

Circle of Willis variants are not associated with thrombectomy outcomes

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To cite: Seifert-Held T, Eberhard K, Christensen S, *et al.* Circle of Willis variants are not associated with thrombectomy outcomes. *Stroke & Vascular Neurology* 2021;**6**: e000491. doi:10.1136/svn-2020-000491

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Received 9 July 2020

Revised 3 August 2020

Accepted 9 September 2020

Published Online First

12 October 2020

ABSTRACT

Background The circle of Willis (COW) is part of the brain collateral system. The absence of COW segments may affect functional outcome in patients with ischaemic stroke undergoing endovascular therapy.

Methods In 182 patients in the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 Study and the CT Perfusion to Predict Response to Recanalisation in Ischaemic Stroke Project, COW anatomy was evaluated on postinterventional magnetic resonance angiography. The absence of the posterior communicating artery or the first segments of posterior or anterior cerebral arteries ipsilateral to the ischaemic infarction was rated as an incomplete COW. Logistic regression was applied to evaluate an association with the patients' modified Rankin scale (mRS) at 90 days after stroke

Results An incomplete ipsilateral COW was not predictive of the patients' mRS at 90 days after stroke. Significant associations were shown for the patients' baseline National Institutes of Health Stroke Scale (NIHSS), age and reperfusion status. The effect size suggests that a significant association of an incomplete COW with the mRS at 90 days may be obtained in cohorts of more than 3000 patients.

Conclusions Compared with the established predictors NIHSS, age and reperfusion status, an incomplete COW is not associated with functional outcome after endovascular therapy.

INTRODUCTION

Endovascular therapy has revolutionised ischaemic stroke treatment in early and late time windows.^{1–3} Cerebral arterial collaterals maintain salvageable brain tissue and enable extended onset-to-reperfusion time windows.⁴ These collaterals include segments of the circle of Willis (COW) and leptomeningeal anastomoses. Previous studies have suggested an impact of missing COW segments on functional outcome in patients with ischaemic stroke.^{5–7} We analysed COW variants on postinterventional time-of-flight magnetic resonance angiography (TOF-MRA) in patients in the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 Study (DEFUSE 2) and the CT Perfusion to Predict Response to Recanalisation in Ischaemic Stroke Project (CRISP).^{8,9} We postulated that the presence or absence

of COW segments ipsilateral to the ischaemic infarction provides prognostic information.

METHODS

Study design and participants

In patients in the DEFUSE 2 and CRISP studies, COW anatomy was evaluated after endovascular therapy on early (within 12 hours) or a late (day 5 after stroke) follow-up 1.5T or 3T TOF-MRA by an investigator blinded to demographic, clinical and other imaging data (TS-H.). Both studies had included ischaemic stroke patients with acute distal internal carotid artery (ICA) or proximal middle cerebral artery (MCA) occlusions. Patients in both studies were not randomised and all scheduled to undergo endovascular therapy irrespective of their mismatch status on imaging. In the DEFUSE 2 and CRISP studies, 200/294 (68%) patients had hypertension, 64/294 (22%) diabetes mellitus, 129/294 (44%) hyperlipidaemia, 96/294 (33%) atrial fibrillation and 46/294 (16%) had a prior stroke or transient ischaemic attack.^{8,9}

Ipsilateral to the occluded ICA or MCA, the absence of either the posterior communicating artery (PcomA), the first segment of the posterior cerebral artery (P1) or the first segment of the anterior cerebral artery (A1) were all rated as an incomplete COW. We considered that the anterior communicating artery (AcomA) cannot reliably be detected on 1.5T TOF-MRA based on our previous experience and published data.¹⁰ Therefore, the AcomA was not included into the analysis.

Reperfusion after endovascular therapy was defined as a more than 50% reduction in the volume of the perfusion-weighted MRI lesion ($T_{max} > 6s$) between baseline and an early follow-up scan. If the early follow-up scan was of insufficient quality, not obtained or obtained more than 18 hours after the endovascular procedure, then reperfusion was based on angiographic criteria: perfusion re-established to more than 50% of the tissue supplied by the occluded vessel at completion of the angiographic procedure



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(ie, thrombolysis in cerebral infarction score 2b or 3).¹¹ Scoring of leptomeningeal collaterals on baseline interventional angiograms was done using a previously defined system where 0 is no collateral flow and 4 is complete and rapid collateral flow to the ischaemic territory.¹² Patients were dichotomised whether they had poor (0–2) vs good (3–4) collaterals.

