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Influence of the circle of Willis on leptomeningeal collateral flow in anterior circulation occlusive stroke: Friend or foe?

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ABSTRACT

Background: Clinical outcome after large vessel occlusion (LVO) stroke depends on collateral integrity. We aimed to evaluate whether the completeness of the circle of Willis (CoW) and anterior temporal artery (ATA) determines the status of leptomeningeal collaterals (LC) in patients with acute LVO (internal carotid artery (ICA) and middle cerebral artery M1 (MCA) occlusion) treated with endovascular thrombectomy.

Patients and methods: LC, cross-flow through the anterior communicating artery (ACoA), presence of the ipsilateral posterior communicating artery (IpsiPCoA) and presence of the ATA were evaluated using CT angiography. LC was graded as good when ≥50% collateral filling was noted compared to the unaffected hemisphere.

Results: We included 159 patients with a median age of 75 years (IQR 63–82), MCA M1 occlusion in 96 (60%) and good outcome in 68 (45.6%). The LC were good in 129 (81.1%) patients. Complete IpsiPCoA and incomplete ACoA status was inversely associated with good LC in LVO (OR 0.51 (95% CI 0.02–0.07)). A complete CoW was associated with good LC in ICA occlusions, OR 8.4 (p = .025). Good outcome (modified Rankin scale 0–2 at 3 months) was associated with good LC (OR 5.63 (95% CI 1.11–28.4)), small ischemic lesion volume (OR 0.94 (95% CI 0.97–0.98)) and absence of the ACoA and IpsiPCoA (OR 4.47 (95% CI 1.09–18.3)).

Conclusions: ATA presence was associated with good leptomeningeal collaterals in LVO (OR 8.13 (95% CI 1.69–39.0)) and in MCA M1 patients (OR 7.9 (95% CI 1.7–36.4)). The effect of ATA was most pronounced in MCA M1 occlusions, and that of ACoA was most pronounced in ICA occlusions.

1. Introduction

Stroke due to large vessel occlusion (LVO) in anterior circulation is amenable to reperfusion treatments using intravenous rt-PA and endovascular thrombectomy (EVT) [1]. Although, after EVT, up to 71.0% of patients reach good clinical outcome at 3 months (mRS 0–2), these rates vary [2–4]. Well-known predictors of outcome are age, clinical status at admission (NIHSS), blood glucose at admission, and reperfusion success measured by modified thrombolysis in cerebral infarction score (mTICI), among others.

However, the outcome after LVO may also be influenced by the presence of collateral vessel status. Collaterals can be divided into primary collaterals consisting of the anterior communicating and posterior communicating arteries (circle of Willis) and secondary (or distal) collaterals consisting of leptomeningeal anastomotic vessels of up to 1 mm in diameter. Leptomeningeal collaterals, representing the connection between distal regions of the intracerebral arterial system, are known to be markers of good outcome. They can salvage the penumbra in the event of unsuccessful reperfusion or possibly deliver thrombolytic agents to both sides of the thrombus [5–9]. On the other hand, the influence of primary collaterals (or proximal collaterome), defined as a complete circle of Willis (CoW), on the same outcome point is underinvestigated. Furthermore, good clinical outcome after MCA M1 occlusion is associated with the presence of the anterior temporal artery (ATA) [10]. Therefore, there is a possible interplay among a functional proximal CoW, ATA and distal leptomeningeal collateralization, although the exact mechanism is not known. Indeed, the completeness of the CoW could play a major role in ameliorating reperfusion injury by optimizing perfusion pressure during the critical period [11]. It is known from previous studies that patients with stroke have suboptimally developed collaterals in the CoW [12,13]. Additionally, a well-developed CoW can protect against ischemia in the presence of

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severe internal carotid artery (ICA) stenosis [14–18]. Intravascular flow redistribution in the event of acute proximal vessel occlusion is a complex process that is dependent on genetic and acquired factors.

