UNIVERSITÄTSKLINIKUM HAMBURG-EPPENDORF

Klinik und Poliklinik für Neuroradiologische Diagnostik und Intervention

Direktor Prof. Dr. med. J. Fiehler

Mediation of the Relationship between Functional Outcome and the Degree of Recanalization by Penumbra Salvage Volume in Acute Ischemic Stroke

Dissertation

zur Erlangung des Grades eines Doktors der Medizin
an der Medizinischen Fakultät der Universität Hamburg

vorgelegt von:

Hashim Jafarov

Hamburg 2021

Angenommen von der Medizinischen Fakultät am: 10.11.2021

Veröffentlicht mit Genehmigung der Medizinischen Fakultät der Universität Hamburg.

Prüfungsausschuss, der/die Vorsitzende: PD Dr. Bastian Cheng

Prüfungsausschuss, 2. Gutachter/in: PD Dr. Uta Hanning

TABLE OF CONTENTS

1. Paper 4

2. Description of the paper 13

3. Summary/Zusammenfassung.. 21

4. References 23

5. Explanation of own contribution.. 27

6. Acknowledgements... 28

7. Lebenslauf…………………………………………………………………… 29

8. Affidavit.. 31

1. Paper

Journal of Neurology
https://doi.org/10.1007/s00415-021-10410-2

ORIGINAL COMMUNICATION

Relationship between the degree of recanalization and functional outcome in acute ischemic stroke is mediated by penumbra salvage volume

Gabriel Broocks[1] · Hashim Jafarov[1] · Rosalie McDonough[1] · Friederike Austein[1] · Lukas Meyer[1] · Matthias Bechstein[1] · Noel van Horn[1] · Marie Teresa Nawka[1] · Gerhard Schön[2] · Jens Fiehler[1] · Helge Kniep[1] · Uta Hanning[1]

Received: 19 November 2020 / Revised: 13 January 2021 / Accepted: 13 January 2021

Abstract

Background The presence of metabolically viable brain tissue that may be salvageable with rapid cerebral blood flow restoration is the fundament rationale for reperfusion therapy in patients with large vessel occlusion stroke. The effect of endovascular treatment (EVT) on functional outcome largely depends on the degree of recanalization. However, the relationship of recanalization degree and penumbra salvage has not yet been investigated. We hypothesized that penumbra salvage volume mediates the effect of thrombectomy on functional outcome.

Methods 99 acute anterior circulation stroke patients who received multimodal CT and underwent thrombectomy with resulting partial to complete reperfusion (modified thrombolysis in cerebral infarction scale (mTICI) ≥ 2a) were retrospectively analyzed. Penumbra volume was quantified on CT perfusion and penumbra salvage volume (PSV) was calculated as difference of penumbra and net infarct growth from admission to follow-up imaging.

Results In patients with complete reperfusion (mTICI ≥ 2c), the median PSV was significantly higher than the median PSV in patients with partial or incomplete (mTICI 2a–2b) reperfusion (median 224 mL, IQR: 168–303 versus 158 mL, IQR: 129–225; $p < 0.01$). A higher degree of recanalization was associated with increased PSV (+63 mL per grade, 95% CI: 17–110; $p < 0.01$). Higher PSV was also associated with improved functional outcome (OR/mRS shift: 0.89; 95% CI: 0.85–0.95, $p < 0.0001$).

Conclusions PSV may be an important mediator between functional outcome and recanalization degree in EVT patients and could serve as a more accurate instrument to compare treatment effects than infarct volumes.

Keywords Stroke · Imaging · Computed Tomography · Thrombolysis · Thrombectomy · Ischemia · Infarction

Introduction

Mechanical thrombectomy (MT) in acute ischemic stroke substantially improves functional outcome in patients with large vessel occlusion [18, 34]. Yet, the time-sensitive selection of patients who will most likely benefit from MT is a critical factor in clinical practice. Neuroimaging may be used to guide endovascular treatment, and may serve as a prognostic biomarker [1, 2, 35]. Past MT landmark trials including patients 0–6 h from symptom onset applied different brain imaging criteria for treatment selection, for instance using computed tomography (CT) perfusion to estimate ischemic core volume (i.e. volume that is thought to represent irreversible tissue injury), compared to the total volume of hypoperfused brain tissue [1, 22, 28].

Gabriel Broocks and Hashim Jafarov contributed equally to this work.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-021-10410-2.

✉ Gabriel Broocks
g.broocks@uke.de

1 Department of Diagnostic and Interventional Neuroradiology, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany

2 Institute of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Published online: 24 January 2021

Accordingly, the presence of ischemic penumbra (metabolically viable brain tissue that may be salvageable with rapid cerebral blood flow restoration) is the fundamental rationale for reperfusion therapy [11]. However, the effect of endovascular treatment on functional outcome highly depends on the degree of recanalization as exemplified in previous studies [15, 20, 21]. Recently, a meta-analysis found an incremental association between the degree of recanalization and clinical outcome [21]. Currently, the American Heart Association (AHA) guidelines recommend a score of ≥ 2b on the modified Thrombolysis in Cerebral Infarction (mTICI) scale as the angiographic goal of MT [29, 30]. However, a wide range of outcome is still evident even in cases of successful reperfusion, indicating that outcome is completely mediated by further baseline and procedural covariates [9, 21].

Currently, it remains uncertain how the volume of penumbra salvage (PSV) mediates the effect of thrombectomy on functional outcome. Moreover, the relationship of penumbra salvage and the degree of recanalization has not yet been investigated.

We hypothesized twofold: First, a higher degree of recanalization is incrementally associated with higher PSV. Second, we hypothesized that PSV is directly linked to functional outcome.

Materials and methods

Patients

For this retrospective study, we consecutively analyzed all ischemic stroke patients with acute large vessel occlusion of the middle cerebral artery admitted between June 2015 and October 2019 at our university hospital, which is a high-volume tertiary stroke center (> 300 stroke thrombectomy procedures per year). Only anonymized data were analyzed after ethical review board approval, and the local ethics committee (Ethikkommission der Ärztekammer Hamburg) waived informed consent after review. The data that support the findings of this study are available from the corresponding author upon reasonable request. The study was conducted in accordance with the ethical guidelines ("Leitlinien der Ärztekammer Hamburg") of the local ethics committee and in accordance with the Declaration of Helsinki.

All ischemic stroke patients admitted in the aforementioned time period were screened based on the following a priori defined inclusion criteria: (1) acute anterior circulation stroke in the territory of the middle cerebral artery (MCA) and MCA occlusion; (2) multimodal CT imaging protocol at admission including CT Angiography (CTA) and CT Perfusion (CTP); (3) known time window from symptom onset to admission imaging; (4) follow-up CT (FCT) 24 h after admission (max. range 23–25 h after onset); (5) admission National Institutes of Health Stroke Scale (NIHSS) score above 3; (6) documented functional outcome after 3 months based on modified Ranking Scale (mRS) score; (7) Absence of intracranial hemorrhage with significant mass effect (parenchymal hemorrhage (PH) type 2) according to Fiorelli et al. [14] and preexisting thromboembolic or hemodynamic infarctions in admission non-enhanced CT (NECT) or preexisting significant carotid stenosis; (8) Absence of significant motion artifacts.

Only patients fulfilling all criteria were included in this study. Baseline patient characteristics were retrieved from the medical records, including the modified Rankin Scale (mRS) score after 90 days.

Recanalization rates were classified as complete, incomplete and partial recanalization by the responsible neuroradiologists according to the mTICI score; reperfusion grade 2a indicates antegrade reperfusion of less than half of the occluded target artery previously ischemic territory; grade 2b, antegrade reperfusion of more than half of the previously occluded target artery ischemic territory; grade 2c, near-complete perfusion except for slow flow in a few distal cortical vessels or presence of small distal cortical emboli and grade 3, complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches.

Complete recanalization was defined as mTICI 2c/3, based on recent studies recommending this recanalization degree as primary aim of MT [12]. Patients with complete recanalization were compared to patients with successful but incomplete (mTICI 2b), and partial recanalization (mTICI 2a). For dichotomized analysis, patients with complete recanalization were compared to patients with mTICI 2a–2b.

A binary clinical outcome was defined based on modified Rankin Scale (mRS) after 90 days with 0–2 as functional independence and mRS ≥ 3 as poor outcome.

Image acquisitions

All patients received multimodal stroke imaging at admission with NECT, CTA, and CTP performed in equal order on 256 dual slice scanners (Philips iCT 256). NECT: 120 kV, 280–340 mA, 5.0 mm slice reconstruction, 1 mm increment; CTA: 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; CTP: 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 6 ml/s, followed by a 30 ml sodium chloride chaser bolus.

CT-perfusion analysis

Infarct core and penumbra have been assessed using CT-perfusion (CTP) with whole brain coverage. Penumbra has been determined using relative mean transit time (MTT) with a threshold of 145% and infarct core has been defined using absolute cerebral blood volume (CBV) with a threshold at 2.0 ml × 100 g^{-1}, as described by Wintermark et al. [36]. Based on the CTP-derived volumes for ischemic core and hypoperfusion volumes, we calculated penumbra volumes as their difference (Eq. 1). Secondly, we determined net infarct growth from admission CT to FCT based on the difference of the total infarct volume in FCT and ischemic core in admission CT (Eq. 2). Finally, we subtracted the net infarct growth volume from penumbra volume to determine penumbra salvage volume (PSV) (Eq. 3). Figure 1 illustrates a case, and how PSV was determined.

$$Penumbravolume = V(hypoperfusion) - V(core) \tag{1}$$

$$Netinfarctgrowth = V(followupinfarct) - V(core) \tag{2}$$

$$PSV = V(penumbra) - V(netinfarctgrowth) \tag{3}$$

Anonymized data was processed at an imaging core lab. Image analysis including volumetric analysis was performed using commercially available software (Analyze 11.0, Biomedical Imaging Resource, Mayo Clinic, Rochester, MN). All analyses were conducted by an experienced neuroradiologist (> 10 years of experience). Subsequently, all cases were screened in a consensus reading with a second experienced neuroradiologist.