All patients or—if the patient was unable to—a relative provided informed written consent.

Statistical analyses

After data closure, all variables passed a plausibility check to detect outliers. No values have been excluded from the full data set. Associations between categorical variables were analysed by Welch's test (patients' age) or Fisher's exact test (all other variables). Binary logistic regression analyses were performed to assess the influence of an ipsilateral incomplete COW, baseline National Institutes of Health Stroke Scale (NIHSS), the patients' age, reperfusion status and leptomeningeal collateral status on functional outcome. Patients were dichotomised whether they had favourable (modified Rankin Scale, mRS, 0–2) or unfavourable (mRS 3–6) functional outcomes at day 90 following stroke. ORs estimated from logistic regression models were obtained with corresponding 95% CIs. Model performance was evaluated using the Hosmer-Lemeshow test for goodness-of-fit. Improvements in prediction were assessed using Nagelkerke's R^2 . Variables not related to functional outcome or with only small effects were removed from the final model with the exception of an incomplete ipsilateral COW. Variable selection was done with stepwise procedures, forward selection with possible re-exclusion and backward selection with possible reinclusion. Backward and forward elimination procedures resulted in the same variable selection for the final model. Receiver operating characteristics analysis was performed to find the optimal cut-off for baseline NIHSS, estimated by the highest Youden index to consider consequences of false positive and false negative predictions. Categorical data are presented as total numbers and percentages, continuous data as mean \pm SD. A $p < 0.05$ was considered as

statistically significant. Statistical analyses were performed using IBM SPSS statistics V.23 (IBM) and PASS V.15.

RESULTS

One hundred and eighty-two patients had a follow-up TOF-MRA of sufficient quality (92 men, 90 women; mean age 65.6 years; median NIHSS 16). An incomplete ipsilateral COW was found in 117 (64.3%) of them. Ipsilateral PcomA or P1 segments were absent in 115 (98.3%) of these 117 patients, and the A1 segment was absent in 8 (6.8%). Demographic and clinical characteristics of patients are given in table 1. Patients with an incomplete ipsilateral COW were older and had higher NIHSS scores compared with patients with a complete ipsilateral COW.

In univariate analysis (table 2), baseline NIHSS (cut-off >15), age, and reperfusion status were identified to be predictive of the patients' functional outcome. ICA occlusion or scoring of leptomeningeal collaterals on baseline interventional angiograms were not predictive. Leptomeningeal collateral scores were available in 114/182 (62.6%) patients. In patients who achieved reperfusion, a non-significant trend for a favourable functional outcome was observed with good versus poor collaterals.

For the final multivariate logistic regression model (table 2), Hosmer and Lemeshow's goodness of fit test indicated a good fitting model ($p = 0.615$). The logistic regression model was statistically significant ($\chi^2(4) = 59.30$, $p < 0.0001$). The model explained 37.1% (Nagelkerke's R^2) of the variance in functional outcome and correctly classified 73.1% of cases with a sensitivity of 70.5%, a specificity of 75.5%, a positive predictive value of 72.9%, and a negative predictive value of 73.2%. Of the four predictor variables, three of them reached statistical significance: baseline NIHSS (cut-off >15), the patients' age and reperfusion status (table 2). Baseline NIHSS (cut-off >15) was the most predictive variable for functional outcome (ratio 0.192:1). Increasing age was associated with a decreased likelihood of a favourable functional outcome. Patients with reperfusion were 7.6 times more likely to have a favourable functional outcome.

