Brain edema growth after thrombectomy is associated with comprehensive collateral blood flow

Tobias D Faizy 1, Laurens Winkelmeier 1, Michael Mlynash 2, Gabriel Broocks 1, Christian Heitkamp 1, Christian Thaler 1, Noel van Horn 1, Pierre Seners 3, Helge Kniep 1, Paul Stracke 4, Kamil Zelenak 5,6, Maarten G Lansberg 2, Gregory W Albers 7, Max Wintermark 8, Jens Fiehler 1, Jeremy J Heit 9

ABSTRACT

Background  We determined whether a comprehensive assessment of cerebral collateral blood flow is associated with ischemic lesion edema growth in patients successfully treated by thrombectomy.

Methods  This was a multicenter retrospective study of ischemic stroke patients who underwent thrombectomy treatment of large vessel occlusions. Collateral status was determined using the cerebral collateral cascade (CCC) model, which comprises three components: arterial collaterals (Tan Scale) and venous outflow profiles (Cortical Vein Opacification Score) on CT angiography, and tissue-level collaterals (hypoperfusion intensity ratio) on CT perfusion. Quantitative ischemic lesion net water uptake (NWU) was used to determine edema growth between admission and follow-up non-contrast head CT (ΔNWU). Three groups were defined: CCC+ (good pial collaterals, tissue-level collaterals, and venous outflow), CCC− (poor pial collaterals, tissue-level collaterals, and venous outflow), and CCCmixed (remainder of patients).

Primary outcome was ischemic lesion edema growth (ΔNWU). Multivariable regression models were used to assess the primary and secondary outcomes.

Results  538 patients were included. 157 patients had CCC+, 274 patients CCCmixed, and 107 patients CCC− profiles. Multivariable regression analysis showed that compared with patients with CCC+ profiles, CCC− (β 1.99, 95% CI 0.68 to 3.30, P=0.003) and CCC mixed (β 1.65, 95% CI 0.75 to 2.56, P<0.001) profiles were associated with greater ischemic lesion edema growth (ΔNWU) after successful thrombectomy treatment. ΔNWU (OR 0.74, 95% CI 0.68 to 0.8, P<0.001) and CCC+ (OR 13.39, 95% CI 4.88 to 36.76, P<0.001) were independently associated with functional independence.

Conclusion  A comprehensive assessment of cerebral collaterals using the CCC model is strongly associated with edema growth and functional independence in acute stroke patients successfully treated by endovascular thrombectomy.

INTRODUCTION

Endovascular thrombectomy (EVT) has become the standard of care for the treatment of patients with acute ischemic stroke and large vessel occlusion (AIS-LVO).1 Timely restoration of blood flow to ischemic brain tissue is crucial for a potential neurological recovery of these patients. However, poor clinical outcomes are still observed in a substantial number of patients treated by EVT despite successful vessel reperfusion.2 3 One explanation for that may be the occurrence of extensive brain edema formation, which is strongly related to collateral blood flow during the period of brain ischemia.4 5 Consequently, reliable imaging biomarkers that identify patients at risk of brain edema growth are needed.

Cerebral edema can be quantified directly by ischemic lesion net water uptake (NWU) using densitometry of hypoattenuated infarct areas
on non-contrast head CT. Extensive ischemic lesion NWU correlates with poor microvascular perfusion status and more severe ischemic damage to the brain tissue. However, successful vessel reperfusion during EVT was found to be associated with reduced formation of ischemic brain edema. A favorable collateral status is associated with better procedural and clinical outcomes of AIS-LVO patients after thrombectomy treatment. Notably, quantitative changes of NWU over time also seem to be linked to the cerebral collateral status. A favorable collateral status is usually associated with increased brain edema growth compared with patients with less favorable collateral profiles, and that both less edema growth and favorable collateral profiles are correlated with good clinical outcomes. Our findings may have important implications for cerebral edema biology and stroke pathophysiology in the setting of AIS-LVO.

METHODS

Study design
This was a retrospective multicenter cohort study of AIS-LVO patients treated by endovascular thrombectomy at two comprehensive stroke centers (University Medical Center Hamburg-Eppendorf, Germany, and Stanford University Hospital, USA) between May 2015 and December 2021.