Statistical analysis

Univariable distribution of metric variables is described by median and interquartile range (IQR). Absolute and relative frequencies are given for categorical data. To compare two independent samples regarding a metric or categorical outcome we used Mann–Whitney *U* test or $\chi 2$ test, respectively (Table 1). The impact of recanalization degree on PSV was illustrated in boxplots (Fig. 2).

Univariable and multivariable linear regression analyses were performed with PSV as dependent variable, and age, ASPECTS, core lesion volume, penumbra volume, application of intravenous alteplase, degree of recanalization (partial, incomplete, complete), NIHSS, and time from onset to recanalization as independent parameters. For multivariable analysis, backward selection was used integrating all above-mentioned variables that showed a significant association to PSV in univariable analysis (Table 2). The impact of recanalization degree on PSV according to the baseline penumbra volume is shown in Fig. 3.

Secondly, uni- and multivariable ordinal regression analyses were performed with modified Ranking Scale score at day 90 (mRS) as dependent variable using the same aforementioned independent variables. The ordinal form of the day 90 mRS was chosen due to its better relation to long-term outcomes in patients following ischemic stroke than dichotomized mRS [16] (Table 2). Figure 4 shows effect

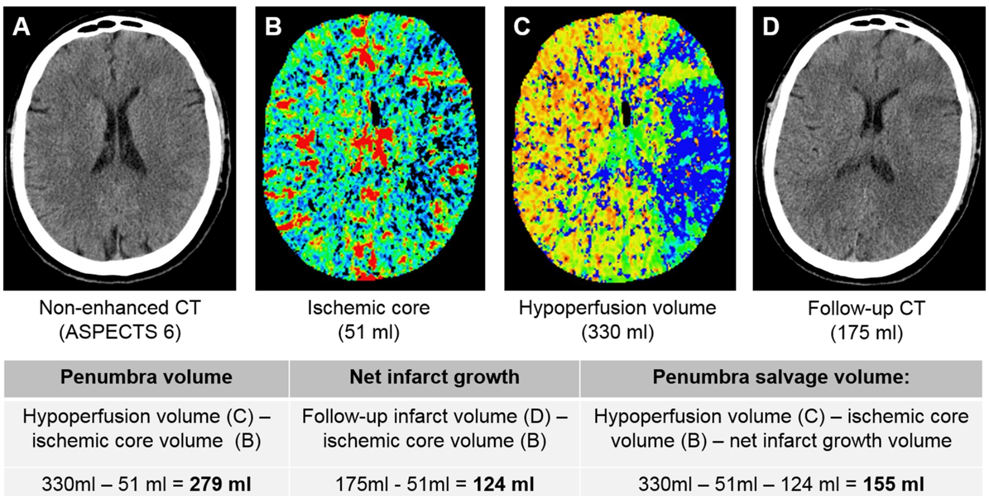

Fig. 1 Quantification of penumbra salvage volume. Illustration of the quantification of penumbra salvage volume (PSV). Baseline non-enhanced CT is displayed on the left hand side (**a**), and perfusion imaging besides (**b** for ischemic core, **c** for hypoperfusion volume). Follow-up CT is displayed on the right hand side, where follow-up infarct volume was calculated

Table 1 Patient characteristics

Patient characteristics	Functional independence (mRS 0–2)	Poor outcome (mRS 3–6)	*p* value
Subjects, *n* (%)	39 (39)	60 (61)	
Baseline parameter			
Age in years, median (IQR)	68 (59–78)	77 (69–82)	< 0.01
Female sex, *n* (%)	18 (47)	34 (57)	0.34
Admission NIHSS, median (IQR)	13 (9–17)	17 (15–20)	< 0.001
ASPECTS, median (IQR)	8 (7–9)	8 (6–9)	0.48
Imaging lesion volumes			
Ischemic core volume (mL), median (IQR)	9 (0–33)	19 (5–55)	0.05
Penumbra volume (mL), median (IQR)	211 (188–268)	214 (165–265)	0.71
Follow-up infarct volume (mL), median (IQR)	12 (3–26)	49 (7–120)	< 0.01
Treatment and outcomes			
Intravenous alteplase, *n* (%)	30 (78)	33 (55)	0.02
Time to recanalization in min, median (IQR)	264 (216–382)	308 (255–404)	0.15
Complete recanalization (TICI ≥ 2c), *n* (%)	28 (71)	31 (52)	0.04
Modified Rankin Scale, median (IQR)	1 (0–1)	5 (4–6)	< 0.001
Parenchymal hemorrhage type 1, *n* (%)	2 (4)	3 (5)	0.67
Penumbra salvage volume, median (IQR)	200 (157–253)	190 (121–224)	0.23

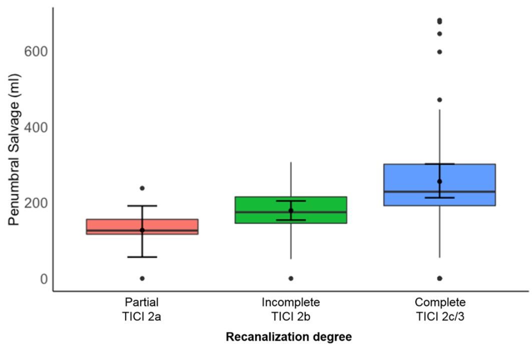

Fig. 2 Relationship of recanalization degree and penumbra salvage volume. Illustration of the relationship of recanalization degree, and penumbra salvage volume (y-axis), separately for patients with partial, incomplete, or complete recanalization

plots for ordinal regression analysis with probability for mRS shift (y-axis) depending on baseline ischemic core volume (x-axis) separately for different levels of PSV. Further effect plots are displayed in the supplemental material (Supplemental Fig. 1 for ASPECTS, Supplemental Fig. 2 for age).

Finally, two multivariate logistic regression models to predict functional independence were tested against each other to determine the additional value of PSV for the prediction of functional outcome. Both models included baseline ischemic core volume, penumbra volume, adjusted for age and degree of recanalization. In model 2, PSV was added as further variable. For both models (model 1 − PSV; model 2 + PSV), the predictive values were plotted against each other using receiver operating characteristic (ROC) curve analyses. Area under curve (AUC) of both models was compared using DeLong test. The dependent variable was functional independence (mRS 0–2 at day 90).

A statistically significant difference was accepted at a *p* value of less than 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 statement

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

Results

Patients

A total of 99 patients fulfilled the inclusion criteria. The median age of the patients was 76 years (IQR: 65–80). 52 (53%) patients were female and 47 (47%) were male. The median NIHSS was 16 (interquartile range (IQR): 12–19) and the initial ASPECTS was 8 (IQR: 7–9). Functional independence at day 90 (mRS 0–2) was observed in 45 patients (45%). Patient characteristics are summarized in Table 1.

Table 2 Univariable and multivariable linear regression to predict penumbra salvage volume (PSV) and univariable and multivariable ordinal regression analyses to predict clinical outcome (mRS shift at day 90)

Parameter	*β*	95% CI	*p* value
Univariable linear regression analysis (Penumbra salvage volume)			
Recanalization degree	63.4 mL	16.8–110.1 mL	<0.01
Hypoperfusion volume (per 1 mL)	0.85 mL	0.72–0.98 mL	<0.001
Penumbra volume (per 1 mL)	0.88 mL	0.74–1.0 mL	<0.001
Multivariable linear regression analysis (Penumbra salvage volume)			
Recanalization degree	32.1 mL	8.39–55.8 mL	0.009
Penumbra volume (per 1 mL)	0.83 mL	0.71–1.00 mL	<0.001
Time onset-recanalization (per minute)	− 0.11 min	− 0.22–0.02 min	0.03
Clinical outcome (mRS shift day 90)			
Parameter	OR	95% CI	*p* value
Univariable ordinal regression analysis (mRS shift day 90)			
Age (per year)	1.04	1.008–1.070	0.012
NIHSS	1.09	1.02–1.16	0.010
ASPECTS	0.71	0.57–0.89	0.003
Ischemic core volume (per 10 mL)	1.11	1.03–1.19	0.005
Complete reperfusion	0.46	0.22–0.97	0.040
Penumbra salvage volume (per 10 mL)	0.96	0.93–0.99	0.019
Multivariable ordinal regression analysis (mRS shift day 90)			
Age	1.07	1.04–1.11	<0.001
Penumbra salvage volume (per 10 mL)	0.89	0.85–0.95	<0.0001
Ischemic core volume (per 10 mL)	1.18	1.09–1.28	<0.001
Penumbra volume (per 10 mL)	1.08	1.02–1.15	0.011
Complete reperfusion	0.41	0.18–0.96	0.039

NIHSS National Institute of Health Stroke Scale, *ASPECTS* Alberta Stroke Program Early CT Score, *OR* odds ratio

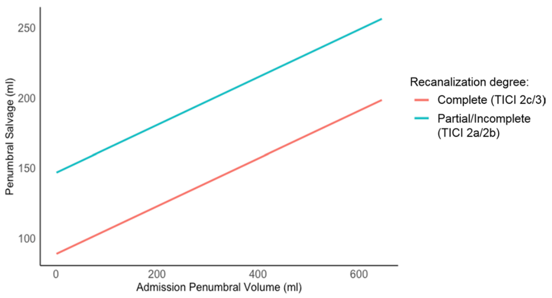

Fig. 3 Relationship of baseline penumbra volume, and recanalization degree on penumbra salvage. Impact of a higher recanalization degree on penumbra salvage volume (y-axis), according to the baseline penumbral volume (x-axis)

All patients underwent MT with partial to complete recanalization, 12 patients with partial (mTICI 2a) (12%), 35 patients with successful but incomplete (mTICI 2b) (35%), and 52 patients (52%) with complete recanalization (16 patients with mTICI 2c, and 36 patients with mTICI3). The median time from onset to recanalization was 291 min (IQR: 233–395 min). At baseline, the median ischemic core volume was 15.6 mL (IQR: 1.2–47.5 mL), and the median penumbra volume was 213.7 mL (IQR: 175.5–265.0 mL).

