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MAGNETIC RESONANCE

Increased volumes of mildly elevated capillary transit time heterogeneity positively predict favorable outcome and negatively predict intracranial hemorrhage in acute ischemic stroke with large vessel occlusion

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Abstract

Objectives In patients with acute ischemic stroke, we aimed to investigate whether microvascular changes, as indexed by capillary transit time heterogeneity (CTH), contribute to the decline of the chance for favorable outcome over time and whether they are a predictor of an intracranial hemorrhage (ICH).

Methods We retrospectively calculated CTH maps for 131 consecutive patients with acute ischemic stroke due to large vessel occlusion of the anterior circulation who had a relevant MRI PWI-DWI mismatch and were treated with endovascular thrombectomy (ET). Multivariable logistic regressions were conducted with favorable outcome (mRS ≤ 2 after 3 months) and occurrence of an ICH as dependent variables and the volume of mildly elevated CTH as independent variable adjusted for age, successful recanalization, hypertension, diabetes, atrial fibrillation, NIHSS score on admission, DWI lesion volume, and symptom-onset-to-treatment time (OTT).

Results A larger volume of mildly elevated CTH was a positive predictor of favorable outcome (OR 1.17; 1.03–1.33; $p = 0.019$) and a negative predictor of ICH (OR 0.83; 0.73–0.96; $p = 0.009$). As expected, successful recanalization (OR 5.54; 1.8–17; $p = 0.003$), low NIHSS on admission (OR 0.9; 0.82–1.00; $p = 0.045$), short OTT (OR 0.96; 0.94–0.99; $p = 0.006$), and low DWI volume (OR 0.68; 0.49–0.94; $p = 0.021$) were also predictors of favorable outcome, whereas other negative predictors of ICH were atrial fibrillation (OR 2.69; 1.10–6.57; $p = 0.030$), high NIHSS score on admission (OR 1.10 (1.01–1.19); $p = 0.030$), and large DWI volume (OR 1.51; 1.17–1.19; $p = 0.002$).

Conclusion An increased volume of mildly elevated CTH is a positive predictor of favorable outcome and a negative predictor for ICH in patients with acute ischemic stroke and mismatch undergoing ET.

Key Points

- *The classification of potentially salvageable tissue and infarct core based on traditional net perfusion parameters (as Tmax or CBF) does not account for the microvascular distribution of blood.*
- *However, the microvascular distribution of blood, as indexed by the capillary transit time heterogeneity (CTH), directly affects the availability of oxygen within the hypoperfused tissue and should therefore be respected in acute ischemic stroke imaging.*
- *In our study, mildly elevated CTH is found to be a positive predictor for a favorable clinical outcome and a negative predictor for the occurrence of an intracranial hemorrhage in patients with acute ischemic stroke and homogenous mismatch who underwent ET.*

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Keywords Stroke · Mechanical thrombectomy · Perfusion imaging · Capillary transit time heterogeneity · Mismatch

Abbreviations

CBF	Cerebral blood flow
CBV	Cerebral blood volume
CTH	Capillary transit time heterogeneity
ET	Endovascular thrombectomy
ICA	Internal carotid artery
LVO	Large vessel occlusion
MCA	Middle cerebral artery
mRS	Modified Rankin scale
MTT	Mean transit time
NECT	Non-enhanced CT imaging
NIHSS	National Institute of Health Stroke Scale
OEF	Oxygen extraction fraction
OTT	Symptom-onset-to-treatment time