There are some data showing that in the presence of the MCA (M1 and M2 represented), occlusion LC is dependent on CoW completeness [5]. Indeed, when the ipsilateral posterior communicating artery (PCoA) is not present and the ACoA is, there is a higher chance of having poor collaterals. Mechanistically, if one pathway is available for flow redirection and the other is not, the blood can be actually siphoned to available shunts, following the path of least resistance. However, the site of occlusion could be of critical importance. When the ICA is acutely occluded, the flow from the involved ICA cannot reach the ACoA and PCoA, and these vessels receive blood from the contralateral ICA and ipsilateral PCA. On the other hand, when the MCA M1 portion is occluded, the ipsilateral ICA supplies blood to the ACoA and PCoA, and this flow can be either redirected to boost the LC or siphoned away from the affected hemisphere. Additionally, the "third collateral", in the form of the anterior temporal artery, as shown by Liu et al., plays a role in determining outcome after MCA M1 occlusion (only atherosclerotic occlusions included), although they could not find a link between LC and ATA using digital subtraction angiography [10].

Taking these uncertainties and especially the lack of comparison between ICA and MCA occlusions regarding the status of LC, we sought to fill the knowledge gap on the role of CoW integrity and ATA patency on LC and ultimately on stroke outcome in the context of acute major anterior LVO treated with endovascular thrombectomy.

2. Subjects and methods

We retrospectively studied a database of prospectively collected stroke patients treated with endovascular thrombectomy due to anterior large vessel occlusive stroke in one tertiary clinical center (Christian Doppler Medical Center, Salzburg, Austria). The ethics commission's approval was obtained prior to study according to local laws as practices. The study period lasted 5 years, January 2012 until December 2016. We selected patients according to the following criteria: 1) age ≥ 18 years; 2) National institutes of health stroke scale (NIHSS) > 6; 3)-modified Rankin scale (mRS) prior to intervention < 4 points; and 4) time from presentation within 6 h of onset. We did not recruit patients with intracranial bleeding or primary expansive processes.

For the purpose of this study, a multidetector CT scanner SOMATOM® Definition AS+ from Siemens Healthcare was used. The CT scans were reconstructed into 4 mm thick adjacent slices through the whole brain with specifications of 120 kV and 390 mAs (mean value, using automatic exposure control), pitch of 0.55 and matrix size of 512 × 512. The mean equivalent dose was 2.1 mSv (mean DLP of 950 mGy × cm). A total of 60 ml of contrast (350 mg J/ml) was injected through the peripheral vein (mostly ante-cubital vein) via an automated injector at a flow rate of 4 ml/s. A contrast-enhanced image was obtained with the following parameters: 100 kV, 160 mA, pitch of 1.2, section thickness of 0.6 mm, 0.4 mm increment, 180 mm field-of-view, 512 × 512 matrix with H20f smooth reconstruction kernel. Image postprocessing was performed at a workstation (*Syngo*.via®, *Siemens Healthcare*). After successful acquisition of CTA datasets, the source images were reformatted as 3D volume rendering (VR) and maximum intensity projection (MIP) angiograms.

We used preinterventional CT angiography to assess the presence of flow in PCoAs. Experienced neuroradiologists assessed the presence of the ATA, ACoA and both PCoAs on CTA and confirmed ACoA patency by examining interventional digital subtraction angiography (DSA) images. Flow through ACoA was considered functional when present via the ACoA to the contralateral pre- and postcommunicating segments and to the MCA main trunk (Fig. 1). The ipsilateral trifurcations, i.e., both ACAs arising from the MCA trunk, were considered nonfunctional. The neuroradiologist was blinded to the clinical and radiological outcomes. The leptomeningeal collaterals were assessed using CTA source images and maximum intensity projections across the entire MCA territory. To assess leptomeningeal collaterals, we used the grading system proposed by Angermaier et al. 2010, i.e., when no collaterals were visible in the MCA territory of the affected hemisphere, the grade was "poor"; when some but not equal filling of collaterals was visible, the grade was "less than affected hemisphere", when collateral filling was equal or greater, the grade was "equal" [7]. Furthermore, leptomeningeal collaterals were dichotomized as good or poor, with the former category encompassing "equal" and "less then affected hemisphere". The patency of the circle of Willis was categorized as follows: 1) complete CoW, representing an ACoA and ipsilateral PCoA (IpsiPCoA); 2) an incomplete IpsiPCoA and a complete ACoA; 3) a complete IpsiPCoA and an incomplete ACoA; and 4) an incomplete IpsiPCoA and an incomplete ACoA (Fig. 1) [5].

When MCA M1 occlusion was detected, we used MIP images to measure the distance in millimeters between the origin of the MCA and intravascular contrast abruption, representing the proximal clot surface.

