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Clinical benefit of thrombectomy in stroke patients with low ASPECTS is mediated by oedema reduction

Gabriel Broocks,[1] Uta Hanning,[1] Fabian Flottmann,[1] Michael Schönfeld,[1] Tobias Djamsched Faizy,[1] Peter Sporns,[2] Michael Baumgart,[1] Hannes Leischner,[1] Gerhard Schön,[3] Jens Minnerup,[4] Götz Thomalla,[5] Jens Fiehler[1] and Andre Kemmling[1,6,7]

The impact of endovascular vessel recanalization on patients with a low initial Alberta Stroke Program Early Computer Tomography Score (ASPECTS) is still uncertain. We hypothesized that vessel recanalization leads to an improvement in mortality and degree of disability by reducing brain oedema and malignant mass effect. In this multicentre observational study, patients with acute ischaemic stroke due to large vessel occlusion in the anterior circulation and an ASPECTS of ≤ 5 were analysed. Patients were assembled into two groups: successful vessel recanalization (thrombolysis in cerebral infarctions, TICI scale 2b/3) or persistent vessel occlusion (no endovascular procedure or TICI scale 0–2a). Observers were blinded to clinical data. Net water uptake within brain infarct, a quantitative biomarker based on CT densitometry, was used to quantify oedema in admission and follow-up CT and Δ-water uptake was calculated as difference between water uptake at both time points. Occurrence of malignant infarctions and secondary parenchymal haemorrhage was documented. Furthermore, modified Rankin scale score at 90 days was used for functional outcome. We included 117 patients admitted between March 2015 and August 2017 in three German stroke centres: 71 with persistent vessel occlusion and 46 with successful recanalization. The mean water uptake in the admission imaging was not different between both groups: 10.0% ($\pm$4.8) in patients with persistent vessel occlusion and 9.0% ($\pm$4.8) in patients with vessel recanalization ($P = 0.4$). After follow-up CT, the mean Δ-water uptake was 16.0% ($\pm$7.5) in patients with persistent vessel occlusion and 8.0% ($\pm$5.7) in patients with vessel recanalization ($P < 0.001$). Successful reperfusion was independently associated with a lowered Δ-water uptake of 8.0% (95% confidence interval, CI: −10.5 to −5.3%; $P < 0.001$) and lowered modifed Rankin scale score after 90 days of 1.5 (95% CI: −2.2 to −0.8; $P < 0.001$). The prevalence of malignant infarctions was 44.3% in patients with persistent vessel occlusion and 26.1% in patients with vessel recanalization. There was no significant difference for secondary haemorrhage in both groups ($P = 0.7$). In conclusion, successful recanalization in patients with low initial ASPECTS resulted in a significant reduction of oedema formation and was associated with a decreased prevalence of malignant infarctions and an improvement of clinical outcome.

1 Department of Diagnostic and Interventional Neuroradiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
2 Department of Clinical Radiology, University Hospital Münster, Münster, Germany
3 Institute of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
4 Department of Neurology, University Hospital Münster, Münster, Germany
5 Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
6 Department of Neuroradiology, University Hospital Schleswig-Holstein, Luebeck, Germany
7 Department of Neuroradiology, University Hospital Münster, Münster, Germany

Correspondence to: Gabriel Broocks, MD
Department of Diagnostic and Interventional Neuroradiology

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University Medical Center Hamburg-Eppendorf, Germany
Martinistrasse 52, 20246 Hamburg, Germany
E-mail: g.broocks@uke.de

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Abbreviations: ASPECTS = Alberta Stroke Program Early Computed Tomography Score; LVO = large vessel occlusion; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; NWU = net water uptake; TICI = thrombolysis in cerebral infarctions

Introduction

Endovascular thrombectomy is of benefit to patients with acute ischaemic stroke caused by an occlusion of the proximal anterior circulation (Goyal *et al.*, 2016). However, this benefit is based on common inclusion criteria of previous trials that apply to patients with an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of 6 or more; hence, the American Heart Association (AHA) recommends mechanical thrombectomy in acute stroke patients with an ASPECTS of >5 (Gupta *et al.*, 2012). Yet, few actual data exist that indicate the effect of vessel recanalization in patients with lower ASPECTS (Gilgen *et al.*, 2015; Goyal *et al.*, 2016; Yoo *et al.*, 2016; Mourand *et al.*, 2018; Roman *et al.*, 2018). Potential clinical benefit or harm of mechanical thrombectomy in patients with low inital ASPECTS therefore remain a subject of current debate (Goyal *et al.*, 2016; von Kummer, 2016; Yoo *et al.*, 2016; Mourand *et al.*, 2018; Roman *et al.*, 2018).

There is an increasing trend to select patients with a low ASPECTS for mechanical thrombectomy supported by the recently published subanalysis of the HERMES meta-analysis suggesting that patients with an ASPECTS of 3–5 may benefit from mechanical thrombectomy (Goyal *et al.*, 2018; Roman *et al.*, 2018). Although there are various individual reasons to treat these patients, for instance younger patient age, short time interval from symptom onset, or specific request by familiy members, the decision for treatment still depends on the interventional neuroradiologist on duty after weighing patient individual factors and personal experiences.

The primary therapeutic target of mechanical thrombectomy defined by the salvageable tissue at risk is minimized in patients with low ASPECTS. In contrast, the risk of developing malignant infarctions is maximized in patients with a large early ischaemic core, which can lead to severe complications by progressive ischaemic oedema within the first days after stroke onset with mortality up to 80% (Hacke *et al.*, 1996; Thomalla *et al.*, 2003, 2010; Hofmeijer *et al.*, 2009; Minnerup *et al.*, 2011; Neugebauer and Juttler, 2014; Ong *et al.*, 2017). The effect of endovascular vessel recanalization on patients with a large ischaemic core is ambiguous with regard to developing oedematous mass effects and the risk of malignant infarctions and haemorrhage (Sporns *et al.*, 2017; Broocks *et al.*, 2018*c*). Lately, the effect of revascularization in patients with a diffusion weighted imaging (DWI) derived ASPECTS of ≤ 5 was reported and an increased rate of patients with a favourable clinical outcome compared to patients without reperfusion was observed. Moreover, surgical decompression was performed less frequently (Mourand *et al.*, 2018).