Introduction

Endovascular thrombectomy (ET) has been proven to be an effective therapy in acute ischemic stroke caused by large vessel occlusion (LVO) [1]. For patients with clinical-imaging or perfusion-diffusion mismatch, the DAWN and the DEFUSE 3 trials recently showed that this treatment remains efficacious, even in a prolonged time window of up to 24 h [2, 3]. This mismatch approach is a widely accepted method to differentiate between potentially salvageable tissue (the penumbra) and the irreversibly damaged infarct core [4]. The latter can either be identified by MRI (DWI lesion) or CT (e.g., critical relative CBF reduction for CT (perfusion-weighted imaging) PWI [5]) while the penumbra itself is usually defined in terms of its perfusion delay, *T*max [6], which is accessible through bolus-delay insensitive deconvolution techniques [7]. *T*max quantifies the time to the maximum of the residue curve and provides information mainly on bolus delay and dispersion and hence mainly on macrovascular hemodynamics [8]. Although the mismatch approach remains an established method to identify patients that might benefit from ET [9–11], the clinical outcome after ET still remains time dependent. Identical mismatches observed in patients early and late after symptom onset do not seem to have identical prognostic value; rather, the chance of a favorable outcome is lower in the later time windows [12]. While both the EXTEND-IA trial and the DEFUSE 3 trial enrolled patients based on such an imaging-mismatch concept, 71% of the patients who underwent ET had a favorable outcome in the EXTEND-IA trial (OTT < 6 h) [4] compared with only 45% in the DEFUSE 3 trial (6 h < OTT < 16 h) [3].

One potential reason for the poorer predictive value of *T*max late after symptom onset could be its sensitivity to blood supply, but less so to the microvascular distribution of blood [13]. The ischemic penumbra is classically defined in terms of a cerebral blood flow threshold [14], but more recently, it was realized that the microscopic distribution of blood, as indexed by the capillary transit time heterogeneity (CTH), may limit the oxygen extraction efficacy from blood dramatically [15]. In the absence of near-complete occlusion across the capillary bed, traditional net perfusion parameters, such as CBF, the plasma mean transit time (MTT), or *T*max, may not capture or characterize the underlying maldistribution of blood. Thus, even if capillaries remain open in ischemic tissue, cellular oxygen delivery may be impacted by microvascular constrictions [16], and recent studies confirm that knowledge of both blood supply and the microvascular distribution of blood is required to predict tissue fate in ischemia [17].

CTH quantifies the extent of flow heterogeneity within the capillary bed and is robustly accessible through a flexible, model-based Bayesian framework from MRI-DSC perfusion imaging [18, 19]. It characterizes intra-voxel transit times in terms of their standard deviation, in addition to their more commonly used mean, MTT. While the mean transit time is an estimate of voxel-wise net tissue perfusion and is believed to be inversely proportional to local cerebral perfusion pressure [20], the capillary transit time heterogeneity reflects the (intra-voxel) microvascular distribution of blood, and together with MTT, it allows the estimation of the oxygen extraction fraction (OEF) for a given tissue oxygen tension [15]. CTH tends to covary with MTT [21] and hypoperfusion may therefore contribute to elevated CTH, which is associated with some shunting of oxygenated blood through the microvasculature and thereby reduced oxygen extraction efficacy, at normal tissue oxygen tension [15]. On the other hand, in acute ischemic stroke with critically reduced CBF, reduced CTH may represent a relative homogenization of microvascular blood flow patterns as blood starts to bypass occluded parts of the capillary bed, paralleled by subtle reductions in local cerebral blood volume (CBV), but dramatically increased infarct risk [17].

In this work, we therefore hypothesize that there is a regime of mildly elevated CTH which reflects the physiological reaction of the microvascular compartment to critical hypoperfusion and which is a positive predictor of favorable outcome in patients with mismatch undergoing ET. As a surrogate parameter for the integrity of the capillary bed, a larger volume with mildly elevated CTH should also be associated with a reduced risk of intracranial hemorrhage.

Material and methods

This retrospective study was approved by our local ethics committee (statement S-330/2012). Due to the retrospective character of the conducted analysis, requirement of subsequent informed written consent was waived. Further details on the methods can be found in our supplementary material.