When detected, hyperdense clots were measured for density, length and area by methods already described [19]. Briefly, intravascular hyperdensity was manually delineated on native CT scans and measured for average density, length of hyperdense portion and area in cm^2.

Endovascular thrombectomy was performed almost exclusively with modern stent-retriever devices and under general anesthesia, according to the local preferences. After EVT, the patients were exclusively monitored in the neurological intensive care unit and later transferred to the stroke unit department.

We collected various demographic and radiological data, including NIHSS at onset, systolic blood pressure in mmHg on admission, occurrence of hospital death, three-month outcome as measured by mRS, ischemic lesion volume in cm^3 as measured on control CT after 24 h but no < 96 h after stroke. To calculate the ischemic lesion volume, we manually delineated the infarct area on each CT slice on a control CT. The computed area was multiplied with slice thickness (4 mm) to produce volume in cm^3 [19]. Time from stroke onset to first imaging, time to needle (systemic thrombolysis with rt-PA, when applicable), time to vessel punction (time-to-intervention), total intervention time and presence of postinterventional hemorrhage were prospectively collected.

Stroke etiology was determined according to Trial of Org 10172 in Acute Stroke Treatment (TOAST). All patients received noninvasive ultrasound diagnoses of the neck and brain arteries along with transthoracic (transesophageal when deemed necessary) heart ultrasound, 24-h electroradiogram (Holter) and determination of various blood parameters [20].

Success of EVT was measured according to modified thrombolysis in cerebral infarction (mTICI) grading with grades that range from 0 to 3: 0 – no reperfusion, 3 – successful reperfusion. We grouped patients into nonsufficient reperfusion (mTICI 0-2a) and sufficient reperfusion (mTICI 2b and 3) groups [21]. The Primary outcome was defined as an mRS score of 0–2 at 3 months poststroke.

3. Statistical analysis

Descriptive statistics were used to present data about patients' demographic, clinical and radiological data using number with percentages or median and interquartile range (IQR). Due to the nonnormality of our interval variables, we performed a Kruskal-Wallis nonparametric test for differences between groups. Fisher's exact test was performed on categorical variables. We calculated the relative risk as the odds ratio (OR) using logistic regression to evaluate univariate associations with LC. Analysis of variance with Bonferroni correction was used to test for difference of time to first imaging between CW groups. Multivariate associations between different variables were analyzed

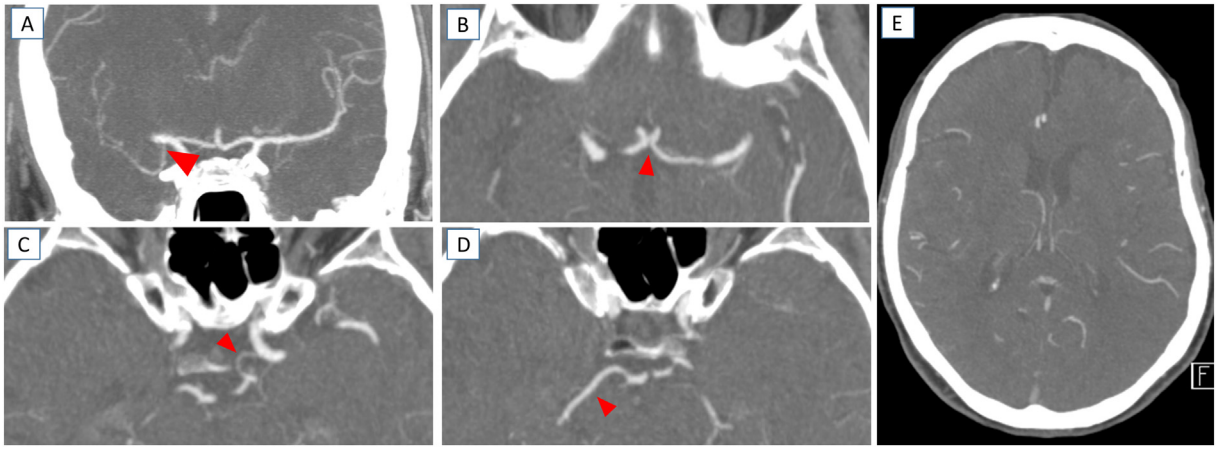

Fig. 1. CT angiography showing acute occlusion of the proximal portion of the middle cerebral artery on the right side and patency of the anterior temporal artery (Panel A). The cross-flow through the anterior communicating artery and contralateral posterior communicating artery (PCoA) is visible (Panel B, C). However, ipsilateral PCoA is absent (Panel D). Example of good leptomeningeal collaterals (Panel E).

using logistic regression with binary outcomes, reporting the odds ratio. Statistical significance was considered positive below $p = .05$. Statistical analysis was performed using STATA 13.0 (StataCorp LLC, TX).

