiválónak bizonyult (Cohen κ=0.75–1.0).

12 posztoperatív stroke fordult elő (2.2%), INE 20 esetben (ebből 8 stroke, 12 TIA). 34 iMCA-t találtunk, ebből 8 esetben (24%) fordult elő INE (2 stroke, 6 TIA). Az iMCA az INE független prediktorának bizonyult (esélyhányados (OR): 11.1; 95%-os konfidencia-intervallum (CI): 3.6-35.9; p<0.001). A többi paraméter közül a preoperatív tünetek és az INE között találtunk szignifikáns összefüggést (OR: 3.3; 95% CI: 1.2-9.7; p=0.02).

Összegzés: A CoW anatómia tekintetében szignifikáns különbség mutatkozott a nyaki verőér műtétes és kontroll csoportok között, a hiányos CoW és az agyi iszkémia szignifikáns összefüggésével. A sönt alkalmazása nélkül végzett CEA esetén az iMCA INE szempontjából >10-szeres rizikót jelent. A CoW preoperatív leképezése fontos, és amennyiben iMCA-t bizonyít, sönt rutinszerű alkalmazása javasolt a neurológia szövődmények megelőzésére.

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List of publications

Publications related to the present thesis (cumulative IF 7.344)

articles

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Banga PV, **Varga A**, Csobay-Novak C, Kolossvary M, Szanto E, Oderich GS, Entz L, Sotonyi P. (2018) Incomplete circle of Willis is associated with a higher incidence of neurologic events during carotid eversion endarterectomy without shunting. J Vasc Surg, 68: 1764-1771 (**IF: 3.243**).

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Varga A, Barsi P. (2016) A szuszceptibilitás leképezése a rutin agyi MRI-protokoll részeként? Példák a klinikai alkalmazásra. Magyar Radiológia Online 70:1-25.

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