According to a recently introduced CT-based method, the volume of net water uptake (NWU) in ischaemic tissue can be directly quantified as a pathophysiological imaging biomarker of ischaemic oedema (Dzialowski *et al.*, 2004; Minnerup *et al.*, 2016; Broocks *et al.*, 2018*b*). Elevated levels of early NWU in ischaemic core lesions assessed by this quantitative biomarker were associated with the development of malignant oedema (Broocks *et al.*, 2018*c*). Although there are prior *ex vivo* experimental studies discussing the relationship between vessel recanalization and quantitative oedema formation in rat stroke models, the effect of vessel recanalization on the progression of ischaemic oedema by quantitative measurement of lesion water uptake in patients with a large ischaemic core has not been investigated so far (Dzialowski *et al.*, 2004; Gerriets *et al.*, 2004; Broocks *et al.*, 2018*b*). We hypothesized that successful recanalization may improve mortality and degree of disability by reducing oedema formation and malignant mass effect. Our aim was therefore to investigate potential therapy effects of vessel recanalization in patients with low ASPECTS by a 2-fold hypothesis-driven approach: (i) evaluate effects on lesion pathophysiology by quantifying the progression of ischaemic oedema using NWU between admission and follow-up CT; and (ii) evaluate effects on patient outcome and risk of maligant infarction on clinical follow-up.

Materials and methods

Patient characteristics

In this study, anonymized registry data of three high-volume German stroke centres were assessed retrospectively. The study was conducted in accordance with the ethical guidelines of the local ethics committee and in accordance with the Declaration of Helsinki. The institutional review board waived informed consent (WF-04/13; 04.07.2013). All ischaemic stroke patients with an acute large vessel occlusion (LVO) in the anterior circulation admitted between March 2015 and August 2017 were screened based on the following *a priori* defined inclusion criteria: (i) acute ischaemic stroke with occlusion of the M1 segment of the middle cerebral artery or distal occlusion of the internal carotid artery; (ii) admission multimodal CT protocol with non-enhanced CT (NECT), CT angiography and perfusion CT performed within 12 h from symptom onset; (iii) an initial ASPECTS ≤ 5 in admission CT; (iv) follow-up CT after 24 h; (v) admission National Institutes of Health Stroke Scale (NIHSS) score > 3; and (vi) absence of intracranial haemorrhage and pre-existing thromboembolic or haemodynamic infarctions in admission NECT or pre-existing significant carotid stenosis.

Baseline clinical characteristics and demographic information were extracted from the medical records, including the modified Rankin Scale (mRS) after 90 days. Malignant middle cerebral artery infarctions were defined by imaging with clinical assessment: infarct lesions with significant space-occupying mass effect with $> 1/2$ affected middle cerebral artery territory (at follow-up CT imaging targeted 24–48 h after admission) with imaging signs of herniation (significant midline shift) and/or and clinical signs of herniation (worsening symptoms with decline of consciousness and anisocoria) requiring decompressive hemicraniectomy and/or leading to death due to direct implications of stroke (Hacke *et al.*, 1996; Thomalla *et al.*, 2010; Minnerup *et al.*, 2011; Souza *et al.*, 2012; Neugebauer and Juttler, 2014). The follow-up CT was screened for secondary parenchymal haemorrhage according to Fiorelli *et al.* (1999). Parenchymal haematoma type 1 was defined as homogenous hyperdensity occupying $< 30\%$ of the infarct zone; parenchymal haematoma type 2 was defined as homogenous hyperdensity occupying $> 30\%$ of the infarct zone with significant mass effect (Fiorelli *et al.*, 1999).

Patients were dichotomized by vessel status: (i) vessel recanalization after mechanical thrombectomy [thrombolysis in cerebral infarctions (TICI) 2b or 3]; (ii) persistent LVO in patients with failed recanalization after mechanical thrombectomy (TICI 0–2a) or patients who did not receive treatment. In patients who did not undergo an endovascular procedure, the persistence of LVO was confirmed via dense artery sign in follow-up CT and/or transcranial colour-coded duplex ultrasonography. There were several individual reasons for attempting endovascular thrombectomy in patients despite a low initial ASPECT score. Due to former focusing on time window guidelines, patients presenting early within a timeframe up to 4.5 h or 6 h from symptom onset (Hacke *et al.*, 2008; Nogueira *et al.*, 2018) were often treated although signs of large ischaemia might have already been recognizable. Further factors were perfusion mismatch despite large early ischaemic core with tissue at risk in eloquent regions beyond areas contributing to the low ASPECTS, younger patient age, or specific request for therapy by family members.

Image acquisition

All patients received a comprehensive stroke imaging protocol at admission with NECT, CT angiography, and dynamic time resolved perfusion CT performed in equal order on 128 or 256 dual slice scanners (Philips iCT 256, Siemens Somatom Definition Flash). NECT: 120 kV, 280–340 mA, 5.0 mm slice reconstruction, 1 mm increment; CT angiography: 100–120 kV, 260–300 mAs, 5.0-mm slice reconstruction, 1-mm increment, 80 ml highly iodinated contrast medium and 50 ml NaCl flush at 4 ml/s. Perfusion CT: 80 kV, 200–250 mA, 5-mm slice reconstruction (max. 10 mm), slice sampling rate 1.50 s (min. 1.33 s), scan time 45 s (max 60 s), biphasic injection with 30 ml (max 40 ml) of highly iodinated contrast medium with 350 mg iodine/ml (max 400 mg/ml) injected with at least 4 ml/s (max 6 ml/s) followed by 30 ml NaCl chaser bolus. All perfusion datasets were inspected for quality and excluded in case of severe motion artefacts.