4. Results

4.1. Demographics

In this five-year study, there were 282 endovascular interventions due to acute stroke. Of these, 73 were performed in posterior circulation and were excluded. Thirty-five patients were excluded due to a lack of quality imaging data in the radiological digital system and 15 due to MCA M2 occlusions. That left 159 patients with MCA M1 (further MCA) and ICA occlusions for final analysis. The patients' demographics are given in Table 1. The median age was 75 (63–82), and 69 (43.4%) of the participants were men. Good outcome at three months (defined as mRS 0–2) was recorded in nearly 45.6% of patients (68/149), while 10 had no data on outcome. Only 2 patients had I-Type ICA occlusion and were included in the group of ICA occlusions (Table 2).

4.2. Intracranial vessels

A complete functional CoW (ACoA + PCoA on both sides) was detected in 27 (16.9%) patients. Trifurcations of ACA were present in 7 (4.4%) patients, and these patients were not considered to have a functional ACoA. An IpsiPCoA and ACoA were found in 31 (19.5%) patients. A fetal (primitive) version of the posterior cerebral artery (FTP) was present on the right and left in 17 (11.8%) patients and 18 (11.1%) patients, respectively, ipsilateral to the LVO side. An FTP ipsilateral to LVO occlusion has no correlation with the status of leptomeningeal collaterals. An anterior temporal artery (ATA) in MCA occlusion was present in 37 (48.0%) patients. The distance to clot was 9.4 mm (4.5–14.2) mm median. The IpsiPCoA was weakly associated with noncardioembolic stroke, $p = .084$. The presence of an ACoA was not associated with a history of carotid stenosis or presumed stroke etiology in any LVO. The presence of a complete CoW was associated with higher systolic BP at admission, irrespective of LVO site, $p = .017$ and with shorter time to first imaging $p = .036$, whereas LC showed no such association, indicating time-dependent und BP-associated recruitment of CoW collaterals. The presence of a complete CoW (both PCoA and ACoA) was associated with higher systolic BP at admission, 147 vs. 163 mmHg, $p = .017$.

4.3. Leptomeningeal collaterals

Good leptomeningeal collaterals (LC) were found in 129 (81.1%) LVO cases, 77 (80.2%) MCA cases and 52 (82.5%) ICA cases. Good LC was univariately inversely associated with the presence of an incomplete ACoA and a complete IpsiPCoA, OR 0.15 (95% CI 0.03–0.71), irrespective of the LVO site. When MCA occlusions were analyzed separately, the presence of ATA was univariately associated with good LC, OR 7.86 (95% CI 1.69–36.3), whereas distance to clot was not. In MCA occlusions, good LC were found more often in the presence of an incomplete CoW (35; 45.4%) than in ICA occlusions, $p = .069$. In ICA occlusions, there was only 1 patient (1.9%) with good LC and an incomplete CoW, $p = .011$. When good LC are analyzed separately, the proportions of various CoW configurations are significantly different between MCA and ICA (MCA) occlusions, $p < .001$ (Fig. 2). Due to the small number, we compared patients with a patent ACoA and IpsiPCoA against all other variants; when thus dichotomized, the presence of the ACoA and IpsiPCoA was significantly correlated with good LC, OR 8.39 (95% CI 1.25-∞), $p = .024$ (Table 3).

4.4. Multivariate analyses

In multivariable logistic regression analysis in 141 patients for good LC, adjusted for blood glucose, systolic blood pressure at admission in mmHg, time to first imaging in minutes, anterior temporal artery presence (OR 8.13 (95% CI 1.69–39.0)), complete IpsiPCoA and incomplete ACoA status (OR 0.15 (95% CI 0.02–0.07)) were associated with good LC (Table 4).