Comparing patients with functional independence at day 90 (mRS 0–2) to patients with an mRS 3–6, we observed that patients with functional independence were younger (68 versus 77 years) ($p<0.01$), and showed a lower NIHSS on admission (13–17) ($p<0.001$). On baseline imaging, ischemic core volume was by trend lower (9–19 mL) ($p=0.71$) in the patients with functional independence at day 90. Furthermore, patients with functional independence received intravenous alteplase more often (78 versus 55%) ($p=0.02$), and the degree of recanalization after MT was higher (complete recanalization 71 versus 52%) ($p=0.04$). Total infarct volume in FCT was lower in patients with functional independence (12–49 mL) ($p<0.01$) (Table 1).

In patients with complete recanalization, the median PSV was significantly higher than the median PSV in patients with partial or incomplete recanalization (median 224 mL, IQR: 168–303 versus 158 mL, IQR: 129–225; $p<0.01$). Correspondingly, the median relative penumbra salvage (proportion of rescued penumbra/total penumbral volume

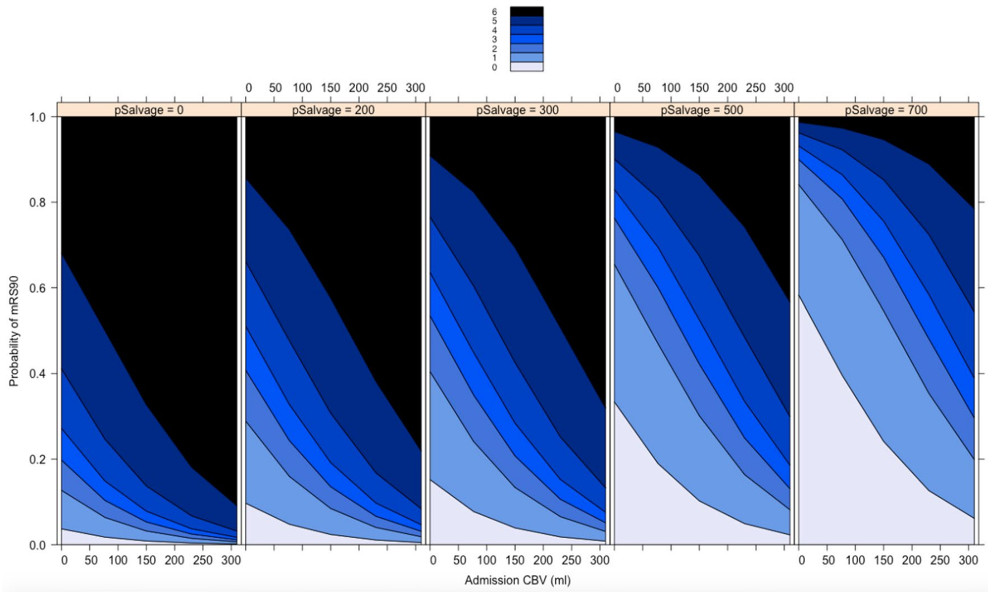

Fig. 4 Relationship of the baseline ischemic core volume and penumbra salvage volume, and its impact on functional outcome at 90 days**.** Impact of baseline ischemic core volume (x-axis), and penumbra salvage volume (5 plots from 0 to 700 mL), on probability for mRS at day 90 (0–6, indicated by blue colors)

at baseline) was 95% (IQR: 77–99%) for patients with complete recanalization, which was significantly higher than the median relative penumbra salvage in patients with partial or incomplete recanalization (82%, IQR: 56–96%; $p=0.04$).

Penumbra salvage volume—linear regression analyses

In univariable linear regression analysis, degree of recanalization, hypoperfusion volume, and penumbra volume were significantly associated with PSV as dependent parameter (Table 2). In multivariable linear regression analysis, degree of recanalization ($\beta=32.1$; $p=0.009$), penumbra volume (per 1 mL) ($\beta=0.83$; $p<0.001$), and time from symptom onset to recanalization ($\beta=-0.11$, $p=0.03$), were significantly and independently associated with PSV (Table 2). There was no association between age and PSV, and no association between baseline core lesion volume and PSV.

Functional outcome—ordinal regression analyses

In univariable ordinal regression analysis, age, ASPECTS, baseline NIHSS, ischemic core volume, PSV, and degree of recanalization were significantly associated with mRS shift at day 90 as dependent parameter (Table 2, lower part). In multivariable ordinal regression analysis, PSV (odds ratio: 0.89; $p<0.0001$), penumbra volume (odds ratio: 1.08; $p=0.011$), ischemic core lesion volume (per mL) (odds ratio: 1.18; $p<0.001$), age (odds ratio: 1.07; $p<0.001$), and degree of recanalization (odds ratio: 0.41; $p=0.039$) were significantly and independently associated with mRS shift at day 90 (Table 2, lower part). Time from symptom onset to recanalization, and baseline NIHSS were not significantly associated with outcome.

Multivariable prediction model

The AUC for model 1 (− PSV) to classify functional independence (mRS 0–2 at day 90) was 0.71 (95% CI: 0.60–0.80; $p<0.001$). The AUC for model 2 (+PSV) to classify functional independence was 0.80 (95% CI: 0.70–0.88; $p<0.0001$). In pairwise comparison using DeLong tests, we observed a significant difference between both models (difference 0.09, 95% CI: 0.02–0.16; $p=0.015$).

Discussion

Our study on the relationship of recanalization degree and PSV, and its impact on functional outcome revealed several findings: (1) higher degree of recanalization was directly associated with increased PSV: every increase in reperfusion (partial (mTICI 2a), incomplete (mTICI 2b), and complete (mTICI ≥ 2c) recanalization), was associated with a 63 mL increased PSV; (2) that was associated with improved functional outcome at 90-days follow-up; (3) this effect was shown even when comparing patients with mTICI 2b to patients with mTICI ≥ 2c.

In detail, we observed that penumbra salvage depends on three parameters: penumbra volume at baseline, degree of recanalization, and time from onset to reperfusion. However, penumbra salvage was independent from baseline ischemic core volume and ASPECTS, highlighting that penumbra may be rescued even in patients presenting with extensive stroke at admission. Furthermore, we observed that higher PSV and complete reperfusion were significantly and independently associated with improved functional outcome at 90-days. Corroborating previous studies, baseline ischemic core volume, and age had a significant impact on functional outcome [13]. Nevertheless, a higher degree of penumbra salvage might lead to a better clinical outcome even in older patients, or patients with large baseline ischemic core, as exemplified in Fig. 4 (see also supplemental figures for age effect plot) [11, 23, 24]. Interestingly, time from onset to reperfusion had no significant impact on functional outcome, illustrating that patients in the extended time window may benefit from endovascular treatment [1]. Although the impact of higher recanalization degree on functional outcome is well-established, penumbra salvage may improve outcome prediction, as exemplified by comparing two multivariable predictive models. A model that included PSV exhibited a significantly better diagnostic ability to classify functional outcome (AUC: 0.71 versus 0.80).

Penumbra salvage may be considered as a measure of success of MT, hence associated with functional outcome. Yet, the effect of endovascular treatment on clinical outcome is not completely understood. Contributing factors beyond reperfusion, including the underlying pathophysiology such as magnitude of immanent tissue injury, collateral circulation, clinical variables, or subsequent developments like recurring stroke or secondary hemorrhage, reasonably influence the clinical outcomes [11, 31]. Additionally, the effect of MT on outcome may not only be attributed to penumbral salvage, but also on reducing secondary injury volumes, in particular ischemic brain edema [8–10, 19, 32]. To illustrate this, we observed that complete reperfusion was associated with a penumbra salvage of 74 mL. Estimating the effect of PSV on mRS at day 90 in linear regression, a PSV of 74 mL would equal a decrease in mRS of 0.22. Complete reperfusion, however, was associated with a lower mRS of 0.95. Therefore, the effect of successful reperfusion on clinical outcomes is not comprehensively explained by penumbral salvage and may be multifactorial. Lately, it has been observed that successful MT was associated with a reduced ischemic formation of 6.3%, and improved mRS at day 90 of − 1.1 [8]. Thus, edema reduction may be an explanation of the discrepancy between outcome improvement and penumbra salvage following MT [8, 9, 26].

So far, it is well known that increasing reperfusion is directly associated with improved functional outcome [20, 21]. A recent analysis of the HERMES data observed the increasing rate of favorable outcome with increasing degree of recanalization [21]. A further recent study observed that even in the subgroup of patients with "successful" MT (i.e. mTICI ≥ 2b) the highest possible reperfusion grade should be pursued [20]. However, both studies did not discuss any pathophysiological reasons regarding the relationship of functional outcome and reperfusion degree.

To our knowledge, this is the first study that directly quantified the volume of penumbra salvage and investigated its relationship to the degree of recanalization and functional outcome. This study might help to better understand how endovascular treatment effects outcome, and how to further improve functional outcome in patients. Additionally, PSV could be tested as an imaging biomarker to compare treatment effects in ischemic stroke, as measuring infarct volume in follow-up imaging may not be an optimal parameter for this concern [5]. A previous study observed, that reduced infarct volume in follow-up imaging after MT only explained 12% of the treatment benefit [5]. However, this study did not describe baseline ischemic core volume, or penumbral volume, which might represent a major limitation of that study.

Future studies may investigate whether penumbra salvage is a better mediator of the relationship of endovascular treatment and functional outcome. Furthermore, it is important to realize that in the referred study, infarct volume was derived in follow-up imaging that has been acquired between 12 h to 2 weeks after admission. This directly impairs the interindividual comparability of lesion volumes due to the significantly ranging proportion of ischemic edema. At 24 h after onset, it has been observed that edema contributes to approximately 30% of the total lesion, while after 12 h, the mean edema proportion is around 20% [7, 17, 33]. This proportion, however, significantly varies depending on time, reperfusion treatment, and individual progression [7, 25, 27]. Consequently, future research is needed to investigate how edema-corrected lesion volumes perform as a mediator between outcome and EVT, and how these volumes may improve the comparability of treatment effects.