Patients

We identified all consecutive patients between 2009 and 2014 with acute ischemic stroke due to internal carotid artery (ICA) occlusion, middle cerebral artery (MCA) occlusion, or the combination thereof, who underwent acute stroke MRI including dynamic-susceptibility-contrast-enhanced perfusion-weighted imaging (DSC-PWI) and subsequent mechanical thrombectomy at our institution ($N = 156$). Favorable clinical outcome was defined as functional independence (mRS ≤ 2) at 3-month follow-up.

Imaging

Images were acquired in the routine clinical workup using 3 T MRI (Magnetom Verio/Trio TIM; Siemens Healthineers) with a 12-channel head matrix coil. DWI was performed using a single-shot spin-echo echo-planar imaging (EPI) sequence with a TR/TE = 5300 ms/90 ms, a flip angle of 90°, and a slice thickness (ST) of 5 mm. Diffusion-sensitizing gradients were applied sequentially in three orthogonal directions with $b = 0$ and $b = 1200$ s/mm^2. T2-weighted images were acquired with TR/TE = 5000 ms/85 ms and ST = 5 mm. DSC-PWI was performed with a T2*-weighted gradient-echo EPI sequence (TR/TE = 1920 ms/36 ms; flip angle, 90°; ST = 5 mm; 50–75 dynamic measurements) and was started simultaneously with bolus injection of a standard dose (0.1 mmol/kg) of intravenous gadoterate meglumine using a pneumatically driven injection pump at an injection rate of 5 mL/s [22]. Follow-up non-enhanced CT imaging (NECT) was carried out in the clinical setting within 18–24 h after ET using a 64-row multislice CT (Somatom Definition AS, Siemens Healthineers) at 120 KV in X-care technique (automatically adjusting the tube current to reduce radiation dose).

Post-processing

To compute CTH maps, the software PGUI (Perfusion Graphical User Interface, http://cfin.au.dk/software/pgui/) was used, which is a non-commercial software which was developed at the Center of Functionally Integrative Neuroscience (CFIN), Aarhus, and which is, by now, used for research purposes only. From a preceding work [23], we learned that typical values for baseline capillary flow heterogeneity (which can be found also in non-hypoperfused tissue) reach up to 5 s. Therefore, values below 5 s were excluded from our analysis. Following further the rationale that typical values of MTT within the penumbra range from 10 to 20 s (e.g., Smith et al found typical MTT values of 13.3 ± 3.5 s within the penumbral tissue [24]), we suspected that for a passive, compliant microvascular compartment (which should be represented by mildly elevated CTH), CTH values should also lie between 10 and 20 s. As a sensitivity analysis, additional thresholds (10–25 s and 10–30 s) were tested as well. Using in-house developed software based on Matlab (Matlab, Mathworks, https://de.mathworks.com/products/matlab.html), thresholds were applied to the CTH maps and automated volumetric analysis was conducted. Thereby, an analysis considering the absolute volume of mildly elevated CTH, as well as an analysis considering the ratio of the volume with mildly elevated CTH compared to the volume with *T*max > 6 s (mildly elevated CTH/*T*max ratio), was conducted.

Statistics

Statistical analysis was conducted using Excel 2010 (Excel 2010, Microsoft Corporation) and SPSS Version 22 (IBM SPSS Statistics, IBM). Depending on the level of measurement, univariate analysis was performed using the Mann-Whitney *U* test or chi-square test/Fisher's exact test. All variables with a p value below 0.25 in the univariate analysis were included in a multivariable regression. Multivariable analysis was performed as complete case analysis using binary logistic regression with backward variable elimination based on likelihood ratio tests, where variables were removed from the analysis if the related p value fell above 0.10. The alpha-level was determined to be 0.05. All reported p values are two-sided.