4.5. Outcomes

Lower than 3 stent-retriever passes were associated with the presence of good LC, OR 0.28 (95% CI 0.11–0.69). Ischemic lesion volume was inversely associated with good LC in both LVO sites, $p < .001$ and with completeness of CoW but only in ICA occlusions where the smallest ischemic lesion volume was associated with complete CoW, $p = .032$. Hospital death occurred in 29 (18.2%) of patients in the median of 4 days (IQR 2–10). Hospital death overall was associated with an incomplete ACoA and complete IpsiPCoA, OR 15.8 (95% CI 1.70–146.8). A good clinical outcome after 3 months was associated with good LC, but not in the ICA group. Good clinical outcome was not associated with CoW completeness. In multivariable analysis, after adjustment with NIHSS at admission, TICI outcome (0-2a vs. 2b and 3), age OR 0.92 (95% CI 0.88–0.96), ischemic lesion volume OR 0.94 (95% CI 0.97–0.98), absence of ACoA and IpsiPCoA OR 4.47 (95% CI

Table 1
Baseline clinical characteristics in 159 patients treated with endovascular thrombectomy due to large artery occlusive stroke.

Age (years), median, IQR	75 (63–82)
Men (%)	69 (43.4)
Premorbid mRS > 1 (%)	7 (4.4)
mRS at 3 months 0–2	68 (45.6)
Admission NIHSS score	18 (14–23)
Admission systolic BP, mmHg	151 (125–170)
TOAST classification	
Cardioembolism + unknown	127 (79.9)
Other causes	32 (20.1)
Medical history	
TIA/Stroke	20 (12.6)
Peripheral arterial occlusive disease	9 (5.7)
Atrial fibrillation	62 (38.9)
Diabetes	20 (12.7)
Arterial hypertension	99 (62.3)
Carotid stenosis ≥50%	19 (11.9)
Glucose mg/dl	121 (108–143)
Antithrombotics	
Aspirin	39 (24.7)
Anticoagulant	24 (15.1)
Internal carotid artery	63 (39.6)
Tandem occlusion	33 (50.8)
Intracranial occlusion + MCA	30 (49.2)
ASPECTS	8 (8–9)
Leptomeningeal collateralization	
Absent on the affected side (poor)	30 (18.9)
Equal or less than on the unaffected side (good)	129 (81.1)
Anterior temporal artery (only MCA accounted)	39 (40.6)
Circle of Willis	
Complete anterior und ipsilateral posterior	31 (19.5)
Incomplete ipsilateral posterior, complete anterior	68 (42.8)
Incomplete anterior, complete ipsilateral posterior	17 (10.7)
Incomplete anterior and ipsilateral posterior	43 (27.0)
Distance to clot in mm	9.0 (5.3–13.8)
Treatment	
EVT and thrombolysis	116 (72.9)
Time to CT (min)	93 (65–127)
Time to needle	110 (82–147)
Time to vessel puncture	186 (147–225)
Time to recanalization	242 (192–313)
EVT Intervention time	52 (27–92)
Number of passes > 3	66 (50.0)
mTICI outcome	
0–2a	37 (23.3)
2b–3	122 (76.7)
Symptomatic intracranial hemorrhage	14 (8.8)
Ischemic lesion volume in cm^3	34.4 (4.4–158.9)

MCA – middle cerebral artery; PCoA – posterior communicating artery (ipsilateral: denoting visibility of PCoA on CT angiography on the same side as occluded middle cerebral artery); ACoA – presence of cross-flow through anterior communicating artery; APECTS – Alberta stroke program early CT Score; EVT – endovascular thrombectomy; ICA – internal carotid artery; NIHSS – National Institutes of Health stroke scale; EVT – endovascular thrombectomy; mTICI – modified thrombolysis in cerebral infarction.

1.09–18.3) (i.e., absence of CoW) and good LC OR 5.63 (95% CI 1.11–28.4) were associated with good clinical outcome at 3 months. When the MCA and ICA were analyzed separately, the CoW association lost significance.