Revascularization protocol

Intravenous lysis was administered to patients within 4.5 h after symptom onset. Laboratory and conventional clinical inclusion and exclusion criteria for intravenous thrombolysis were applied. Mechanical thrombectomy was performed via a femoral artery approach under general anaesthesia or conscious sedation. Mechanical thrombectomy procedures were performed standardized in each centre using either clot retrieval or direct aspiration. The choice of thrombectomy device was left to the operator.

Image analysis

The initial ASPECTS in admission CT was rated by two experienced neuroradiologists separately with subsequent consensus reading. The anonymized CT images were processed at an external core lab and were segmented manually using commercially available software (Analyze 11.0, Biomedical Imaging Resource, Mayo Clinic, Rochester, MN).

To determine effects of vessel recanalization on the progression of brain oedema we used a recently described imaging biomarker of ischaemic lesion water uptake, which is based on CT densitometry as described elsewhere (Minnerup *et al.*, 2016; Broocks *et al.*, 2018*a*, *b*) (Equation 1). Ischaemic water uptake at the time of admission and follow-up imaging was assessed in each patient. CT images were skull stripped and realigned if necessary. A visually evident circumscribable hypoattenuation was identified for quantifying water uptake within early infarct. We used CT perfusion images to confirm our judgement of NECT hypoattenuation when identifying oedematous infarct lesions (Minnerup *et al.*, 2016; Broocks *et al.*, 2018*b*). In brief, within the area of maximum ischaemic perfusion extent (mean transit time maps), we identified the cerebral blood volume core lesion as early infarct and used this visual cue to further identify and specify the ischaemic lesion in NECT for region of interest placement for density measurements. $D_{ischaemic}$ was measured in a region of interest defining the hypoattenuated ischaemic lesion in NECT. The corresponding normal density (D_{normal}) was determined in a region of interest mirrored symmetrically to the normal non-ischaemic hemisphere and adjusted anatomically to exclude sulci. The region of interest histogram was sampled between 20 and 80 Hounsfield units (HU). Based on $D_{ischaemic}$ and D_{normal} we calculated NWU per volume of infarct (Minnerup *et al.*, 2016; Broocks *et al.*, 2018*b*). In the follow-up CT, $D_{ischaemic}$ was determined in a region of interest representing the demarcated hypoattenuated ischaemic lesion and was mirrored symmetrically to obtain D_{normal} as described above.

$$Net\ water\ uptake = \left(1 - \frac{D_{ischaemic}}{D_{normal}}\right) \times 100 \qquad (1)$$

Subsequently, ΔNWU was calculated as difference of NWU in follow-up CT and NWU in admission CT. Moreover, total infarct volume was captured using manual segmentation of the hypoattenuated infarct lesion in the follow-up CT. We further measured midline shift in millimetres in admission CT and follow-up CT at the level of the septum pellucidum.

Statistical analysis

Continuous variables were presented as means, confidence intervals (CI) of means, standard deviations (SD) or medians and ranges. Kolmogorov-smirnov tests were used to determine if the datasets were well modelled by a normal distribution. To compare the groups (patients with vessel recanalization or persistent vessel occlusion) Student *t*-tests (normal distribution) with confidence intervals or standard deviation or Mann-Whitney U-tests (non-normal distribution) with interquartile range (IQR) were used to determine differences of acquired parameters (Table 1). The impact of vessel recanalization on the progression of ischaemic brain oedema (ΔNWU) and clinical outcome assessed by mRS was examined using multivariate lineare regression analysis. The dependent variable was ΔNWU (Fig. 3), adjusted for ASPECTS, age, sex and NIHSS. In Fig. 4, the dependent variable was mRS after 90 days, again adjusted for ASPECTS, ΔNWU, age, sex and NIHSS. Functional outcome was displayed using bar plots (Fig. 5). A statistcally significant difference was accepted at a P-value of < 0.05. Analyses were performed using MedCalc (version 11.5.1.0; Mariakerke, Belgium) and R (R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Vienna, Austria, 2017).

Data availability

The anonymized data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

One hundred and seventeen patients fulfilled inclusion criteria and were analysed. Patient characteristics are listed in Table 1. In 46 patients, successful vessel recanalization was achieved (TICI score of 2b and 3). Seventy-one patients suffered from persistent LVO. Of those, 20 patients received endovascular treatment with TICI score of 0–2a. The remaining 51 patients did not receive endovascular treatment and were only treated with intravenous lysis (24 patients) or did not receive thrombolytic treatment (27 patients). In these patients, persistent LVO was confirmed by persistent dense artery sign in follow-up CT and/or transcranial colour-coded duplex ultrasonography. Comparing both groups there were no significant differences in time from symptom onset to admission imaging or application of intravenous lysis. The median initial ASPECTS in patients with persistent LVO was 4 (IQR: 3–5). In patients with successfull recanalization, the median initial ASPECTS score was 5 (IQR: 4–5). Figure 1 shows follow-up infarcts of exemplary patients (two with and two without vessel recanalization) who were equally affected by early infarct with low ASPECTS.