Limitations

Limitations of this study include the relatively small number of patients, due to rigorous inclusion criteria. The intention was to obtain a homogenous patient cohort. Patients with parenchymal hemorrhage type 2 were excluded. Future studies could investigate the relationship of PSV and secondary hemorrhage. Furthermore, there is no coherent definition of the true ischemic core and penumbra, and this concept has its natural limitations [6]. Alternative approaches could use relative cerebral blood flow to define ischemic core, but this may indicate a higher occurrence of core volume overestimation [3, 4].

Conclusion

Penumbra salvage volumes increased with higher degrees of recanalization and were significantly associated with improved functional outcome at day 90. These results further emphasize the importance of complete reperfusion as a result of EVT. Penumbra salvage was independent from baseline ischemic core volume, highlighting that penumbra may be rescued even in patients presenting with extensive ischemic core at admission.

Funding Open Access funding enabled and organized by Projekt DEAL.. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest JF: Research support: German Ministry of Science and Education (BMBF), German Ministry of Economy and Innovation (BMWi), German Research Foundation (DFG), European Union (EU), Hamburgische Investitions- und Förderbank (IFB), Medtronic, Microvention, Route92, Stryker. Consultant for: Acandis, Bayer, Boehringer Ingelheim, Cerenovus, Evasc Neurovascular, MD Clinicals, Medtronic, Microvention, Penumbra, Phenox, Stryker, Transverse Medical. Stock holder: Tegus Medical. All other authors declare that they have no conflict of interest.

Ethical approval Anonymized data was recorded in accordance with ethical review board approval and institutional review board waived informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request. The study protocol was in accordance with the declaration of Helsinki.

References

1. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, Sarraj A, Kasner SE, Ansari SA, Yeatts SD, Hamilton S, Mlynash M, Heit JJ, Zaharchuk G, Kim S, Carrozzella J, Palesch YY, Demchuk AM, Bammer R, Lavori PW, Broderick JP, Lansberg MG, DEFUSE 3 Investigators (2018) Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med 378:708–718
2. Albers GW, Marks MP, Lansberg MG (2018) Thrombectomy for stroke with selection by perfusion imaging. N Engl J Med 378:1849–1850
3. Bivard A, Kleinig T, Miteff F, Butcher K, Lin L, Levi C, Parsons M (2017) Ischemic core thresholds change with time to reperfusion: a case control study. Ann Neurol 82:995–1003
4. Bivard A, McElduff P, Spratt N, Levi C, Parsons M (2011) Defining the extent of irreversible brain ischemia using perfusion computed tomography. Cerebrovasc Dis 31:238–245
5. Boers AMM, Jansen IGH, Brown S, Lingsma HF, Beenen LFM, Devlin TG, Roman LS, Heo JH, Ribo M, Almekhlafi MA, Liebeskind DS, Teitelbaum J, Cuadras P, du Mesnil de Rochemont R, Beaumont M, Brown MM, Yoo AJ, Donnan GA, Mas JL, Oppenheim C, Dowling RJ, Moulin T, Agrinier N, Lopes DK, Aja Rodriguez L, Compagne KCJ, Al-Ajlan FS, Madigan J, Albers GW, Soize S, Blasco J, Davis SM, Nogueira RG, Davalos A, Menon BK, van der Lugt A, Muir KW, Roos Y, White P, Mitchell PJ, Demchuk AM, van Zwam WH, Jovin TG, van Oostenbrugge RJ, Dippel DWJ, Campbell BCV, Guillemin F, Bracard S, Hill MD, Goyal M, Marquering HA, Majoie C (2019) Mediation of the relationship between endovascular therapy and functional outcome by follow-up infarct volume in patients with acute ischemic stroke. JAMA Neurol 76:194–202
6. Boned S, Padroni M, Rubiera M, Tomasello A, Coscojuela P, Romero N, Muchada M, Rodriguez-Luna D, Flores A, Rodriguez N, Juega J, Pagola J, Alvarez-Sabin J, Molina CA, Ribo M (2017) Admission CT perfusion may overestimate initial infarct core: the ghost infarct core concept. J Neurointerv Surg 9:66–69
7. Broocks G, Faizy TD, Flottmann F, Schon G, Langner S, Fiehler J, Kemmling A, Gellissen S (2018) Subacute infarct volume with edema correction in computed tomography is equivalent to final infarct volume after ischemic stroke: improving the comparability of infarct imaging endpoints in clinical trials. Invest Radiol 53:472–476
8. Broocks G, Flottmann F, Hanning U, Schon G, Sporns P, Minnerup J, Fiehler J, Kemmling A (2020) Impact of endovascular recanalization on quantitative lesion water uptake in ischemic anterior circulation strokes. J Cereb Blood Flow Metab 40:437–445
9. Broocks G, Hanning U, Flottmann F, Schonfeld M, Faizy TD, Sporns P, Baumgart M, Leischner H, Schon G, Minnerup J, Thomalla G, Fiehler J, Kemmling A (2019) Clinical benefit of thrombectomy in stroke patients with low ASPECTS is mediated by oedema reduction. Brain 142:1399–1407
10. Broocks G, Leischner H, Hanning U, Flottmann F, Faizy TD, Schon G, Sporns P, Thomalla G, Kamalian S, Lev MH, Fiehler J, Kemmling A (2020) Lesion age imaging in acute stroke: water uptake in CT versus DWI-FLAIR mismatch. Ann Neurol 88:1144–1152
11. Campbell BCV, Majoie C, Albers GW, Menon BK, Yassi N, Sharma G, van Zwam WH, van Oostenbrugge RJ, Demchuk AM, Guillemin F, White P, Davalos A, van der Lugt A, Butcher KS, Cherifi A, Marquering HA, Cloud G, Macho Fernandez JM, Madigan J, Oppenheim C, Donnan GA, Roos Y, Shankar J, Lingsma H, Bonafe A, Raoult H, Hernandez-Perez M, Bharatha A, Jahan R, Jansen O, Richard S, Levy EI, Berkhemer OA, Soudant M, Aja L, Davis SM, Krings T, Tisserand M, San Roman L, Tomasello A, Beumer D, Brown S, Liebeskind DS, Bracard S, Muir KW, Dippel DWJ, Goyal M, Saver JL, Jovin TG, Hill MD, Mitchell PJ, HERMES Collaborators (2019) Penumbral imaging and

functional outcome in patients with anterior circulation ischaemic stroke treated with endovascular thrombectomy versus medical therapy: a meta-analysis of individual patient-level data. Lancet Neurol 18:46–55
12. Dargazanli C, Fahed R, Blanc R, Gory B, Labreuche J, Duhamel A, Marnat G, Saleme S, Costalat V, Bracard S, Desal H, Mazighi M, Consoli A, Piotin M, Lapergue B, AT Investigators (2018) Modified thrombolysis in cerebral infarction 2C/thrombolysis in cerebral infarction 3 reperfusion should be the aim of mechanical thrombectomy: insights from the ASTER Trial (contact aspiration versus stent retriever for successful revascularization). Stroke 49:1189–1196
13. Demeestere J, Scheldeman L, Cornelissen SA, Heye S, Wouters A, Dupont P, Christensen S, Mlynash M, Albers GW, Lansberg M, Lemmens R (2018) Alberta stroke program early CT score versus computed tomographic perfusion to predict functional outcome after successful reperfusion in acute ischemic stroke. Stroke 49:2361–2367
14. Fiorelli M, Bastianello S, von Kummer R, del Zoppo GJ, Larrue V, Lesaffre E, Ringleb AP, Lorenzano S, Manelfe C, Bozzao L (1999) 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 30:2280–2284
15. Flottmann F, Broocks G, Faizy TD, McDonough R, Watermann L, Deb-Chatterji M, Thomalla G, Herzberg M, Nolte CH, Fiehler J, Leischner H, Brekenfeld C, GSR Investigators (2020) Factors associated with failure of reperfusion in endovascular therapy for acute ischemic stroke: a multicenter analysis. Clin Neuroradiol. https://doi.org/10.1007/s00062-020-00880-8
16. Ganesh A, Luengo-Fernandez R, Wharton RM, Rothwell PM, Oxford Vascular Study (2018) Ordinal vs dichotomous analyses of modified Rankin Scale, 5-year outcome, and cost of stroke. Neurology 91:e1951–e1960
17. Gerriets T, Stolz E, Walberer M, Muller C, Kluge A, Bachmann A, Fisher M, Kaps M, Bachmann G (2004) Noninvasive quantification of brain edema and the space-occupying effect in rat stroke models using magnetic resonance imaging. Stroke 35:566–571
18. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Davalos A, Majoie CB, van der Lugt A, de Miquel MA, Donnan GA, Roos YB, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millan M, Davis SM, Roy D, Thornton J, Roman LS, Ribo M, Beumer D, Stouch B, Brown S, Campbell BC, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG, HERMES Collaborators (2016) Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 387:1723–1731
19. Harston GWJ, Carone D, Sheerin F, Jenkinson M, Kennedy J (2018) Quantifying infarct growth and secondary injury volumes: comparing multimodal image registration measures. Stroke 49:1647–1655
20. LeCouffe NE, Kappelhof M, Treurniet KM, Lingsma HF, Zhang G, van den Wijngaard IR, van Es A, Emmer BJ, Majoie C, Roos Y, Coutinho JM, MR CLEAN Registry Investigators (2020) 2B, 2C, or 3: what should be the angiographic target for endovascular treatment in ischemic stroke? Stroke 51:1790–1796
21. Liebeskind DS, Bracard S, Guillemin F, Jahan R, Jovin TG, Majoie CB, Mitchell PJ, van der Lugt A, Menon BK, San Roman L, Campbell BC, Muir KW, Hill MD, Dippel DW, Saver JL, Demchuk AM, Davalos A, White P, Brown S, Goyal M, HERMES Collaborators (2019) eTICI reperfusion: defining success in endovascular stroke therapy. J Neurointerv Surg 11:433–438
22. Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, Kleinig TJ, Wijeratne T, Curtze S, Dewey HM, Miteff F, Tsai CH, Lee JT, Phan TG, Mahant N, Sun MC, Krause M, Sturm J, Grimley R, Chen CH, Hu CJ, Wong AA, Field D, Sun Y, Barber PA, Sabet A, Jannes J, Jeng JS, Clissold B, Markus R, Lin CH, Lien LM, Bladin CF, Christensen S, Yassi N, Sharma G, Bivard A, Desmond PM, Yan B, Mitchell PJ, Thijs V, Carey L, Meretoja A, Davis SM, Donnan GA, EXTEND Investigators (2019) Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. N Engl J Med 380:1795–1803
23. McDonough R, Elsayed S, Faizy TD, Austein F, Sporns PB, Meyer L, Bechstein M, van Horn N, Nawka MT, Schon G, Kniep H, Hanning U, Fiehler J, Heit JJ, Broocks G (2020) Computed tomography-based triage of extensive baseline infarction: ASPECTS and collaterals versus perfusion imaging for outcome prediction. J Neurointerv Surg. https://doi.org/10.1136/neurintsurg-2020-016848
24. Meyer L, Schonfeld M, Bechstein M, Hanning U, Cheng B, Thomalla G, Schon G, Kemmling A, Fiehler J, Broocks G (2020) Ischemic lesion water homeostasis after thrombectomy for large vessel occlusion stroke within the anterior circulation: the impact of age. J Cereb Blood Flow Metab. https://doi.org/10.1177/0271678X20915792
25. Minnerup J, Broocks G, Kalkoffen J, Langner S, Knauth M, Psychogios MN, Wersching H, Teuber A, Heindel W, Eckert B, Wiendl H, Schramm P, Fiehler J, Kemmling A (2016) Computed tomography-based quantification of lesion water uptake identifies patients within 4.5 hours of stroke onset: a multicenter observational study. Ann Neurol 80:924–934
26. Nawabi J, Flottmann F, Hanning U, Bechstein M, Schoen G, Kemmling A, Fiehler J, Broocks G (2018) Futile recanalization with poor clinical outcome is associated with increased edema volume after ischemic stroke. Invest Radiol 54:282–287
27. Nawabi J, Flottmann F, Kemmling A, Kniep H, Leischner H, Sporns P, Schon G, Hanning U, Thomalla G, Fiehler J, Broocks G (2019) Elevated early lesion water uptake in acute stroke predicts poor outcome despite successful recanalization—when "tissue clock" and "time clock" are desynchronized. Int J Stroke. https://doi.org/10.1177/1747493019884522
28. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA, Sila CA, Hassan AE, Millan M, Levy EI, Mitchell P, Chen M, English JD, Shah QA, Silver FL, Pereira VM, Mehta BP, Baxter BW, Abraham MG, Cardona P, Veznedaroglu E, Hellinger FR, Feng L, Kirmani JF, Lopes DK, Jankowitz BT, Frankel MR, Costalat V, Vora NA, Yoo AJ, Malik AM, Furlan AJ, Rubiera M, Aghaebrahim A, Olivot JM, Tekle WG, Shields R, Graves T, Lewis RJ, Smith WS, Liebeskind DS, Saver JL, Jovin TG, DT Investigators (2018) Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med 378:11–21
29. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL (2019) Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 50:e344–e418
30. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL, American Heart Association Stroke Council (2018) 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 49:e46–e110