Standard protocol approvals, registrations, and patient consents
The study protocol was approved by the institutional review boards of both study centers (ID 689–15), complied with the Health Insurance Portability and Accountability Act (HIPAA), and followed the guidelines of the Declaration of Helsinki. Patient informed consent was waived by our review boards for assessment on patient admission including non-contrast head CT. Patient informed consent was waived by our review boards for determination and interpretable CT perfusion imaging studies; (3) anterior circulation large vessel occlusion of the internal carotid artery or first (M1) or second (M2) segment of the middle cerebral artery; (4) successful vessel recanalization during EVT (defined as modified Thrombolysis In Cerebral Infarction Score (TICI) 2b-3); (5) availability of a non-contrast head CT 24–48 hours following EVT to determine post-treatment NWU.

Exclusion criteria were: (1) poor CT angiography image quality due to excessive patient motion or incomplete contrast opacification of target cerebral arteries and veins; (2) poor CT perfusion imaging quality due to excessive motion degradation or failed contrast bolus.

Imaging analysis
All perfusion imaging studies were automatically analyzed with RAPID (iSchemaView, Menlo Park, CA).

The three components of the CCC model were analyzed according to the approach described by Faizy et al.

Pial arterial collaterals were assessed using the Tan scale on CT angiography images by consensus reading of two neuroradiologists (TDF and JH with 11 and 16 years of experience, respectively). Good collaterals were defined as filling of ≥50%, and poor collaterals were defined as <50% filling of the middle cerebral artery territory. The hypoperfusion intensity ratio (HIR), defined as volume of brain tissue with a delay of Tmax >10 s divided by the volume of brain tissue with a Tmax delay of >6 s, was automatically derived from CT perfusion imaging to determine tissue-level collaterals. Favorable tissue-level collaterals were defined as HIR ≤0.4, whereas poor tissue-level collaterals were defined as HIR >0.4.

Venous outflow profiles were determined by two experienced neuroradiologists (TDF, JH) in the vein of Labbé, sphenoparietal sinus, and superficial middle cerebral vein using the Cortical Vein Opacification Score (COVES) on single-phase CT angiography. Discrepancies were settled by consensus. Favorable venous outflow was defined as a score of 3–6 and unfavorable venous outflow was regarded a score of 0–2.

Successful vessel recanalization after thrombectomy treatment was defined as modified TICI scores of 2b-3.

The Alberta Stroke Program Early CT Score (ASPECTS) was determined on pre-treatment head non-contrast CT images. Ischemic lesion NWU (%) was determined on both admission and follow-up non-contrast head CT images as described by Broocks et al. The density of ischemic tissue was measured in a region of interest (ROI) defining the demarcated hypoattenuated ischemic lesion on non-contrast head CTs. The corresponding normal density was determined as an ROI mirrored symmetrically to the non-ischemic hemisphere and adjusted anatomically to exclude sulci and cerebrospinal fluid. NWU was calculated per volume of infarct. Ischemic lesion edema growth (ΔNWU) was specified as the difference of NWU at follow-up and on admission.

Study group definitions
A favorable (CCC+) profile was defined as: Tan ≥50%, HIR ≤0.4, and COVES of 3–6. An unfavorable (CCC−) profile was regarded as: Tan <50%, HIR >0.4, and COVES of 0–2. CCCmixed profiles were assigned to patients who did not fulfill the criteria of the CCC+ or CCC− groups.

Outcome measures
Primary outcome was ischemic lesion edema growth (ΔNWU) between patient admission and follow-up after thrombectomy treatment. Secondary outcome was favorable functional outcome and follow-up clinical outcomes of AIS-LVO patients successfully treated by thrombectomy. We hypothesized that favorable collateral profiles on all three distinct levels of the collateral cascade are associated with reduced brain edema growth compared with patients with less favorable collateral profiles, and that both less edema growth and favorable collateral profiles are correlated with good clinical outcomes. Our findings may have important implications for cerebral edema biology and stroke pathophysiology in the setting of AIS-LVO.

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defined as functional independence (mRS score of 0–2) 90 days after thrombectomy treatment.

**Statistical analysis**

Continuous and ordinal variables were described by median (IQR) and categorical variables by N (%). Patient demographics, clinical variables, and neuroimaging data were compared between either two or three CCC groups using \( \chi^2 \) tests, and Mann Whitney U or Kruskal-Wallis tests, or trend statistics (Cochran-Armitage Trend Test or Jonckheere-Terpstra Test for Ordered Alternatives), respectively.