The mean (SD) NWU of early infarct in the admission imaging was not different between both groups: 10.0% (4.8) in patients with persistent LVO and 9.0% (4.8) in patients with vessel recanalization ($P = 0.4$). In follow-up CT, the mean (SD) ΔNWU was 16.0% (7.5) in patients with persistent LVO and 8.0% (5.7) with vessel

Table 1 Patient characteristics

Baseline characteristics	Vessel recanalization	Persistent vessel occlusion	Group comparison *P*-value
Subjects, *n* (%)	46 (39.3)	71 (60.7)	
Age in years, median (IQR)	71 (58.8–81.0)	74 (69.3–86.5)	0.10
Female sex, *n* (%)	19 (40.5)	35 (49.2)	0.27
Admission NIHSS, mean (SD)	17.5 (5.0)	17.9 (5.0)	0.74
ASPECTS, median (IQR)	5 (4–5)	4 (3–5)	< 0.01
Systolic blood pressure on admission, mmHG, mean (SD)	159.7 (27.3)	160.9 (24.4)	0.88
Blood glucose on admission, mg/dl, median (IQR)	133 (110–156)	128 (110–145)	0.45
Time from onset to imaging, h, median (IQR)	4 (3.0–4.8)	3.9 (2.5–4.8)	0.70
Administered intravenous lysis, *n* (%)	28 (60.9)	36 (50.1)	0.29
Mechanical thrombectomy, *n* (%)	46 (100)	20 (28)	< 0.01
Follow-up infarct volume, ml, median (IQR)	82.0 (37.9–129.1)	122.2 (56.0–200.6)	0.01
Midline shift at admission imaging, mm, mean (SD)	0.5 (1.1)	0.5 (1.7)	0.84
Midline shift at follow-up imaging, mm, mean (SD)	2.7 (3.1)	3.6 (4.7)	< 0.01
Mortality, %	17.4	33.8	0.05
Malignant infarctions, %	26.1	44.3	0.048
Secondary parenchymal haemorrhage, *n* (%)	6 (13)	5 (7)	0.74
mRS, median (IQR)	3.5 (2–5)	5 (4–6)	< 0.001
0–2, *n* (%)	20 (42.8)	1 (1.6)	< 0.001
3–4, *n* (%)	11 (23.8)	21 (30.5)	0.83
5–6, *n* (%)	15 (33.4)	49 (68.9)	< 0.001

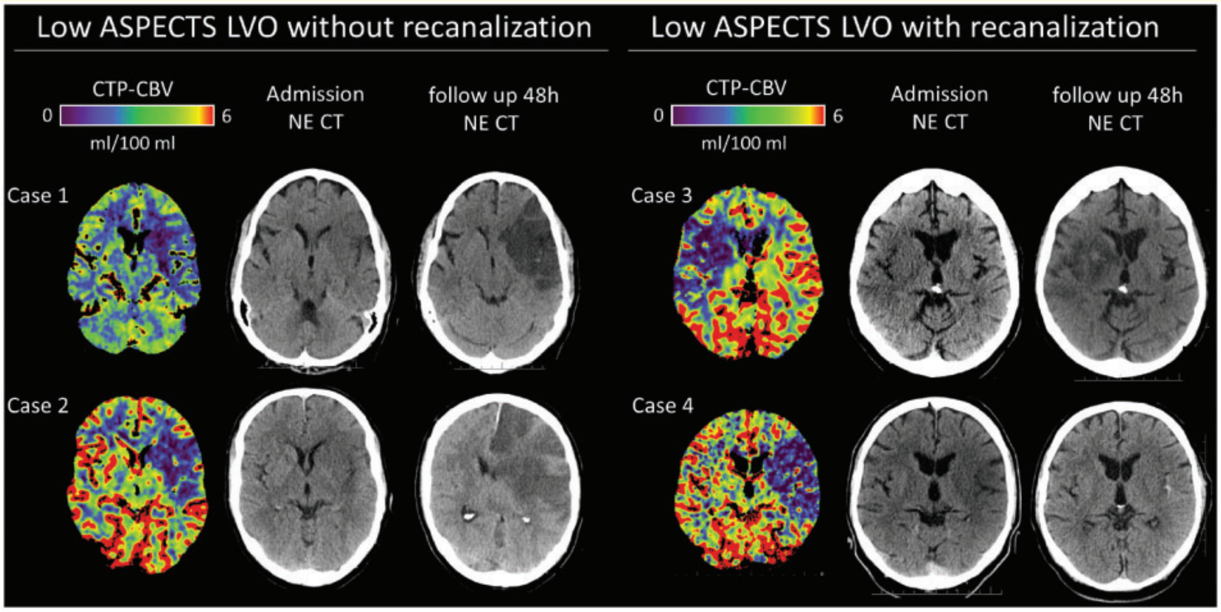

Figure 1 Example of low ASPECTS patients with and without vessel recanalization. Illustration of four patients with large vessel occlusion (LVO) and low ASPECTS. On the *left*, patients are displayed with admission CT and follow-up CT without vessel recanalization compared to the patients after successful vessel recanalization (*right*). CBV = cerebral blood volume; CTP = perfusion CT; NE CT = non-enhanced CT.