2. Description of the paper

Acute ischemic stroke is a medical emergency that requires prompt treatment. Early and successful therapy reduces brain damage and improves outcome. Introduction of neurological stroke units in 1994, and the initiation of the National Institute of Neurological Disorders and Stroke (NINDS) study in 1996 became the two significant milestones in stroke treatment history [1] [2]. They provided the evidence in favor of intravenous thrombolysis (IVT) using tissue-type plasminogen activator (tPA). These trials changed the concept of primary care for patients in stroke units and reduced lasting impairment and mortality (odds ratio [OR]: 0.76; 95% confidence interval [CI]: 0.67 to 0.86; p = 0.0001; combined outcome versus care outside stroke units) [3].

Initially in the early 1980s, acute stroke emergencies were treated with intra-arterial fibrinolysis. In 2015 authors of five independent randomised trials (ESCAPE [4], EXTEND-IA [5], MR CLEAN [6], REVASCAT [7], and SWIFT-PRIME [8]) argued that mechanical thrombectomy (MT), mainly in combination with IVT, is superior to the best medical treatment alone. This ground-breaking method can prevent severe disabilities after a heavy stroke by early recanalization of an occluded vessel.

Further studies like Dargazanli et al. in 2018 have shown that successful reperfusion is the main predictor of the positive outcome after mechanical thrombectomy (MT) for acute large-vessel occlusions [9]. The success of MT graded by the “Thrombolysis in cerebral infarction” (TICI) (Figure 2) scale is a widely used scoring system to evaluate the degree of reperfusion achieved after MT [10] [11] [12].

Unfortunately, not every stroke with a large vessel occlusion can successfully be treated with mechanical thrombectomy. There are different important clinical and imaging criteria that are considered before MT in ischemic stroke.

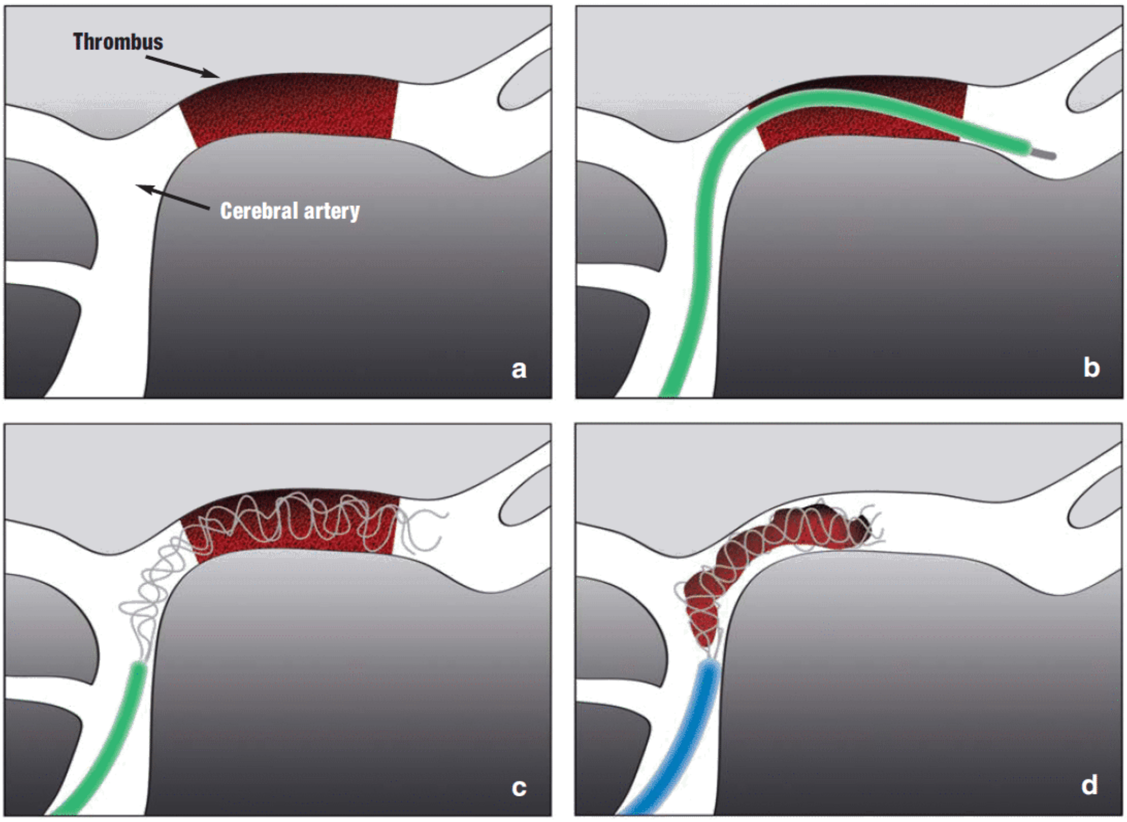

Figure 1. If there is a proximal thromboembolic occlusion of the middle cerebral artery (a), the stent retriever is run past the intra-arterial thrombus in a microcatheter (b). When the microcatheter is retracted, the stent retriever is pushed out and released inside the thrombus. After a few minutes, the stent expands into the thrombus so that the mesh of the stent hooks into thrombus (c). The expanded stent, together with the whole thrombus, is then removed into a larger catheter (d). Mechanical Thrombectomy in Stroke. Fiehler, J; Gerloff, C. Dtsch Arztebl Int 2015; 112: 830-6. DOI: 10.3238/arztebl.2015.0830

TICI Grade	Original TICI	Modified TICI	Modified TICI With 2c
0/1	No/minimal reperfusion	No/minimal reperfusion	No/minimal reperfusion
2a	Partial filling <2/3 territory	Partial filling <50% territory	Partial filling <50% territory
2b	Partial filling ≥2/3 territory	Partial filling ≥50% territory	Partial filling ≥50% territory
2c	…	…	Near complete perfusion except slow flow or few distal cortical emboli
3	Complete perfusion	Complete perfusion	Complete perfusion

TICI indicates thrombolysis in cerebral infarction.

Figure 2. Comparison of the Existing TICI Grading Scale Criteria. TICI indicates thrombolysis in cerebral infarction[13]. Fiehler J, Gerloff C. Mechanical Thrombectomy in Stroke. *Dtsch Arztebl Int*. 2015;112(49):830-836.

Defining the criteria to evaluate and select patients with large vessel occlusion for endovascular treatment is critically important, since between 3% and 22% of patients with AIS are potentially eligible for mechanical thrombectomy, depending on the specific selection criteria used [14–16]. Patient selection must be judicious, like B. Yan et al. argued in his publication in the American Journal of Neuroradiology in 2019 "Selection of Patients with Stroke for Thrombectomy Must Be Judicious and Should Not Be Offered to Any Patient with Large-Vessel Occlusion with a Femoral Pulse" [17].