Clinical and imaging variables association with \( \Delta NWU \) and functional outcome was assessed using multivariable models: univariate general linear model, and binary logistic regression, respectively. The models were adjusted for imbalances between CCC groups: age, presentation National Institutes of Health Stroke Scale (NIHSS), serum glucose at enrollment, penumbra and estimated core volumes determined by CT perfusion, admission ASPECTS, and vessel occlusion localization. \( \Delta NWU \) was added as an independent variable for functional outcome model. \( \alpha \) was set at the 0.05 level, and all reported results are two-sided. Statistical analysis was done using IBM SPSS statistics, v. 28.0 and SAS 9.4.

**RESULTS**

A total number of 813 patients underwent thrombectomy triage, and 538 met inclusion criteria (online supplemental figure 1).

### Table 1 Patient characteristics and stroke presentation details

<table>
<thead>
<tr>
<th></th>
<th>CCC+ (n=157)</th>
<th>CCCmixed (n=274)</th>
<th>CCC− (n=107)</th>
<th>P value (difference between groups)</th>
<th>P value (trend test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>75 (64–83)</td>
<td>77 (68–83)</td>
<td>77 (68–83)</td>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>81 (52)</td>
<td>131 (48)</td>
<td>52 (49)</td>
<td>0.75</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>65 (41)</td>
<td>110 (40)</td>
<td>53 (50)</td>
<td>0.24</td>
<td>0.25</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>105 (67)</td>
<td>187 (68)</td>
<td>75 (70)</td>
<td>0.86</td>
<td>0.58</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>50 (34)</td>
<td>72 (29)</td>
<td>20 (22)</td>
<td>0.12</td>
<td>0.04</td>
</tr>
<tr>
<td>Blood glucose (mg/dL), median (IQR)</td>
<td>116 (99–141)</td>
<td>122 (105–153)</td>
<td>121 (106–157)</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>30 (19)</td>
<td>56 (20)</td>
<td>22 (21)</td>
<td>0.94</td>
<td>0.75</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg), median (IQR)</td>
<td>149 (132–163)</td>
<td>152 (133–170)</td>
<td>157 (132–180)</td>
<td>0.09</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>13 (8)</td>
<td>33 (12)</td>
<td>16 (15)</td>
<td></td>
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<tr>
<td>Never smoked, n (%)</td>
<td>110 (70)</td>
<td>191 (70)</td>
<td>76 (71)</td>
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</tr>
<tr>
<td>Prior smokers, n (%)</td>
<td>26 (17)</td>
<td>38 (14)</td>
<td>9 (8)</td>
<td></td>
<td></td>
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<tr>
<td>Unknown smoking status, n (%)</td>
<td>8 (5)</td>
<td>12 (4)</td>
<td>6 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke presentation details</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presentation NIHSS, median (IQR)</td>
<td>10 (6–14)</td>
<td>15 (10–19)</td>
<td>18 (15–21)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from symptom onset to alteplase administration (min), median (IQR)</td>
<td>109 (75–160)</td>
<td>90 (70–146)</td>
<td>110 (63–146)</td>
<td>0.43</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Treatment details</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous thrombolyis administration, n (%)</td>
<td>95 (61)</td>
<td>133 (49)</td>
<td>48 (45)</td>
<td>0.02</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The cerebral collateral cascade (CCC) comprises pial arterial collaterals defined by the Tan scale and venous outflow profiles determined by the Cortical Vein Opacification Score (COVES) on admission single-phase CT angiography images, and tissue-level collaterals determined by the hypoperfusion intensity ratio (HIR) derived from CT perfusion imaging. A favorable CCC (CCC+) profile was defined as: \( \text{Tan} \geq 50\% \), HIR \leq 0.4, COVES 3–6. An unfavorable CCC (CCC−) profile was regarded as: \( \text{Tan} <50\% \), HIR >0.4, COVES 0–2. CCCmixed profiles were assigned to patients who did not fulfill the criteria of the CCC+ or CCC− groups.

CCC, cerebral collateral cascade; COVES, Cortical Vein Opacification Score; HIR, hypoperfusion intensity ratio; NIHSS, National Institutes of Health Stroke Scale.
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ASPECTS, Alberta Stroke Program Early CT Score; CBF, cerebral blood flow; CCC, cerebral collateral cascade; COVES, Cortical Vein Opacification Score; HIR, hypoperfusion intensity ratio; MCA, middle cerebral artery; mRS, modified Rankin Scale; NCCT, non-contrast head CT; NWU, net water uptake; Tmax, tissue residue function.