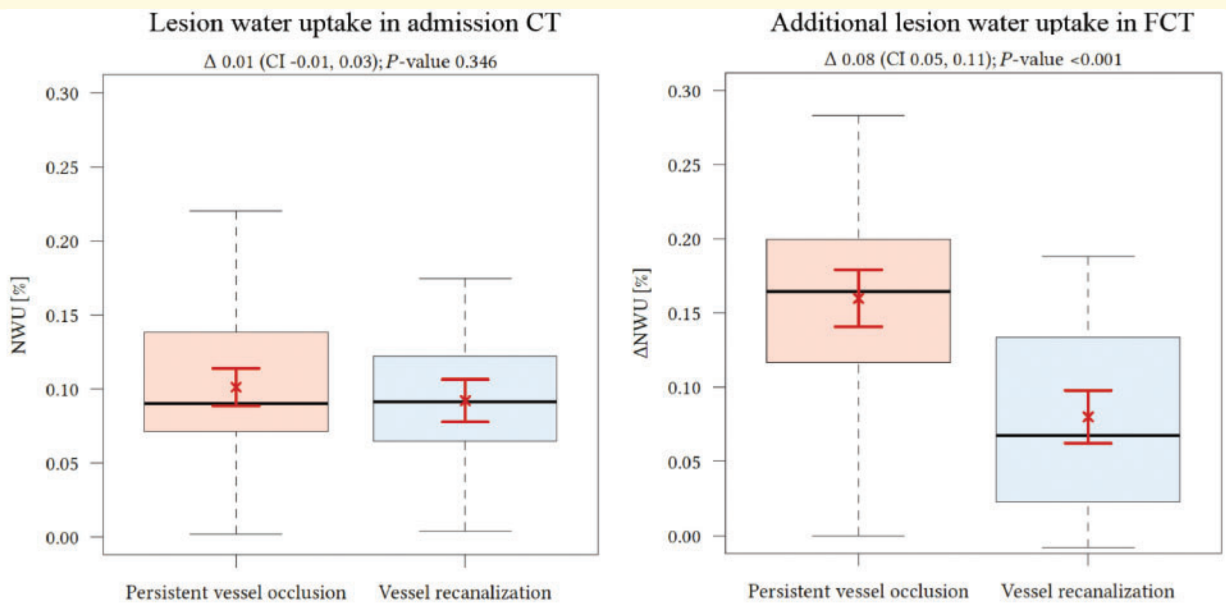

Figure 2 Measurements of NWU. NWU measured in the admission imaging (*left*) and difference of NWU in follow-up and admission imaging (ΔNWU) (*right*) compared in patients after successful recanalization versus patients with persistent LVO. FCT = follow-up CT.

recanalization ($P < 0.001$) (Fig. 2). In multivariate regression analysis, vessel recanalization was associated with a lowered ΔNWU of 8.0% (95% CI: −10.5 to −5.3%; $P < 0.001$) adjusted for ASPECTS, sex, age and NIHSS (Fig. 3 and Table 2).

The median mRS score was 5.0 (IQR 4–6) in patients with persistent LVO and 3.5 (IQR 2–5) in patients with vessel recanalization ($P < 0.001$) (Fig. 5). In multivariate regression analysis, vessel recanalization was associated with a lowered mRS score of 1.4 (95% CI: −2.0 to

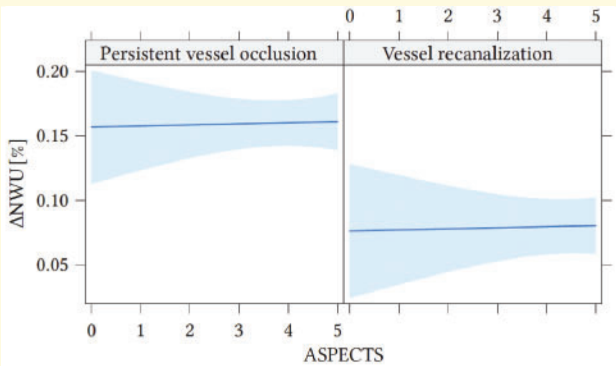

Figure 3 Multivariate regression analysis to display the impact of recanalization on the formation of ischaemic brain oedema. Effect plot for vessel recanalization on ΔNWU, adjusted for ASPECTS, NIHSS, sex and age. Vessel recanalization was associated with a lowered ΔNWU of 8.0% (95% CI: −10.5 to −5.3).

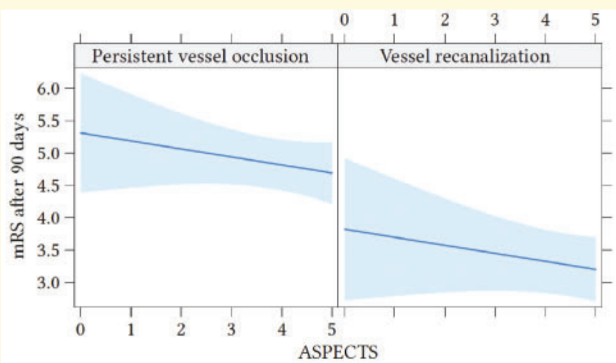

Figure 4 Multivariate regression analysis to display the impact of recanalization on functional outcome assessed by modified Rankin scale after 90 days. Regression analysis displays the impact of recanalization on clinical outcome defined by mRS after 90 days, adjusted for ASPECTS, NIHSS, sex and age.

−0.7; $P < 0.001$) adjusted for ASPECTS, ΔNWU, age, sex and NIHSS (Table 2). An increase of one point in a patient's NIHSS score was associated with an mRS increase of 0.09 (95%CI: 0.03–0.15; $P < 0.01$), adjusted for ASPECTS, recanalization status, age, sex and ΔNWU. The prevalance of very poor outcome (mRS 5/6) was 68.9% in patients with persistent LVO and 33.4% in patients who received vessel recanalization ($P < 0.001$). Overall, functional independence (mRS 0–2) occurred rarely among patients (19/117; 16.3%). In these patients, the median infarct volume was comparably low: 66.8 ml (median infarct volume of all patients: 120.6 ml). In patients with persistent LVO, only one patient obtained a mRS score of 2 after 90 days. This patient had an ASPECTS of 5 but a comparably low infarct volume of 55 ml. Comparing the relative occurrence of functional independence in both patient groups, 1.6% of patients with persistent LVO and 42.8% of patients with vessel recanalization achieved functional independence after 90 days (mRS 0–2; $P < 0.001$).

The mean (SD) midline shift measured in the follow-up CT was 3.6 mm (4.7) in patients with persistent LVO versus 2.7 mm (3.1) in the group with vessel recanalization ($P < 0.01$). The prevalence of malignant infarctions was 44.3% in patients with persistent LVO and 26.1% in patients with vessel recanalization. In successfully recanalized patients, six patients sustained parenchymal haematoma (13%), two of them with parenchymal haematoma type 2 (4.3%), which was not statistically different from the frequency of secondary parenchymal haematoma in patients without revascularization [$n = 5$ (7%), four of those patients with parenchymal haematoma type 2 (5.6%); $P = 0.74$].