5. Discussion

Our study shows that patency of the circle of Willis is associated with leptomeningeal collaterals, a finding already acknowledged previously [5]. However, we add to the existing knowledge by observing that the pattern of association was heavily dependent on the site of large vessel occlusion. Indeed, in the setting of acute internal carotid artery occlusion, good leptomeningeal collaterals were associated with the patency of anterior communicating and ipsilateral posterior communicating artery. In contrast, when the M1 portion of the middle cerebral artery was occluded, good leptomeningeal collaterals were associated with patency of the anterior temporal artery and not with CoW status. Notably, we found the same frequency of good leptomeningeal collaterals in both MCA and ICA occlusions. Good leptomeningeal collaterals were associated with good clinical outcome at three months, together with the absence of the ACoA and IpsiPCoA, age and ischemic lesion volume.

The presence of leptomeningeal collaterals is dependent on a multitude of factors, some of which are genetic in nature [22]. However, a mechanistic role may be of importance, namely, when MCA M1 is occluded, the blood flow coming from patent ICA may be siphoned to the path of least resistance, i.e., through ACoA and through PCoA away from the lesion. The only collateral that could feed leptomeningeal collaterals in the setting of MCA M1 occlusion may well be ATA. Our finding is in concordance with a report from Liu Dehzi 2014 that showed better clinical outcome in M1 occlusion and associated presence of ATA, although they did not assess leptomeningeal collateral status with CTA [10]. On the other hand, in the setting of acute ICA occlusion, there is no ipsilateral blood pressure to the ACoA and PCoA, and the only flow that can reach the MCA territory is through the contralateral ACI and posterior cerebral artery. The observed higher frequency of good leptomeningeal collaterals in MCA M1 occlusions in the absence of the IpsiPCoA supports this hypothesis, together with the higher frequency of leptomeningeal collaterals in ICA occlusions in the presence of the ACoA and IpsiPCoA.

In some aspects, the findings of our study are in line with previously published results. The effect of good leptomeningeal collaterals on clinical outcome could be shown in previous studies regardless of methodological differences [6–9,23]. Studies evaluating the CoW are, however, rare and controversial. One study investigated the completeness of the CoW, defined as the absence of 1) an A1 portion of the anterior communicating artery, 2) a posterior communicating artery, 3) an anterior communicating artery, or 4) P1 segments of the posterior cerebral artery. The study was performed in 64 patients who received rt-PA and found a relationship of complete CoW with good outcome. Additionally, patients with incomplete CoW had a 3-fold increase in the rate of symptomatic intracerebral hemorrhage, which we cannot corroborate [24]. The study had a low rate of cardioembolic cause of stroke, and evaluation of the CoW was performed after treatment with rt-PA. As already indicated by others, the presence of a complete CoW could ameliorate reperfusion injury by allowing discharge of the reperfusion pressure [11,25,26].

Among other findings, the IpsiPCoA was weakly associated with noncardioembolic cause of stroke in our dataset. It is already known that the presence of collaterals is associated with progressive degrees of carotid stenosis and caries lower risk of stroke and especially lower risk from fatal or disabling stroke, as shown in the group of patients with ICA stenosis [17]. This effect is most likely due to the washing-out effect on small microemboli coming from the stenosis site. However, we have not accounted for the degree of ACI stenosis, and the number of noncardioembolic strokes was small, so definite conclusions are difficult to reach.

Furthermore, we could not confirm the notion that the development of secondary collaterals is absent in the presence of an FTP because we found no association between FTPs and leptomeningeal collateral status, although some have found the opposite [27].

In contrast to anatomical studies that showed 52% completeness of CoW, we detected both PCoA and ACoA in only 17% of patients [28]. Imaging-based studies performed with the use of magnetic resonance angiography and CTA showed a wide range of complete CoW from 42% in the Western population to 89.7% in the Japanese healthy population [29,30]. This is most likely due to the imperfect method of CTA, with its limited resolution. Our results are most in accordance with the work from Li et al. 2011 that found 27% of complete CoW in the Chinese population using CTA [31]. Overall, the presence of contrast-perfused Vessel in CTA probably better reflects its functionality than the

Table 2
Univariable analyses for the association of various patient and imaging characteristics with the presence of leptomeningeal collaterals (N = 159).