Results

Baseline patient characteristics

Image quality was evaluated blinded to this analysis, excluding data from 24 patients due to insufficient quality of DSC-PWI or CTH maps, respectively, and data from one patient due to poor DWI quality. Finally, 131 patients were included in this study. All patients underwent endovascular therapy and 129 patients (98%) with stent retrievers. Successful recanalization was achieved in 88 patients (67%). Further baseline characteristics are listed in Table 1. All patients included in this study had a relevant DWI-PWI mismatch (ratio of *T*max > 4 s lesion volume and DWI lesion volume > 1.2, infarct core < 100 mL, minimum perfusion lesion volume of 20 mL).

Table 1 Baseline patient characteristics

N	131
Age	73 (62–79)
Female gender	70 (53%)
Side of stroke (left)	75 (57%)
Risk factors	
• Hypertension	93 (71%)
• Diabetes	20 (15%)
• Hyperlipoproteinemia	37 (29%)
• Current smoker	23 (17%)
• Previous stroke	22 (17%)
• Coronary heart disease	29 (33%)
• Peripheral vascular disease	8 (7%)
• Atrial fibrillation	46 (35%)
Premorbid mRS	
• 0	77 (59%)
• 1	28 (21%)
• 2	16 (12%)
• 3	6 (5%)
• 4	4 (3%)
NIHSS on admission	18 (15–21)
Symptom-onset-to-treatment time (min)	342 (227–493)
DWI volume (mL)	13 (5–25)
Site of occlusion	
• ICA	7 (5%)
• ICA and MCA	19 (14%)
• Carotid T	27 (21%)
• MCA M1	67 (51%)
• MCA M2	11 (8%)
Treatment mode	
• Endovascular therapy alone	39 (30%)
• IV thrombolysis combined with endovascular therapy	92 (70%)
• Stent retriever	129 (98%)
Etiology	
• Atherosclerosis	32 (24%)
• Cardioembolic	70 (53%)
• Other determined etiologies	11 (8%)
• Undetermined etiology	18 (14%)

Data are shown as median (IQR) or *n* (%)

Prediction of a favorable outcome

Predictors with a *p* value below 0.25 in the univariate analysis (Table 2) were included in a following multivariable binary logistic regression analysis (due to a perfect separation, the presence of peripheral vascular disease ($N = 8$ patients of whom all had a poor clinical outcome at day 90) could not be included in this further analysis). While the absolute volume of tissue showing a mildly elevated CTH was included in the multivariable analysis ($p = 0.142$ in the univariate analysis), the mildly elevated CTH/*T*max ratio was not a predictor of a favorable outcome in our cohort ($p = 0.484$ in the univariate analysis).

The multivariable binary logistic regression found the following variables to be independent predictors of a favorable outcome: age (OR 0.96 (0.92–1.00), $p = 0.036$), successful recanalization (OR 5.54 (1.80–17.02), $p = 0.003$), NIHSS on admission (OR 0.90 (0.82–1.00), $p = 0.045$), symptom-onset-to-treatment time (per 10 min increase, OR 0.96 (0.94–0.99), $p = 0.006$), DWI infarct volume (per 10 mL increase, OR 0.68 (0.49–0.94), $p = 0.021$), and, especially, the volume of tissue showing a mildly elevated CTH (per 10 mL increase, OR 1.17 (1.03–1.33), $p = 0.019$), see Table 3.

To consider the effect of different sites of occlusion on the volume of potentially hypoperfused tissue and subsequently on the potential volume experiencing a mildly elevated CTH, we performed additional multivariable logistic regressions for subgroups with (a) excluding MCA M2 and isolated ICA occlusions ($N = 103$) and (b) solitary occlusions of the MCA M1 segment ($N = 62$). The results are shown in Table 3. It is noteworthy that not only the extent of tissue showing a mildly elevated CTH remained a significant predictor of a favorable clinical outcome but also that the effect size increased in these more homogeneous subgroups. As a sensitivity analysis, volumes with mildly elevated CTH were varied randomly up to ± 5% and multivariable logistic regression was repeated. Again, the results of the multivariable logistic regression are confirmed and the volume experiencing a mildly elevated CTH remained a significant predictor of a favorable clinical outcome (OR 1.17 (1.03–1.34), $p = 0.020$). In an additional analysis, the volumes with mildly elevated CTH were compared to final infarct size as assessed on follow-up NECT 18–24 h after ET. However, no significant correlation between mildly elevated CTH and final infarct size could be revealed in our cohort, including subgroup analysis with corrections for recanalization status, OTT, site of occlusion, or initial DWI lesion size.