The Society of Neurointerventional Neurosurgery in 2019 listed the most important determinants of candidacy for mechanical thrombectomy, which are: time of symptom onset or when it is unknown the last seen well; early ischemic changes on initial imaging; clinical severity of stroke symptoms; pre-stroke level of functioning; and anatomic location of the emergent large vessel occlusion (ELVO) [18]. The time of symptom onset is the well-known, major, and the first used selection determinant, which suggested between 0- and 6-hours time-period from symptom onset in the more recently well-known multicentric studies. Three recent studies MR CLEAN, EXTEND-IA, and SWIFT PRIME were conducted to evaluate the value of thrombectomy in anterior circulation till 6 hours after symptom onset. The studies demonstrated that 33% of patients could achieve a good clinical outcome (which defined as a modified Ranking Scale (mRS) score 0-2) after mechanical thrombectomy versus 19% with non-invasive medical treatment (MR CLEAN with an OR of 1.67) [4–6]. EXTEND-IA has shown good outcomes, more concretely, 71% with MT versus 40% with medical treatment (OR=2.0); in SWIFT PRIME, it was 60% versus 35%. The vast majority of studies have demonstrated similar results even with a longer time period from symptom onset with good clinical outcomes after MT versus medical management. REVASCAT and ESCAPE trials have shown the benefit of mechanical thrombectomy for a patient with anterior circulation up to 8 hour and 12 hours after symptom onset with better clinical outcomes than only with non-invasive treatment (44% rate of good clinical outcome versus 28% medical management (OR=2.1) and 53% with MT versus 29% with medical management, rate ratio 1.8)[6,7].

Characteristics of the five randomized trials on mechanical thrombectomy published in 2015

Trial	*n* patients: MT/control	IV tPA rate	Groin puncture after symptom onset	Median NIHSS score: MT/control	Vessel occlusion	Recanalization rate: MT	mRS score 0 to 2: control	mRS score 0 to 2: MT	Symptom onset to groin puncture/reperfusion (min)	SICB: MT	SICB: control	NNT (mRS score 0 to 2)
MR CLEAN	233/267	89%	Intra-arterial therapy <6 hours possible	17/18	Distal ICA, M1, M2, A1, A2	59%	19%	33%	260/-	7.7%	6.4%	7
ESCAPE	165/150*[1]	76%	Patient recruitment <12 hours	16/17	ICA + M1, M1, M2	72%	29%	53%	-/241	3.6%	2.7%	4
EXTEND-IA	35/35*[1]	100%	IV <4.5 hours, intra-arterial therapy begun <6 hours, ended <8 hours	17/13	ICA, M1, M2	86%	40%	71%	-/210	0	5.7%	3
SWIFT-PRIME	98/98*[1]	98%	IV <4.5 hours, IA	17/17	ICA, M1	88%	35%	60%	224/252*[2]	0	3.1%	4
REVASCAT	103/103*[1]	73%	Beginning of standard therapy or intra-arterial therapy <8 hours	17/17	ICA + M1, intracranial ICA, M1	66%	28%	44%	269/355	1.9%	1.9%	6

n: Number; MT: Mechanical thrombectomy; tPA: Tissue-type plasminogen activator; I#
VT: Intravenous thrombolysis; IA: Thrombectomy; NIHSS: National Institutes of Health Stroke Scale; ICA: Internal carotid artery; M1: Proximal, horizontal segment of middle cerebral artery; M2: Insular segment of middle cerebral artery following M1; mRS: Modified Rankin Scale; SICB: Symptomatic intracranial bleeding; NNT: Number needed to treat
*[1]Trial halted early due to lack of equipoise
*[2]Time to first deployment of stent retriever

Table 1. Clinical outcomes defined as modified ranking scale in a patients with symptom onset up to 12 hours after mechanical thrombectomy versus medical management [13].

The vast majority of other clinical studies described a treatment effect favoring thrombectomy with similar results. The two more recent studies (DEFUSE 3 and DAWN) have shown that even late presenting patients or wake-up strokes with long time windows up to 24 hours after symptom onset with clinical and neuroimaging (diffusion weighted imaging and CT perfusion) mismatch can highly and safely benefit from mechanical thrombectomy in comparison with non-invasive treatment, with careful patient selection. DEFUSE 3 [19] described 45% of patients with good clinical outcomes with mechanical thrombectomy versus 17% with medical management; and the authors of DAWN trials [20] presented similar results with 49% good clinical outcomes in patients who were treated with mechanical thrombectomy versus 13% with medical treatment.

Two other registries, namely, TACK and NASA have shown that 33% of patients with no imaging based patient selection who were treated with thrombectomy beyond the first 6 hours after symptom onset equally demonstrated safety and efficacy of this treatment to treatment within 6 hours from symptom onset to treatment [21,22]. To our knowledge, there is an extensive amount of data from different multicenter randomized controlled trials and registries providing support for thrombectomy with accurately selected patients up to 24 hours after symptom onset or last known well, including wake up strokes. To date, only a few studies have evaluated the role of thrombectomy beyond 24 hours after stroke [23]. The Table 2 presents the randomized trials and registries of modern approaches to thrombectomy [18].

The accurate selection of patients for mechanical thrombectomy is the main advantage of the clinical practice; however, the selection of patients who most likely benefit from the endovascular treatment is a critical factor. Neuroimaging may be used to provide the selection for treatment and serve as a prognostic biomarker [19,24,25]. Patient selection with imaging criteria aims to exclude the patient who is unlikely to benefit from thrombectomy and may, instead, get harmed by it.

Earlier studies already described the importance of imaging criteria for patient selection for endovascular treatment. However, the flow restoration of an occluded large vessel can be helpful just in case of restoring the blood flow in the still metabolic functional brain parenchyma. If the brain damage is irreversible, it cannot benefit from restoring the blood supply in this area. As mentioned previously, neuroimaging can provide thrombectomy with patient selection with accurate imaging criteria. These can be provided with different imaging modality depending on the stroke situation including non-contrast CT, MRI diffusion-weighted imaging (DWI), collateral imaging on multiphase CT angiography (mCTA) and the most advanced CT and MRI perfusion imaging methods.

Early published trials from years 2015 and 2016 used imaging criteria such as Alberta Stroke Programme Early CT Score (ASPECTS) 6-10, MRI DWI ASPECTS 5-10, good collateral situation on multiphase CTA (over 50% middle cerebral artery territory), infarct core volumes less than 70 ml and significant mismatch of infarct core to ischemic penumbra (area of hypoperfused issue that may be salvaged after flow restoration) for patient selection for EVT (endovascular treatment) up to 6 hours after symptom onset [4–8,26–28]. The data from two recent studies from early 2018 showed that MRI DWI and CT perfusion (CTP) are highly accurate imaging criteria for patient selection with 6 to 24 hours' time window from symptom onset with no significant higher risk of symptomatic intracranial hemorrhage (sICH) [19,20].

Trial	No of patients, total/IA (when applicable)	LVO location	Time window for thrombectomy, hours	Stroke severity (NIHSS score)	Imaging criteria	Treatment groups	mRS score=0–2 at 90 days
Randomized trials: Endovascular vs medical							
MR CLEAN[8]	500/223	ICA, M1, M2, A1, A2	0–6	≥2	No limit	Endovascular arm: stent retrievers in 97% of IA cases, 87% of IA-treated patients received IV rtPA first. Control arm: IV rtPA in 91% of patients	Endovascular group: 33% Control group: 19% NNT=7.1
ESCAPE[13]	215/165	ICA, M1, both (all) M2s	0–12	'Disabling' symptoms but no strict NIHSS limit	CT ASPECTS 6–10, moderate-to-good collateral status on mCTA	Endovascular arm: stent retrievers in 86% of all IA cases. 73% of IA-treated patients received IV rtPA first Control arm: IV rtPA in 79% of patients	Endovascular group: 53% Control group: 29% NNT=4.2
EXTEND-IA[9]	70/35	ICA, M1, M2	0–6	No limit	CTP/MRP core <70 mL	Endovascular arm: IV rtPA plus Solitaire stent retriever in all IA cases. Control arm: IV rtPA in all	Endovascular group: 71% NNT=3.2
SWIFT PRIME[10]	196/98	ICA, M1	0–6	8–29	CTP/MRP core ≤50 mL, CT/MRI ASPECTS 6–10	Endovascular arm: IV rtPA plus Solitaire stent retriever in all IA cases. Control arm: IV rtPA in all	Endovascular group: 60% Control group: 35% NNT=4
REVASCAT[12]	206/103	Anterior circulation LVO	0–8	≥6	CT ASPECTS 7–10, MRI DWI ASPECTS 6–10	Endovascular arm: Solitaire stent retriever thrombectomy. 68% of IA-treated patients received IV rtPA first. Control arm: IV rtPA in 78% of patients.	Endovascular group: 44% Control group: 28% NNT=6.3
THERAPY[50]	108/55	ICA, M1, M2 with clot ≥8 mm in length	No limit but all patients received IV rtPA first	≥8	Exclusion: CT infarct >1/3 MCA territory	Endovascular arm: IV rtPA + aspiration with traditional penumbra separator/3D stent retriever/Solitaire/Trevo. Control arm: IV rtPA in all.	Endovascular group: 38% Control group: 30%
THRACE[11]	414/204	ICA, M1, superior 1/3 of BA	0–5	10–25	No limit	Endovascular arm: IV rtPA + aspiration or different brands of stent retriever devices. Control arm: IV rtPA in all.	Endovascular group: 53% Control group: 42%
DAWN[16]	206/107	ICA, M1	6–24	≥10	CTP, MRP Group A: age ≥80, core <21 mL Group B: ag e<80, NIHSS ≥10, core <31 mL Group C: age <80, NIHSS ≥20, core <51 mL	Endovascular arm: Trevo stent retriever Control arm: medical management (antiplatelets)	Endovascular group: 49% Control group: 13%
DEFUSE 3[15]	182	ICA, M1	6–16	≥6	CTP/MRP core <70 mL, Penumbra/core ≥1.8 mL	Endovascular arm: direct aspiration without stent retriever in 27%, stent retrievers were used in 80% of IA interventions. Control arm: medical management (antiplatelets)	Endovascular group: 45% Control group: 17%
Randomized trials: comparison of endovascular approaches – aspiration vs stent retriever							
ASTER[51]	381	ICA, M1, M2	0–6	No limit	No limit	Two endovascular arms: direct aspiration (n=192) vs primary stent retriever thrombectomy (n=182)	Direct aspiration: 45% Stent retriever: 50%
Penumbra Separator 3D[52]	198	Any LVO ≥2.5 mm diameter	0–8	≥8	Exclusion: CT infarct >1/3 MCA territory	Two endovascular arms: 3D stent retriever + aspiration (n=98) vs primary aspiration (n=100)	Direct aspiration: 46% 3D Stent retriever: 45%
Endovascular registries							
TRACK registry[18]	634	Any LVO	No limit	No limit	No limit	Trevo stent retriever in all. 51% patients received IV tPA first	Endovascular group: 48%
STRATIS registry[53]	984	Any LVO	0–8	8–30	No limit	Solitaire/Mindframe stent retriever in all. 64% patients received IV tPA first	Endovascular group: 57%
NASA registry[19]	354	Any LVO	No limit	No limit	No limit	Solitaire stent retriever in all	Endovascular group: 42%
STAR registry[54]	202	ICA, M1, M2	0–8	8–30	Exclusion: CT infarct >1/3 MCA territory, CT ASPECTS <7, MRI DWI ASPECTS <5	Solitaire stent retriever in all. 59% patients received IV tPA first	Endovascular group: 58%