(4–20) vs 27 mL (10–67) in CCCmixed and 57 mL (25–139) in CCC−. CCC+ patients were less likely to have a more proximal vessel occlusion compared with CCCmixed and CCC− patients (P<0.001). CCC+ patients had more favorable functional outcomes on the modified Rankin Scale (mRS) 90 days after successful EVT treatment (median IQR) mRS 1 (0–2) compared with CCCmixed (4 (1–5)) and CCC− (5 (4–6)) (P<0.001) patients (table 2).

Ischemic lesion edema assessment

CCC+ patients exhibited less median NWU on admission non-contrast head CT (median IQR) 2.42% (0.99–3.96%) compared with CCCmixed (6.54% (3.46–8.93%)) and CCC− (8.38% (6.72–11.18%)) (P<0.001). In addition, the median ischemic lesion NWU at follow-up was lower in CCC+ patients (median IQR) 3.88% (2.80–5.55%) compared with patients with CCCmixed (13.94% (7.75–18.58%) and CCC− (16.66% (11.20–22.96%)) (P<0.001) profiles. Finally, the ischemic lesion edema growth (∆NWU) measured at patient admission and after EVT treatment was found to be significantly lower in patients with a CCC+ profile (median IQR) 3.88% (2.80–5.55%) vs patients with CCCmixed (7.01% (4.01–9.99%)) and unfavorable CCC− profiles (8.51% (5.25–11.21%)) (P<0.001) (table 2, figure 1).

Assessment of the primary outcome (∆NWU)

For the primary outcome analysis, 481 patients were included in a general linear model, which was adjusted for baseline imbalances and predictors of ∆NWU. Fifty-seven patients were excluded due to unknown presentation NIHSS, core and penumbra volumes, or blood glucose values. Compared with patients with CCC+ profiles, CCC− (β 1.99, 95% CI 0.68 to 3.30, P=0.003) and CCCmixed (β 1.65, 95% CI 0.75 to 2.56, P<0.001) profiles were independently associated with higher

Figure 1 Extent of cerebral edema growth after thrombectomy stratified by the distinct cerebral collateral cascade (CCC). Boxplots display the extent of ischemic edema formation growth assessed in patients with distinct CCC profiles. Ischemic lesion net water uptake (NWU, %) was used to quantify edema growth on non-contrast head CT images between patient admission and follow-up (∆NWU). A favorable CCC (CCC+) profile was defined as: Tan ≥50%, hypoperfusion intensity ratio (HIR) ≤0.4, Cortical Vein Opacification Score (COVES) 3–6. An unfavorable CCC (CCC−) profile was regarded as: Tan <50%, HIR >0.4, COVES 0–2. CCCmixed profiles were assigned to patients who did not fulfill the criteria of the CCC+ or CCC− groups.
ischemic edema growth (ΔNWU) in AIS-LVO patients who were successfully treated by endovascular thrombectomy, after controlling for blood glucose, age, presentation NIHSS, baseline ASPECTS, vessel occlusion localization, penumbra, and ischemic core volume. However, when comparing patients with a CCCmixed and CCC− profile, we did not find any difference in association with ΔNWU for these respective patients (β = −0.34, 95% CI −1.40 to 0.72, P = 0.532) (table 3). Online supplemental figures 2 and 3 demonstrate patient examples for distinct CCC profiles.

Assessment of the secondary outcome (mRS 0–2)

For the secondary outcome analysis, 468 patients were included in a multivariable binary logistic regression model (online supplemental table 1). We included the same covariables as in the primary outcome model with the addition of ΔNWU as independent variable. We found that an increase in ΔNWU was independently associated with less odds of functional independence at 90 days (OR 0.74, 95% CI 0.68 to 0.8, P < 0.001). In addition, we found that patients with more favorable collateral blood flow to and through ischemic tissue, as reflected by the CCC model, had higher odds for achieving good functional outcomes after successful thrombectomy treatment. Compared with CCC− (OR 13.39, 95% CI 4.88 to 36.76, P < 0.001) and CCCmixed (OR 4.55, 95% CI 2.33 to 8.33, P < 0.001) profiles, we found that CCC+ profiles were independently associated with good functional outcomes 90 days after successful endovascular treatment. Interestingly, patients who exhibited CCCmixed profiles still had higher odds of achieving good functional outcomes when compared with patients with CCC− profiles (OR 3.00, 95% CI 1.26 to 7.14, P = 0.01).