	Good (N = 129)	Poor (N = 30)	Odds ratio	95% CI
Age (years)	74 (62–80)	77 (66–82)	0.11	0.93–1.00
Admission NIHSS score	18 (13 – 22)	19 (16–23)	0.93	0.87–1.00
Admission systolic BP, mmHg	152 (124–170)	144 (126–165)	1.00	0.99–1.02
TOAST classification				
Cardioembolism + unknown	103 (79.8)	24 (80.0)	1.00	0.37–2.72
Medical history				
Peripheral arterial occlusive disease	3 (10.0)	6 (4.6)	0.43	0.10–1.86
Diabetes	15 (11.7)	5 (16.7)	0.46	0.22–1.99
Arterial hypertension	81 (62.8)	18 (60.0)	1.12	0.49–2.53
Carotid stenosis ≥50%	14 (10.8)	5 (16.7)	0.61	0.20–1.84
Glucose mg/dl	121 (107–143)	131 (113–145)	0.99	0.98–1.00
Occlusion site				
Internal carotid artery	52 (40.3)	11 (36.7)	Reference	Reference
MCA	77 (59.6)	19 (63.3)	1.16	0.51–2.65
ASPECTS	8 (8–9)	8 (8–9)	0.76	0.50–1.17
Circle of Willis				
Complete anterior und ipsilateral posterior	28 (21.7)	3 (10.0)	Reference	Reference
Incomplete ipsilateral posterior, complete anterior	55 (42.6)	13 (43.3)	0.24	0.11–1.72
Incomplete anterior, complete ipsilateral posterior	10 (7.7)	7 (23.3)	0.15	0.03–0.71
Incomplete anterior and ipsilateral posterior	36 (27.9)	7 (23.3)	0.55	0.13–2.32
Anterior temporal artery	45 (34.9)	2 (6.7)	7.5	1.70–32.9
Distance to clot in mm (only MCA, N = 94)	9.4 (4.5–14.2)	7.4 (6.3–9.3)	1.02	0.93–1.21
Time to CT (min)	95 (65–134)	81 (66–107)	1.00	0.99–1.01

MCA – middle cerebral artery; PCoA – posterior communicating artery (ipsilateral: denoting visibility of PCoA on CT angiography on the same side as occluded middle cerebral artery); ACoA – presence of cross-flow through anterior communicating artery; APECTS – Alberta stroke program early CT Score; EVT – endovascular thrombectomy; ICA – internal carotid artery; NIHSS – National Institutes of Health stroke scale; EVT – endovascular thrombectomy.

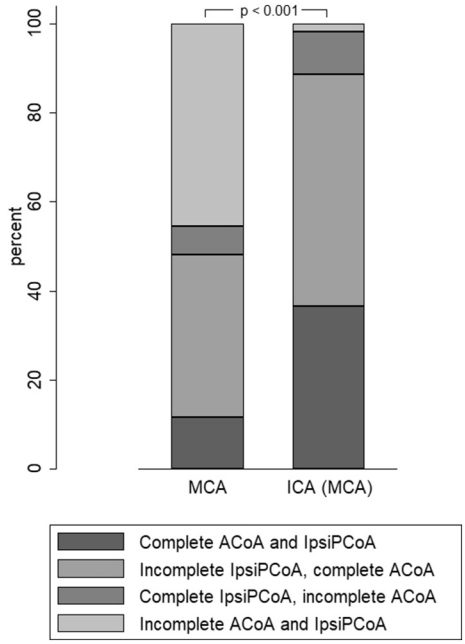

Fig. 2. Circle of Willis configurations by vessel type in good leptomeningeal collateral status. MCA: middle cerebral artery; ICA (MCA): internal carotid artery with simultaneous MCA M1 occlusion; ACoA: anterior communicating artery; IpsiPCoA: ipsilateral posterior communicating artery.

presence of sometimes string-like vessels in anatomic preparation [28]. We also used functional criteria for cross-flow, excluding CW completeness patients with trifurcations and nonfunctional but present ACoA, as confirmed by DSA.

Time to imaging was not associated with visible leptomeningeal collaterals, as already noted by Miteff et al. but disputed by Maas et al. [8,9] However, the patients coming late had more often incomplete CoW. The chance of detecting complete CoW was highest approximately 90 min after symptom onset. There is a possibility that primary collaterals (CoW), mostly the ACoA, are recruited early after LVO occlusion and then vasodilatation is exhausted afterwards.