ASPECTS, Alberta Stroke Programme Early CT Score; BA, basilar artery; CT, computed tomography; CTA, CT angiography; CTP, CT perfusion; DWI, diffusion weighted imaging; ICA, internal carotid artery; IV, intravenous; LVO, large vessel occlusion; MCA, middle cerebral artery; MRI, magnetic resonance imaging; MRP, magnetic resonance perfusion, mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; NNT, number needed to treat; rtPA, recombinant tissue plasminogen activator.

Table 2. Randomized trials and registries of modern approaches to thrombectomy. Mokin M, Ansari SA, McTaggart RA, et al. Indications for thrombectomy in acute ischemic stroke from emergent large vessel occlusion (ELVO): report of the SNIS Standards and Guidelines Committee. *J Neurointerv Surg*. 2019;11(3):215 LP - 220. doi:10.1136/neurintsurg-2018-014640

Currently, in daily clinical practice, the most used imaging modality is CT including CTP, as MRI might not be either affordable in some hospitals or not be constantly available. CTP is a contrast-enhanced dynamic study that analyses the ischemic penumbra and infarct core throughout cerebral blood flow (CBF); mean transit time (MTT) and cerebral blood volume (CBV); and time to drain (TTP). The infarct core is the area of brain tissue with decreased blood flow of less than 70% compared to normal brain parenchyma. At the same time, the infarct core can be determined in CTP as the irreversible area of brain parenchyma with decreased CBF and CBV and increased MTT and TTP. The normal measure for CBF is 50 ml blood flow per 100 g of brain parenchyma per minute, whereas CBV is 5 ml blood volume in 100 g parenchyma. MTT shows the mean time of blood transportation through the given brain region and the TTP means the time of the peak of the contrast concentration in a given region of parenchyma [29]. Using these parameters can determine the salvageable area, so-called ischemic penumbra, which gets some blood supplies through collaterals but causes neuronal dysfunction which produces neurological symptoms. This can be determined in CTP as a mismatch between CBF and CBV. The ischemic penumbra can be saved by restoring the blood supply to the brain parenchyma. If there is no salvageable penumbra (mismatch), it makes little sense to go through thrombectomy to restore the blood supply in that region, which is already infarcted. Figure 3 below shows the CTP images without mismatch. There is no salvageable brain parenchyma that could be saved with faster mechanical thrombectomy.

Several studies like MR CLEAN, EXTENDIA-IA and SWIFT-RPIME described the association of infarct core with poor functional outcomes [6]; [6]; while DEFUSE 3 and DAWN have evaluated the role of ischemic penumbra in patient selection for mechanical thrombectomy in order to show not only the role of the infarct core, but also the role of ischemic penumbra, even in patients within 6-16 h after last known well [30].

The purpose of this study was to evaluate the role of penumbra salvage volume independent from infarct volume for comparing the treatment effects after mechanical thrombectomy in patients with acute stroke. Previous studies investigated the relationship between recanalization degree and functional outcome[31,32]. So far, it is already known that the favored functional outcome is directly associated with increasing reperfusion. However, to our knowledge the previous studies did not observe any pathophysiological reasons explaining the relationship of functional outcome and reperfusion degree. In this study we investigated the impact of PSV as an imaging biomarker to compare the treatment effects after mechanical thrombectomy.

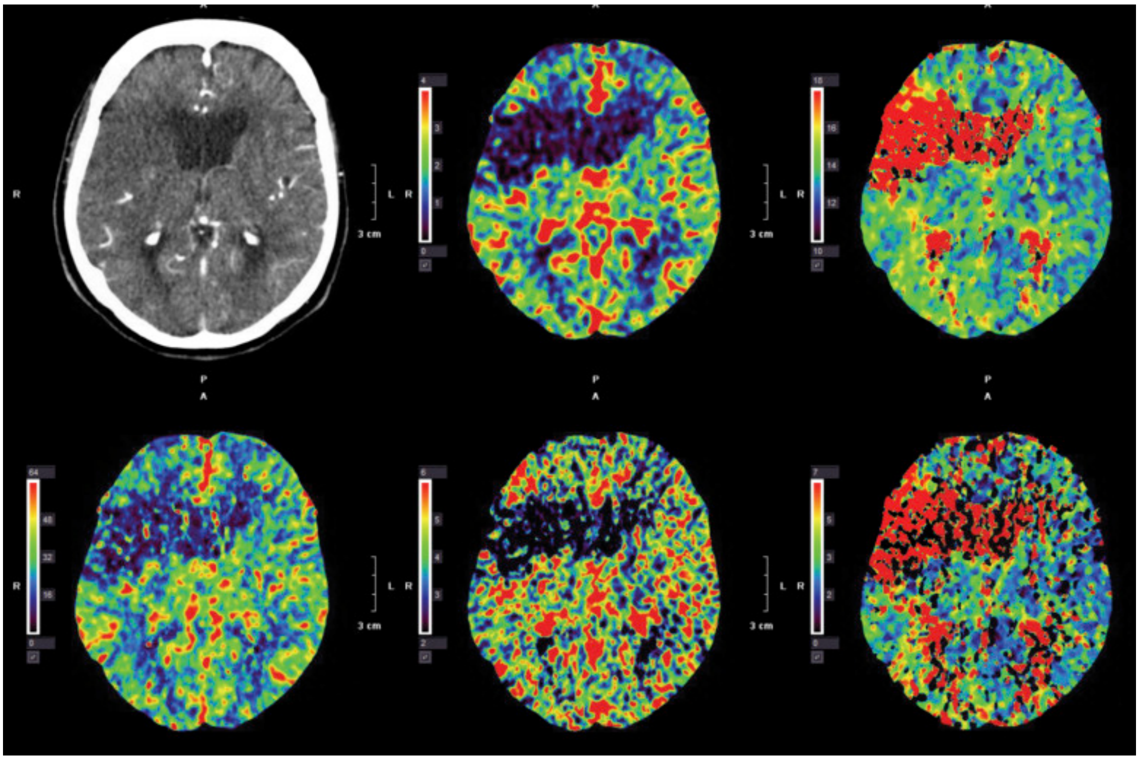

Figure 3. In this case CTP study shows the infarct region of brain parenchyma (dark blue area) without any salvageable ischemic penumbra in a patient with right-sided middle cerebral artery stroke. There is no mismatch between CBF (the low middle image) and CBV (the upper middle image). In this case the intervention was not offered to this patient [29].

We hypothesized that PSV may be a mediator of functional outcome in patients undergoing thrombectomy and can be used as an imaging biomarker after endovascular treatment for comparing treatment effects[33]. Future studies may investigate whether PSV is a better mediator of the relationship of intervention and clinical outcome, and whether PSV may serve as optimized imaging biomarker in stroke trials.

3. Summary

The main treatment target of mechanical thrombectomy in patients with acute ischemic stroke is to restore the blood supply to the region of brain tissue supplied by the occluded vessel. The ischemic penumbra regularly has persisting blood flow through collaterals but can be transformed into infarction in case no recanalization occurs within a sufficient time period. The role of CTP is the time-sensitive selection of patients, that can still benefit from mechanical thrombectomy. The so-called ischemic penumbra is metabolically viable brain tissue that can be salvage after blood flow restoration through thrombectomy. In this study, we hypothesized that the relation between recanalization degree after mechanical thrombectomy and penumbra salvage directly predicts functional outcome in acute stroke patients.

In summary, our results clearly demonstrate that every increase of recanalization has a direct impact on saved brain parenchyma called the salvaged penumbra, which is associated with improved functional outcomes in patients after 90 days of acute stroke. Every degree of recanalization (mTICI 2a to mTICI 3) estimates the salvage of 63 mL of the hypoperfused brain tissue at risk. The results even show the association of penumbra salvage with improved clinical outcomes in 90 days, even in patients with an extensive ischemic core at admission. This once again demonstrates the importance of higher degree of reperfusion after recanalization.