In a subanalysis of patients with an ASPECTS of 4–5 only, vessel recanalization was independently associated with lowered water uptake (ΔNWU) of 8.5% (95% CI: 5.7–11.3%; $P < 0.001$). Correspondingly, vessel recanalization in these patients was associated with a lowered mRS score of 1.6 (95% CI: 0.8–2.4; $P < 0.001$) (Supplementary material).

Discussion

The aim of this study was to investigate the impact of vessel recanalization on oedema formation and clinical outcome in patients with ischaemic stroke who presented with an initial ASPECTS of ≤ 5 due to a large vessel occlusion in the anterior circulation. The main finding of this study was that measured ischaemic NWU on early follow-up was significantly higher in patients with persistent LVO compared to patients who received vessel recanalization, while at admission imaging, NWU was not different in both groups. The effect of vessel recanalization on lesion pathophysiology with lowered oedema progression was directly related to the observed effect on clinical endpoints. Vessel recanalization in patients with low initital ASPECTS lead to clinical benefit with respect to the occurrence of malignant infarctions and death. Moreover, vessel recanalization was associated with improved functional outcome after 90 days.

Our results encourage further prospective studies for endovascular treatment of low ASPECTS patients. *Post hoc* analysis of recent large prospective stroke trials recommended that patients with an ASPECTS < 6 should not be generally excluded from endovascular treatment as there is no subtantially increased risk of adverse events (Berkhemer *et al.*, 2015; von Kummer, 2016; Yoo *et al.*, 2016). Specifically, a recent subgroup analysis of the HERMES meta-analysis suggests that patients with an ASPECTS of 3–5 may benefit from mechanical thrombectomy (odds ratio 2.0; 95% CI: 1.16–2.45) assessed by mRS shift at 90 days (Roman *et al.*, 2018).

In the present study, functional independence occurred in 42.8% of patients with vessel recanalization and in

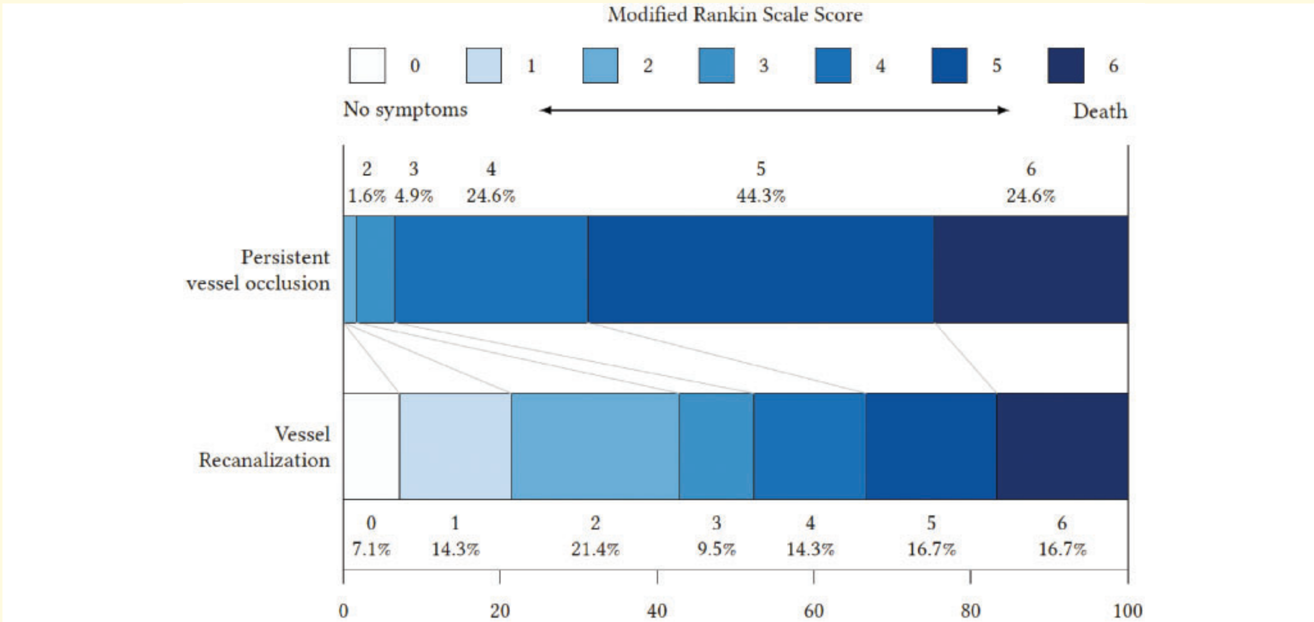

Figure 5 Modified Rankin scale scores at 90 days in the study cohort. Bar graph displays the distribution of mRS scores after 90 days in patients with persistent vessel occlusion versus recanalization. Vessel recanalization was associated with improved clincial outcome with a mean mRS decrease of 1.5 (95% CI: −2.2 to −0.8).

Table 2 Multivariate regression models

	Coefficient	2.5%	97.5%	*P*-value
Multivariate linear regression model with mRS as dependent variable				
ASPECTS	−0.02	−0.7	0.26	0.87
Recanalization status	−1.49	−2.16	−0.82	< 0.001
ΔNWU	0.90	−3.61	5.42	0.69
Age, per 10 years	0.17	−0.06	0.39	0.15
Sex, male	−0.21	−0.78	0.36	0.47
NIHSS	0.89	0.03	0.15	0.003
Multivariate linear regression model with ΔNWU as dependent variable				
ASPECTS	−0.006	−0.017	0.006	0.325
Recanalization status	−0.079	−0.105	−0.053	< 0.001
NIHSS	0.000	−0.003	0.003	0.945
Age, per 10 years	0.001	−0.010	0.011	0.876
Sex, male	0.031	0.005	0.056	0.018

1.6% of patients with a persistent LVO. In the intervention arm of the HERMES subanalysis, 23.3% of patients with low ASPECTS were assessed with an mRS of 0–2 after 90 days versus 13.3% in the control group (Goyal *et al.*, 2016). The less pronounced differential effect on clinical outcome between each treatment arm in the HERMES analysis compared to our cohort may be attributed to the actual frequency of vessel recanalization. The rate of recanalization (TICI 2b/3) in the MR CLEAN trial in the intervention arm was only 58.7%, whereas intravenous thrombolysis also contributed to recanalization within the control arm (up to 10% of all LVO are expected to recanalize with intravenous lysis) (Campbell *et al.*, 2018). In contrast, by study design we *a priori* dichotomized all patients by definite recanalization status (i.e. the rates of recanalization in each group were 100% versus 0%).