We could in part replicate findings from van Seeters et al. that showed that the lack of the IpsiPCoA and the presence of an ACoA is related to poor leptomeningeal collaterals [5]. The aforementioned study investigated a large population of patients with intracranial ICA, MCA M1 and M2 occlusions with 29.3% graded as poor collaterals, which is in broad accordance with our study. They have also not confirmed the patency of the ACoA on DSA images; however, the same classification was in use regarding ACoA trifurcation. The study recruited a significant number of M2 occlusions (37.8%), which we excluded a priori. Furthermore, all our patients were treated with EVT. The study also did not correlate the site of LVO occlusion with the presence of CoW completeness or the assessed status of ATA. Comparably to our results, the absence of an IpsiPCoA and the presence of an ACoA were significantly associated with poor leptomeningeal collaterals in ICA occlusions (7 patients).

The shortcomings of our study are the relatively modest number of patients and the imperfect method of detecting the patency of small vessels. Additionally, we could not measure the amount or direction of blood flowing through collateral vessels or correctly demonstrate the patency of the PCoA on DSA images because most patients lacked high-quality lateral projection images. Furthermore, all patients were consecutive cases that underwent EVT and were all admitted to the neurointensive care unit under a standardized protocol.

In conclusion, the presence of an ATA and a functional ACoA was positively associated with good leptomeningeal collaterals in LVO. The effect of the ATA was most pronounced in MCA M1 occlusions, while that of ACoA was most pronounced in ICA occlusions. Our findings suggest that the CoW and ATA contribute to leptomeningeal collaterals, although they are dependent on the site of LVO. Further prospective studies to detect flow direction in CoW vessels in acute stroke are needed.

Acknowledgments

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Table 3
Predictors of good leptomeningeal collaterals ($N = 159$) in middle cerebral and internal carotid artery occlusions.

MCA ($N = 96$)			
		Odds ratio	95% confidence interval
Glucose (per mg/dl)	118 (103–141)	0.99	0.98–1.01
Anterior temporal artery	39 (40.6)	7.86	1.69–36.4
Circle of Willis			
Complete anterior und ipsilateral posterior	12 (12.5)	Reference	Reference
Incomplete ipsilateral posterior, complete anterior	34 (35.4)	1.55	0.32–7.5
Incomplete anterior, complete ipsilateral posterior	10 (10.4)	0.33	0.05–2.01
Incomplete anterior and ipsilateral posterior	40 (41.7)	2.33	0.46–11.6
ICA ($N = 63$)			
Glucose (per mg/dl)	127 (116–151)	0.99	0.97–1.00
Circle of Willis			
Complete anterior und ipsilateral posterior	19 (36.5)	Reference	Reference
Incomplete ipsilateral posterior, complete anterior	27 (51.9)	8.4	1.25-∞
Incomplete anterior, complete ipsilateral posterior	5 (9.6)		
Incomplete anterior and ipsilateral posterior	1 (1.9)		

Table 4
Multivariable logistic regression analysis reporting odds ratio for good leptomeningeal collaterals adjusted for blood glucose, systolic blood pressure at admission in mmHg, time to first imaging in minutes, anterior temporal artery presence, completeness of circle of Willis in 141 patients treated due to large vessel occlusion with endovascular thrombectomy.

	Good leptomeningeal collaterals		
	Odds ratio	95% confidence interval	*p*-value
Systolic blood pressure at admission in mmHg	1.01	0.99–1.02	0.291
Anterior temporal artery patency	8.13	1.69–39.0	0.009
Internal carotid artery occlusion	2.01	0.68–5.92	0.204
Blood glucose in mg/dl	0.99	0.98–1.01	0.426
Circle of Willis			
Complete ACoA and IpsiPCoA	Reference	Reference	
Incomplete IpsiPCoA, complete ACoA	0.51	0.11–2.11	0.359
Complete IpsiPCoA, incomplete ACoA	0.15	0.02–0.07	0.023
Incomplete IpsiPCoA and ACoA	0.49	0.09–2.47	0.388

IpsiPCoA: ipsilateral posterior communicating artery; ACoA: functional anterior cross-flow.

Author contribution statement

KM, JSM, MKO, SP: conceptualization of the study, final revision of the manuscript; CH, NB, CR: data acquisition, patient follow-up; LM: neuroradiology assessment; SP: planning and execution of the statistical analysis; generation of the figures, tables and modified drafts.

Declaration of conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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