3. Zusammenfassung

Das Hauptziel einer Behandlung mit mechanischer Thrombektomie bei Patienten mit akutem Schlaganfall ist die Wiederherstellung der Blutversorgung der Region des Hirnparenchyms, deren Blutversorgung durch das verschlossene Gefäß vermindert wurde. Die ischämische Penumbra wird durch Kollateralen weiterhin mit Blut versorgt, kann aber irreversibel sein, wenn sie nicht in kurzer Zeit wiederhergestellt wird. Die Rolle der CTP ist die zeitabhängige Auswahl der Patienten, die noch von einer mechanischen Thrombektomie profitieren können. Die so genannte ischämische Penumbra ist metabolisch lebensfähiges Hirngewebe, das nach der Wiederherstellung des Blutflusses durch die Thrombektomie gerettet werden kann. In dieser Studie stellten wir die Hypothese auf, dass die Beziehung zwischen dem Rekanalisationsgrad nach mechanischer Thrombektomie und der Penumbra-Rettung eine direkte Vorhersage für das funktionelle Ergebnis bei akuten Schlaganfallpatienten hat.

Zusammenfassend zeigten unsere Ergebnisse deutlich, dass jede Zunahme der Rekanalisationsrate einen direkten Einfluss auf das gerettete Hirnparenchym, die sogenannte gerettete Penumbra, hat, die mit einem verbesserten funktionellen Ergebnis nach 90 Tagen bei Patienten mit akutem Schlaganfall assoziiert ist. Jeder Grad der Rekanalisation (mTICI 2a bis mTICI 3) schätzt die Rettung von 63 mL des hypoperfundierten, gefährdeten Hirngewebes. Die Ergebnisse zeigten sogar eine Assoziation der Penumbra-Rettung mit einem verbesserten klinischen Outcome nach 90 Tagen, was selbst bei Patienten mit einem ausgedehnten ischämischen Kern bei der Aufnahme deutlich identifiziert wurde. Dies demonstriert erneut die Bedeutung eines höheren Reperfusionsgrades nach der Rekanalisation.

4. References

1. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke t-PA Stroke Study Group. *J Neurosurg Anesthesiol*. 1996;8(2):172. doi:10.1097/00008506-199604000-00018
2. Langhorne P, Williams BO, Gilchrist W, Howie K. Do stroke units save lives? *Lancet*. Published online 1993. doi:10.1016/0140-6736(93)92813-9
3. Langhorne P. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev*. Published online 2013. doi:10.1002/14651858.CD000197.pub3
4. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. Published online 2015. doi:10.1056/NEJMoa1414905
5. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. Published online 2015. doi:10.1056/NEJMoa1414792
6. Berkhemer OA, Fransen PSS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. Published online 2015. doi:10.1056/NEJMoa1411587
7. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. Published online 2015. doi:10.1056/NEJMoa1503780
8. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. Published online 2015. doi:10.1056/NEJMoa1415061
9. Dargazanli C, Fahed R, Blanc R, et al. Modified Thrombolysis in Cerebral Infarction 2C/Thrombolysis in Cerebral Infarction 3 reperfusion should be the aim of mechanical thrombectomy: Insights from the ASTER trial (contact aspiration versus stent retriever for successful revascularization). *Stroke*. 2018;49(5):1189-1196. doi:10.1161/STROKEAHA.118.020700
10. Higashida RT, Furlan AJ, Roberts H, et al. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke*. Published online 2003. doi:10.1161/01.str.0000082721.62796.09

11. Suh SH, Cloft HJ, Fugate JE, Rabinstein AA, Liebeskind DS, Kallmes DF. Clarifying differences among thrombolysis in cerebral infarction scale variants: Is the artery half open or half closed? *Stroke*. Published online 2013. doi:10.1161/STROKEAHA.111.000399
12. Goyal M, Fargen KM, Turk AS, et al. 2C or not 2C: Defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. *J Neurointerv Surg*. Published online 2014. doi:10.1136/neurintsurg-2013-010665
13. Fiehler J, Gerloff C. Mechanical Thrombectomy in Stroke. *Dtsch Arztebl Int*. 2015;112(49):830-836. https://www.aerzteblatt.de/int/article.asp?id=173141
14. Vanacker P, Lambrou D, Eskandari A, Mosimann PJ, Maghraoui A, Michel P. Eligibility and predictors for acute revascularization procedures in a stroke center. *Stroke*. Published online 2016. doi:10.1161/STROKEAHA.115.012577
15. Rai AT, Seldon AE, Boo S, et al. A population-based incidence of acute large vessel occlusions and thrombectomy eligible patients indicates significant potential for growth of endovascular stroke therapy in the USA. *J Neurointerv Surg*. Published online 2017. doi:10.1136/neurintsurg-2016-012515
16. Mokin M, Pendurthi A, Ljubimov V, et al. ASPECTS, Large Vessel Occlusion, and Time of Symptom Onset: Estimation of Eligibility for Endovascular Therapy. *Clin Neurosurg*. Published online 2018. doi:10.1093/neuros/nyx352
17. Yan B. Selection of patients with stroke for thrombectomy must be judicious and should not be offered to any patient with large-vessel occlusion with a femoral pulse. *Am J Neuroradiol*. Published online 2019. doi:10.3174/ajnr.A5928
18. Mokin M, Ansari SA, McTaggart RA, et al. Indications for thrombectomy in acute ischemic stroke from emergent large vessel occlusion (ELVO): report of the SNIS Standards and Guidelines Committee. *J Neurointerv Surg*. 2019;11(3):215 LP - 220. doi:10.1136/neurintsurg-2018-014640

19. 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*. Published online 2018. doi:10.1056/NEJMoa1713973
20. 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*. Published online 2018. doi:10.1056/NEJMoa1706442
21. Zaidat OO, Castonguay AC, Gupta R, et al. North American Solitaire Stent Retriever Acute Stroke registry: Post-marketing revascularization and clinical outcome results. *J Neurointerv Surg*. Published online 2014. doi:10.1136/neurintsurg-2013-010895
22. Zaidat OO, Castonguay AC, Nogueira RG, et al. TREVO stent-retriever mechanical thrombectomy for acute ischemic stroke secondary to large vessel occlusion registry. *J Neurointerv Surg*. Published online 2018. doi:10.1136/neurintsurg-2017-013328
23. Desai SM, Haussen DC, Aghaebrahim A, et al. Thrombectomy 24 hours after stroke: Beyond DAWN. *J Neurointerv Surg*. Published online 2018. doi:10.1136/neurintsurg-2018-013923
24. Vinny PW, Vishnu VY, Srivastava MVP. Thrombectomy for Stroke with Selection by Perfusion Imaging. *N Engl J Med*. Published online 2018. doi:10.1056/NEJMc1803856
25. Wannamaker R, Guinand T, Menon BK, et al. Computed tomographic perfusion predicts poor outcomes in a randomized trial of endovascular therapy. In: *Stroke*. ; 2018. doi:10.1161/STROKEAHA.117.019806
26. Mocco J, Zaidat OO, Von Kummer R, et al. Aspiration Thrombectomy after Intravenous Alteplase Versus Intravenous Alteplase Alone. *Stroke*. Published online 2016. doi:10.1161/STROKEAHA.116.013372
27. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol*. Published online 2016. doi:10.1016/S1474-4422(16)30177-6
28. Muir KW, Ford GA, Messow CM, et al. Endovascular therapy for acute ischaemic stroke: The Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry*. Published online 2017. doi:10.1136/jnnp-2016-314117

29. Munich SA, Shakir HJ, Snyder K V. Role of CT perfusion in acute stroke management. *Cor Vasa*. Published online 2016. doi:10.1016/j.crvasa.2016.01.008
30. Yu W, Jiang WJ. A simple imaging guide for endovascular thrombectomy in acute ischemic stroke: From time window to perfusion mismatch and beyond. *Front Neurol*. 2019;10(MAY). doi:10.3389/fneur.2019.00502
31. Lecouffe NE, Kappelhof M, Treurniet KM, et al. 2B, 2C, or 3: What Should Be the Angiographic Target for Endovascular Treatment in Ischemic Stroke? *Stroke*. Published online 2020:1790-1796. doi:10.1161/STROKEAHA.119.028891
32. Liebeskind DS, Bracard S, Guillemin F, et al. ETICI reperfusion: Defining success in endovascular stroke therapy. *J Neurointerv Surg*. 2019;11(5):433-438. doi:10.1136/neurintsurg-2018-014127
33. Boers AMM, Jansen IGH, Brown S, et al. Mediation of the Relationship Between Endovascular Therapy and Functional Outcome by Follow-up Infarct Volume in Patients With Acute Ischemic Stroke. *JAMA Neurol*. 2019;76(2):194-202. doi:10.1001/jamaneurol.2018.3661

5. Explanation of own contribution

In order to further investigate patients with acute stroke going through mechanical thrombectomy, it is essential to acknowledge the significant role of penumbra salvage volume, which can independently predict clinical outcomes. Besides looking into the relationship between ischemic core and recanalization degree, we investigated that the salvaged volume of ischemic penumbra was independent of baseline ischemic core volume, arguing that penumbra may be rescued even in patients with extensive ischemic core at admission.

Despite all these findings, we should acknowledge that our study faced several limitations, such as the number of patients, exclusion of patients with parenchymal haemorrhage after recanalization, and other natural limitations. The next suggested research step would be to investigate the relationship of PSV and secondary haemorrhage.

6. Acknowledgements

This work would not have been possible without my great team of colleagues, their support and encouragement.

Foremost, I would like to express my deep and sincere gratitude to my supervisor PD Dr. med. U. Hanning for her great support and guidance in every step of this project. Her fruitful feedback and critical thoughts have taught me a lot and helped me greatly in this research.

I would also like to extend my gratitude to Prof. Dr. med. J. Fiehler, Director of the Institute of Neuroradiology, for inspiring me with my thesis topic and giving me the valuable opportunity to do this research in his department.

My sincere thanks also go to PD Dr. med. G. Broocks for his encouragement, great work, and insightful contributions to this work.

Besides my supervisors, I would also like to thank all the co-authors for their contributions.

Last but not least, I would like to thank my family: my wife and parents who have supported me throughout the whole process, believing in me and inspiring me.

7. Curriculum Vitae

„Lebenslauf wurde aus datenschutzrechtlichen Gründen entfernt“

„Lebenslauf wurde aus datenschutzrechtlichen Gründen entfernt“

8. Affidavit

Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: H. Jafarov