With respect to imaging endpoints, it is known that endovascular recanalization reduces final infarct volume, but there are no studies describing the impact of recanalization on the formation of ischaemic oedema in patients with large early infarcts (Berkhemer *et al.*, 2015; Yoo *et al.*, 2016; Coutinho *et al.*, 2017; Broocks *et al.*, 2018*b*). The results of our study are in accordance with a recently published study that investigated the effects of mechanical thrombectomy on ischaemic brain oedema and observed that succesful reperfusion reduced ischaemic oedema measured indirectly via midline shift (Kimberly *et al.*, 2018). In contrast to the referred study, we directly measured progression of brain oedema by a quantitative imaging biomarker of lesion water uptake that is based on CT densitometry (Minnerup *et al.*, 2016; Broocks *et al.*, 2018*b*).

Besides quantifying infarct by spatial extend (i.e. volume or ASPECTS), the quantitative imaging biomarker of oedema used in this study (i.e. NWU) introduces a second imaging dimension of characterizing ischaemic lesion pathophysiology. We investigated how vessel recanalization affects this second dimension, i.e. the progression of oedema attributed to lesion water uptake. Our results suggest that vessel recanalization directly affects the oedematous component of large early infarct lesions by reducing the volume of NWU on follow-up. Averting malignant mass effect may therefore represent the primary therapeutic target of mechanical thrombectomy in patients with low ASPECTS in contrast to volume of salvageable tissue at risk, which is the primary therapeutic target in patients with high ASPECTS. Future studies should investigate if large early infarct volumes (e.g. low ASPECTS) but low levels of NWU represent a favourable constellation to select patients for endovascular treatment to reduce further water uptake and prevent malignant oedema. Moreover, in these patients, assessing NWU may open new opportunities to specifically monitor therapeutic effects of potential agents targeting the formation of ischaemic brain oedema (Sheth *et al.*, 2016*a*, *b*).

Secondary parenchymal haemorrhage occurred rarely and only marginally more often in patients after endovasular thrombectomy and these results are similar to the findings of Mourand *et al.* (2018). The low number of patients suffering from secondary parenchymal haemorrhage suggests that benefit after treatment of patients with a large early infarct likely outweighs the risks, especially by avoiding the development of malignant infarctions with a very poor outcome.

Limitations of our study include the relatively small number of patients, due to strict inclusion and exclusion criteria. Moreover, overall a limited number of screened patients with a large early infarct received endovascular treatment. The reasons to perform thrombectomy in this patient cohort were heterogeneous and patient selection for endovascular treatment was not randomized, which might cause a potential selection bias. Because of focusing on time window guidelines, patients presenting in a hyperacute timeframe were treated in several cases even with a low initial ASPECTS. Other factors were for instance perfusion mismatch with tissue at risk in eloquent regions (e.g. primary motor cortex) beyond regions contributing to the low ASPECTS, younger patient age (in this study, recanalized patients were 3 years younger in median) or specific request for maximum therapy by family members. Other limitations may arise from secondary diseases with perturbed water homeostasis, such as nephrotic syndrome, which may affect dynamics of infarct oedema progression.

A representative cohort of typical stroke patients with large vessel occlusion was screened, primarily due to cardiac or arterio-arterial thromboembolism. We pooled patients with permanent LVO without treatment with patients who were treated by mechanical thrombectomy without successful recanalization (TICI 0–2a). This particular group of patients was too small for a specific analysis and require further research. Another limitation of this study is based on the different admission ASPECTS of both groups. Patients with persistent LVO had a slightly lower ASPECTS, which might have influenced the study results even though statistical analyses adjusted for ASPECTS. A subanalysis of patients with equal ASPECTS distribution in both groups (ASPECTS 4 and 5 only) confirmed the effect of vessel recanalization on oedema progression and clinical outcome.

Conclusion

In stroke patients with LVO and low initial ASPECTS of ≤ 5, vessel recanalization was associated with substantially reduced ischaemic brain water uptake on early follow-up. The observed effect of vessel recanalization on oedema progression was directly related to favourable effects on clinical endpoints with a decreased rate of malignant infarctions and improved mRS. The results encourage prospective studies to investigate robust potential benefits of mechanical thrombectomy in patients with low ASPECTS. Large early infarct volumes with low lesion NWU could serve as CT imaging marker to select patients who benefit from mechanical thrombectomy.

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Competing interests

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Supplementary material

Supplementary material is available at *Brain* online.

References

Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015; 372: 11–20.

Broocks G, Faizy T, Flottmann F, Schoen G, Langner S, Fiehler J, et al. Subacute infarct volume with edema correction in CT is equivalent to final infarct volume after ischemic stroke: improving the comparability of infarct imaging endpoints in clinical trials. Invest Radiol 2018a; 53: 472–6.

Broocks G, Flottmann F, Ernst M, Faizy TD, Minnerup J, Siemonsen S, et al. Computed tomography-based imaging of voxel-wise lesion water uptake in ischemic brain: relationship between density and direct volumetry. Invest Radiol 2018b; 53: 207–13.

Broocks G, Flottmann F, Scheibel A, Aigner A, Faizy T, Hanning U, et al. Quantitative lesion water uptake in acute stroke computed tomography is a predictor of malignant infarction. Stroke 2018c; 49: 1906–12.