DISCUSSION

In this study, we determined whether comprehensive assessment of cerebral collateral status is associated with ischemic lesion edema growth in AIS-LVO patients successfully treated with thrombectomy. Comprehensive cerebral collateral blood flow was assessed using the CCC framework and we evaluated the impact of different collateral profiles on quantitative ischemic lesion NWU changes between patient admission and follow-up (ΔNWU) and clinical outcomes. We found that CCC+ patients developed less ischemic brain edema growth after successful thrombectomy compared with CCC− and CCCmixed patients. More favorable CCC profiles and decreased ΔNWU were independently associated with functional independence 90 days after treatment. Our findings suggest that unhampered collateral blood flow from pial arteries through microvascular tissue-level vessels into draining cerebral cortical veins reflects robust cerebral microperfusion during brain ischemia, which is directly associated with less ischemic damage to the brain.9 27

Our findings have important implications for AIS-LVO patients eligible for EVT. A substantial proportion of AIS-LVO patients still exhibit poor clinical outcomes despite timely and successful vessel reperfusion.2 28–31 Besides other parameters, extensive ischemic brain edema formation is a known cause of poor clinical outcomes despite successful reperfusion.5 8 Our findings indicate that CCC− and CCCmixed patients are at an increased risk of brain edema progression, which may result in less favorable functional outcomes. Therefore, new treatments designed to reduce brain edema progression may be optimally tested in these patients.

NWU in ischemic tissue can be directly quantified as an imaging biomarker of ischaemic edema.12 While NWU assessment is currently still predominantly used in a research environment, this technique illustrates a well-understood and important pathophysiological phenomenon, namely brain edema development by compromised water hemostasis in ischemic brain tissue.5 15 Brain edema biology is complex and governed by multiple mechanisms associated with impaired cerebral tissue microperfusion.13 27 32 33 In addition, aggravated brain edema increases the risk for malignant infarction, which is associated with poor outcomes.12 Over time, extensive brain edema itself impairs microvascular blood flow and prior studies have demonstrated a strong link between hampered collateral blood flow and aggravated edema formation in AIS-LVO patients.10 11 14 While the extent of tissue edema can be directly quantified by means of quantitative NWU, several different ways exist to quantify collateral vessels on radiological imaging.18 One major drawback of many conventional collateral scores is that these approaches are only able to assess a minor proportion of the collateral circuit, thus they are unable to provide comprehensive assessment of collateral blood flow. However, critical patterns of cerebral hypoperfusion are likely reflected by the most distal arteries and their subsequent venous drainage, which are typically not determined by conventional collateral scores.24

The recent introduction of the CCC framework provides a comprehensive collateral vessel assessment in AIS-LVO patients.
A previous study found that a multiparametric evaluation of the collateral status during endovascular treatment triage was strongly associated with radiological and long-term clinical outcomes compared with a single-parameter approach alone, which is in line with our findings. However, the aforementioned study also included patients with unsuccessful vessel reperfusion status (TICI 0-2a) after thrombectomy and did not assess brain edema formation. The findings of this study suggest that hampered comprehensive collateral blood flow may result in aggravated brain edema despite successful vessel reperfusion, which likely promotes the exhibition of poor functional outcomes in this group of patients. Brain edema development represents one of the pathophysiological hallmarks of ischemic stroke pathophysiology and is inherently linked to clinical outcomes and neurological recovery. In addition, the individual collateral status has strong implications for maintaining microvascular blood flow during AIS-LVO, thus indirectly affecting cerebral water hemostasis. Consequently, our study provides an important link between edema development and collateral blood flow status. As brain edema formation and collateral blood flow are both linked to early clinical recovery and long-term functional outcomes after mechanical thrombectomy, a deeper knowledge and proper assessment of these parameters would provide important information to neurointerventionalists and physicians alike before and after treatment.