Table 1 Demographic, clinical and angiographic characteristics of patients

	Complete ipsilateral COW (n=65)	Incomplete ipsilateral COW (n=117)	P value
Mean (SD) age, years	59.6 (17.3)	69.0 (13.9)	<0.001
Female sex, no (%)	31 (47.7)	59 (50.4)	0.759
Baseline NIHSS >15, no (%)	27 (41.5)	68 (58.1)	0.044
ICA occlusion, no (%)	22 (33.8)	35 (29.9)	0.619
Good leptomeningeal collaterals, no (%)	20 (44.4)	27 (39.1)	0.697
Reperfusion, no. (%)	48 (73.8)	93 (79.5)	0.459
mRS 0–2 at 90 days, no (%)	34 (52.3)	54 (46.2)	0.443

COW, circle of Willis; ICA, internal carotid artery; MRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Table 2 Binary logistic regression analysis of predictors of a favourable clinical outcome at 90 days

	Nagelkerke R ²	OR (95% CI)	P value
Univariate binary logistic regression analysis			
baseline NIHSS >15	0.157	0.231 (0.124 to 0.429)	<0.001
Age	0.126	0.958 (0.939 to 0.979)	<0.001
Reperfusion status	0.109	4.530 (2.014 to 10.193)	<0.001
ICA occlusion	0.023	0.562 (0.297 to 1.064)	0.077
Good leptomeningeal collaterals	0.003	1.226 (0.578 to 2.597)	0.595
Incomplete ipsilateral COW	0.005	0.782 (0.426 to 1.435)	0.426
Multivariate binary logistic regression analysis			
Baseline NIHSS >15	0.371	0.192 (0.093 to 0.395)	<0.001
Age		0.951 (0.928 to 0.975)	<0.001
Reperfusion status		7.558 (2.910 to 19.626)	<0.001
Incomplete ipsilateral COW		1.415 (0.655 to 3.060)	0.377

COW, circle of Willis; ICA, internal carotid artery; NIHSS, National Institutes of Health Stroke Scale.

An incomplete ipsilateral COW was not predictive of the patients' functional outcome at 90 days in univariate and multivariate analyses (table 2). No association of an incomplete ipsilateral COW was found in sub-analyses when only patients who achieved reperfusion or who had an ICA or MCA occlusion were included. The effect size of an incomplete ipsilateral COW in the model is 1.280 (95% CI 0.697 to 2.349) based on n=182 patients in this study. A cohort of n=3020 patients would be required to yield an effect size of 2.785 to achieve a power of 90% for a statistically significant association of an incomplete ipsilateral COW with functional outcome. The significant predictors baseline NIHSS, the patients' age, and reperfusion status already yield effect sizes considerably higher than 2.785 in this study with n=182 patients. Therefore, as compared with these established predictors, an incomplete ipsilateral COW does not contribute to outcome prediction in ischaemic stroke patients undergoing endovascular therapy.

DISCUSSION

This study analysed COW anatomy in patients with anterior circulation stroke who underwent endovascular therapy. The patients' baseline NIHSS, age and reperfusion status determine functional outcome at 3 months as already established.¹⁻³ The analysis of COW variants does not add further prognostic information. Patients with an incomplete ipsilateral COW were significantly older which has been described previously in angiographic and pathological studies.^{13 14} A recent postmortem study revealed that these age-related variations are mainly due to aplastic communicating arteries.¹⁵ No association with neurodegenerative pathologies was found.¹⁵ A previous study reporting an association of an incomplete COW with worse functional outcome following non-cardiogenic ischaemic stroke did not correct for these age-dependent variations.⁷ A previously reported association of preserved

ipsilateral anterior and PcomA with favourable functional outcomes in n=38 patients with distal ICA occlusion could not be replicated in our study.⁶ Others have described more fatal outcomes in n=152 patients after thrombectomy in MCA occlusion when both ipsilateral anterior and PcomA were absent on CT angiography.⁵ In our study, when either ICA (n=57) or MCA (n=125) occlusions were analysed separately, the presence or absence of ipsilateral A1 or P1/PcomA segments did not provide prognostic information about functional outcome.