Campbell BC, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Yan B, et al. Tenecteplase versus alteplase before endovascular thrombectomy (EXTEND-IA TNK): a multicenter, randomized, controlled study. Int J Stroke 2018; 13: 328–34.

Coutinho JM, Liebeskind DS, Slater LA, Nogueira RG, Clark W, Davalos A, et al. Combined intravenous thrombolysis and thrombectomy vs thrombectomy alone for acute ischemic stroke: a pooled analysis of the SWIFT and STAR studies. JAMA Neurol 2017; 74: 268–74.

Dzialowski I, Weber J, Doerfler A, Forsting M, von Kummer R. Brain tissue water uptake after middle cerebral artery occlusion assessed with CT. J Neuroimaging 2004; 14: 42–8.

Fiorelli M, Bastianello S, von Kummer R, del Zoppo GJ, Larrue V, Lesaffre E, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. Stroke 1999; 30: 2280–4.

Gerriets T, Stolz E, Walberer M, Muller C, Kluge A, Bachmann A, et al. Noninvasive quantification of brain edema and the space-occupying effect in rat stroke models using magnetic resonance imaging. Stroke 2004; 35: 566–71.

Gilgen MD, Klimek D, Liesirova KT, Meisterernst J, Klinger-Gratz PP, Schroth G, et al. Younger stroke patients with large pretreatment diffusion-weighted imaging lesions may benefit from endovascular treatment. Stroke 2015; 46: 2510–6.

Goyal M, Aquilla T, Froehler MT, Jovin T. How do you manage cases with low ASPECTS? Endovasc Today 2018; 17: 74–7.

Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016; 387: 1723–31.

Gupta AC, Schaefer PW, Chaudhry ZA, Leslie-Mazwi TM, Chandra RV, Gonzalez RG, et al. Interobserver reliability of baseline noncontrast CT Alberta Stroke Program Early CT Score for intra-arterial stroke treatment selection. AJNR Am J Neuroradiol 2012; 33: 1046–9.

Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008; 359: 1317–29.

Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. Arch Neurol 1996; 53: 309–15.

Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB, et al. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. Lancet Neurol 2009; 8: 326–33.

Kimberly WT, Dutra BG, Boers AMM, Alves H, Berkhemer OA, van den Berg L, et al. Association of reperfusion with brain edema in patients with acute ischemic stroke: a secondary analysis of the MR CLEAN trial. JAMA Neurol 2018; 75: 453–61.

Minnerup J, Broocks G, Kalkoffen J, Langner S, Knauth M, Psychogios MN, et al. Computed tomography-based quantification of lesion water uptake identifies patients within 4.5 hours of stroke onset: a multicenter observational study. Ann Neurol 2016; 80: 924–34.

Minnerup J, Wersching H, Ringelstein EB, Heindel W, Niederstadt T, Schilling M, et al. Prediction of malignant middle cerebral artery infarction using computed tomography-based intracranial volume reserve measurements. Stroke 2011; 42: 3403–9.

Mourand I, Abergel E, Mantilla D, Ayrignac X, Sacagiu T, Eker OF, et al. Favorable revascularization therapy in patients with ASPECTS </= 5 on DWI in anterior circulation stroke. J Neurointerv Surg 2018; 10: 5–9.

Neugebauer H, Juttler E. Hemicraniectomy for malignant middle cerebral artery infarction: current status and future directions. Int J Stroke 2014; 9: 460–7.

Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med 2018; 378: 11–21.

Ong CJ, Gluckstein J, Laurido-Soto O, Yan Y, Dhar R, Lee JM. Enhanced detection of edema in malignant anterior circulation stroke (EDEMA) score: a risk prediction tool. Stroke 2017; 48: 1969–72.

Roman LS, Menon BK, Blasco J, Hernandez-Perez M, Davalos A, Majoie C, et al. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. Lancet Neurol 2018; 17: 895–904.

Sheth KN, Elm JJ, Beslow LA, Sze GK, Kimberly WT. Glyburide advantage in malignant edema and stroke (GAMES-RP) trial: rationale and design. Neurocrit Care 2016a; 24: 132–9.

Sheth KN, Elm JJ, Molyneaux BJ, Hinson H, Beslow LA, Sze GK, et al. Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction (GAMES-RP): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2016b; 15: 1160–9.

Souza LC, Yoo AJ, Chaudhry ZA, Payabvash S, Kemmling A, Schaefer PW, et al. Malignant CTA collateral profile is highly specific for large admission DWI infarct core and poor outcome in acute stroke. AJNR Am J Neuroradiol 2012; 33: 1331–6.

Sporns PB, Minnerup J, Warneke N, Dziewas R, Hanning U, Berkemeyer S, et al. Impact of the implementation of thrombectomy with stent retrievers on the frequency of hemicraniectomy in patients with acute ischemic stroke. Clin Neuroradiol 2017; 27: 193–7.

Thomalla G, Hartmann F, Juettler E, Singer OC, Lehnhardt FG, Kohrmann M, et al. Prediction of malignant middle cerebral artery infarction by magnetic resonance imaging within 6 hours of symptom onset: a prospective multicenter observational study. Ann Neurol 2010; 68: 435–45.

Thomalla GJ, Kucinski T, Schoder V, Fiehler J, Knab R, Zeumer H, et al. Prediction of malignant middle cerebral artery infarction by early perfusion- and diffusion-weighted magnetic resonance imaging. Stroke 2003; 34: 1892–9.

von Kummer R. Early CT Score to establish stroke treatment. Lancet Neurol 2016; 15: 651–3.

Yoo AJ, Berkhemer OA, Fransen PSS, van den Berg LA, Beumer D, Lingsma HF, et al. Effect of baseline Alberta Stroke Program Early CT Score on safety and efficacy of intra-arterial treatment: a subgroup analysis of a randomised phase 3 trial (MR CLEAN). Lancet Neurol 2016; 15: 685–94.