Interestingly, other studies found that the components of the CCC model were associated with early edema progression (defined as estimated edema growth from the time of symptom onset to patient admission) and the magnitude of edema formation after thrombectomy. While one study did not find a significant association between pial arterial collaterals and edema formation after treatment, others reported a strong correlation between arterial collaterals and edema development over time. Another study found a strong link between tissue-level collaterals and venous outflow profiles with respect to clinical outcomes in patients treated by thrombectomy. However, differences in the aforementioned findings may result from the use of different collateral scores for pial arterial collateral assessment, different patient characteristics and treatment protocols. In addition, it is important to note that large infarcts do not necessarily have higher ischemic lesion NWU measures and vice versa. In particular, also small infarcts can exhibit elevated NWU percentages indicating more severe tissue damage, which may lead to worse clinical outcomes despite smaller infarct volumes. However, this mechanism is still not well understood and requires additional research. Further prospective studies are needed to investigate the impact of distinct collateral profiles on patient outcomes and thrombectomy efficacy in more detail. Finally, to date, a comprehensive collateral assessment using the CCC model is time consuming. Thus, an automated approach to determine the vasculature of the CCC model would hold appeal.

Our study has limitations. The retrospective design may introduce bias and limit the generalizability of our findings. Although we only included patients with complete opacification of the sigmoid sinuses, the potential technical limitations for the use of single-phase CT angiography images to determine venous outflow have been discussed before. The use of other imaging scores to determine pial arterial collaterals and utilization of different processing software to determine perfusion imaging derived parameters may have led to different results.

In conclusion, in AIS-LVO patients, a comprehensive assessment of the collateral status using the CCC model is strongly associated with ischemic lesion NWU development determined between patient admission and 24–48 hours after successful thrombectomy treatment. This study highlights the importance of a more holistic approach towards collateral blood flow assessment in AIS-LVO patients, and elucidates the crucial role of unhampered cerebral collateral blood flow with regards to cerebral edema formation in ischemic brains.

**Author affiliations**

1. Department of Diagnostic and Interventional Neuroradiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
2. Department of Neurology, Stanford Stroke Center, Stanford University, Stanford, California, USA
3. Neurology, Fondation Rothschild, Paris, France
4. Section of Interventional Neuroradiology, University Hospital Munster, Munster, Germany
5. Clinic of Radiology, Comenius University in Bratislava Jessenius Faculty of Medicine in Martin, Martin, Slovakia
6. Clinic of Radiology, University Hospital Martin, Martin, Slovakia
7. Stanford Stroke Center, Stanford Medicine, Stanford, California, USA
8. Department of Neuroradiology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
9. Radiology, Neuroangiography and Neurointervention Division, Stanford University, Stanford, California, USA
10. Clinic of Diagnostic and Interventional Neuroradiology, Department of Neuroradiology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
11. Clinic of Neuroradiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

**Contributors**

The authors of this study contributed as follows: TDF: Study design and conceptualization. Acquisition of the data. Image processing. Image analysis. Data analysis. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. LW: Study design and conceptualization. Acquisition of the data. Image processing. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. CH: Study design and conceptualization. Acquisition of the data. Image processing. Image analysis. Data analysis. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. MV: Acquisition of the data. Data analysis. Statistical supervisor and statistical analysis. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. CT: Acquisition of the data. Image processing. Data analysis. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. NW: Acquisition of the data. Image processing. Data analysis. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. HB: Data analysis. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. GB: Data analysis. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. TC: Data analysis. Data interpretation. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. HR: Data analysis. Data interpretation. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. PP: Data analysis. Data interpretation. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. KZ: Acquisition of the data. Image processing. Data analysis. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. MG: Data analysis. Data interpretation. Supervision. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. GWA: Conceptualization of the study. Data interpretation. Supervision. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. JJH: Study design and conceptualization. Acquisition of the data. Image processing. Image analysis. Data analysis. Supervision. Drafting the manuscript and revising it critically. Approving a final version of the manuscript to be published. TDF is guarantor of the work.

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**Competing interests**

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Medtronic, Styrker, Phenox and grants from Route 92 outside the submitted work. JH reports consulting for Medtronic and MicroVention and Medical and Scientific Advisory Board membership for iSchemaView.

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ORCID iDs
Tobias D Faizy http://orcid.org/0000-0002-1631-2020
Laurens Winkelmeier http://orcid.org/0000-0002-9103-5983
Gabriel Broocks http://orcid.org/0000-0002-7575-9850
Christian Heitkamp http://orcid.org/0000-0002-8988-0918
Christian Thaler http://orcid.org/0000-0002-7102-9316
Noel van Horn http://orcid.org/0000-0001-5764-1982
Helge Knip http://orcid.org/0000-0001-5258-2370
Jens Fiehler http://orcid.org/0000-0001-8533-7478
Jeremy J Heit http://orcid.org/0000-0003-1055-8000

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