After unsuccessful thrombectomy, postinterventional TOF-MRA may not correctly reflect collateral flow across COW segments. However, in patients who achieved reperfusion, we also did not find an association of an incomplete ipsilateral COW with functional outcome (data not shown). The presence or absence of the AcomA was not included into our analysis because this vessel is not reliably detected on 1.5T TOF-MRA.¹⁰ A robust detection of the AcomA may be obtained at higher field strengths of 3 or 7 Tesla.¹⁶

In summary, this study revealed no added value of the analysis of COW variants for prognosis of stroke patients undergoing endovascular therapy as compared with established predictors. A statistically significant association of an incomplete ipsilateral COW with the mRS at 3 months may potentially be found in larger patient cohorts (n>3000).

Contributors TS-H: Design and concept of study; Data collection and analysis, drafting and revision of manuscript. KE: Data collection and analysis, drafting and revision of manuscript. SC: Data collection and analysis, drafting and revision of manuscript. EH: Data collection and analysis, drafting and revision of manuscript. CE: Drafting and revision for intellectual content. GWA: Drafting and revision for intellectual content. ML: Design and concept of study; Data collection and analysis, drafting and revision of manuscript

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests SC performs consulting work for iSchemaView; GWA is a consultant of iSchemaView and has an equity interest in iSchemaView.

Patient consent for publication Not required.

Ethics approval Stanford Research Compliance Office ID 10752 and ID 22227. Ethics approval was obtained from local institutional review boards.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- 1 Saver JL, Goyal M, van der Lugt A, *et al*. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA* 2016;316:1279–88.
- 2 Nogueira RG, Jadhav AP, Haussen DC, *et al*. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018;378:11–21.
- 3 Albers GW, Marks MP, Kemp S, *et al*. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018;378:708–18.
- 4 Kim BM, Baek J-H, Heo JH, *et al*. Collateral status affects the onset-to-reperfusion time window for good outcome. *J Neurol Neurosurg Psychiatry* 2018;89:903–9.
- 5 Karamyan A, Ramesmayer C, Killer-Oberpfalzer M, *et al*. Brain collateral circuits as outcome determinants following thrombectomy. *Eur J Neurol* 2019;26:203.
- 6 Zhao H, Wang B, Xu G, *et al*. Collateral grade of the Willis' circle predicts outcomes of acute intracranial internal carotid artery occlusion before thrombectomy. *Brain Behav* 2019;9:e01452.
- 7 Zhou H, Sun J, Ji X, *et al*. Correlation between the integrity of the circle of Willis and the severity of initial noncardiac cerebral infarction and clinical prognosis. *Medicine* 2016;95:e2892.
- 8 Lansberg MG, Straka M, Kemp S, *et al*. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. *Lancet Neurol* 2012;11:860–7.
- 9 Lansberg MG, Christensen S, Kemp S, *et al*. Computed tomographic perfusion to predict response to recanalization in ischemic stroke. *Ann Neurol* 2017;81:849–56.
- 10 Stock KW, Wetzel S, Kirsch E, *et al*. Anatomic evaluation of the circle of Willis: MR angiography versus intraarterial digital subtraction angiography. *AJNR Am J Neuroradiol* 1996;17:1495–9.
- 11 Lemmens R, Mlynash M, Straka M, *et al*. Comparison of the response to endovascular reperfusion in relation to site of arterial occlusion. *Neurology* 2013;81:614–8.
- 12 Higashida RT, Furlan AJ, Roberts H, *et al*. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke* 2003;34:e109–37.
- 13 Zaninovich OA, Ramey WL, Walter CM, *et al*. Completion of the circle of Willis varies by gender, age, and indication for computed tomography angiography. *World Neurosurg* 2017;106:953–63.
- 14 Eaton RG, Shah VS, Dornbos D, *et al*. Demographic age-related variation in circle of Willis completeness assessed by digital subtraction angiography. *Brain Circ* 2020;6:31–7.
- 15 Wijesinghe P, Steinbusch HWM, Shankar SK, *et al*. Circle of Willis abnormalities and their clinical importance in ageing brains: a cadaveric anatomical and pathological study. *J Chem Neuroanat* 2020;106:101772.
- 16 Heverhagen JT, Bourekas E, Sammet S, *et al*. Time-Of-Flight magnetic resonance angiography at 7 Tesla. *Invest Radiol* 2008;43:568–73.