Prediction of an ICH

As there were only few cases with symptomatic intracranial hemorrhage (ICH), we used ICH of any kind for further analysis. The occurrence of an ICH was significantly related to an unfavorable clinical outcome: of the 50 patients with an ICH, 41 had a poor clinical outcome ($p < 0.001$) and especially all patients suffering from symptomatic ICH had a poor clinical outcome with mRS > 2 at day 90.

Significant predictors of an ICH in the univariate analysis were diabetes ($p = 0.029$), OTT ($p = 0.016$), and DWI infarct core volume ($p = 0.022$). In contrast to the prediction of a favorable outcome, the mildly elevated CTH/*T*max ratio was also found to be a predictor of an ICH in the univariate analysis ($p = 0.026$) (Table 4). Subsequently, multivariable

Table 2 Results of the univariate analysis of patients with a favorable clinical outcome (mRS ≤ 2) or poor clinical outcome (mRS > 2) at 3-month follow-up

	Favorable clinical outcome (mRS 0–2), $N = 49$ (37%)	Poor clinical outcome (mRS 3–6), $N = 82$ (63%)	p value
Age	69 (58–78)	73 (66–79)	0.062
Female gender	29 (59%)	41 (50%)	0.308
Treatment mode (IVT + ET)	40 (82%)	52 (63%)	0.027
Recanalization	42 (86%)	46 (56%)	< 0.001
Risk factors			
• Hypertension	30 (61%)	63 (77%)	0.057
• Diabetes	3 (6%)	17 (20%)	0.024
• Hyperlipoproteinemia	10 (20%)	27 (33%)	0.113
• Current smoker	7 (14%)	15 (20%)	0.415
• Previous stroke	7 (14%)	15 (19%)	0.533
• Coronary heart disease	9 (19%)	20 (25%)	0.393
• Peripheral vascular disease	0 (0%)	8 (11%)	–
• Atrial fibrillation	11 (22%)	35 (43%)	0.019
NIHSS on admission	17 (13–20)	18 (15–22)	0.086
Symptom-onset-to-treatment time (min)	268 (192–425)	407 (246–584)	0.016
DWI volume (mL)	12 (6–20)	13 (5–32)	0.088
Mildly elevated CTH (mL)	60 (38–84)	57 (34–83)	0.142
Mildly elevated CTH/*T*max mismatch ratio	0.74 (0.54–0.87)	0.58 (0.39–0.79)	0.484

Data are shown as median (IQR) or *n* (%). All variables with a p value below 0.25 in the univariate analysis were included in a multivariable logistic regression; the alpha-level in the multivariable analysis was determined to be 0.05

analysis was conducted with the occurrence of an ICH as the dependent variable and adjusted for all predictors with $p < 0.25$ in the univariate analysis (see Table 4), including either the volume with mildly elevated CTH or the mildly elevated CTH/*T*max ratio. The absolute volume with mildly elevated CTH was a significant predictor of ICH (per 10 mL increase, OR 0.83 (0.73–0.96), $p = 0.009$, Table 5). The mildly elevated CTH/*T*max ratio just missed the significance level in the multivariable analysis (OR 0.242 (0.05–1.18), $p = 0.079$). Also, the same subgroup analysis as for the prediction of a favorable clinical outcome was conducted. Again, the volume with mildly elevated CTH not only proved to remain a negative predictor of an ICH; the effect size again increased as the sites of occlusions became more homogenous (Table 5).

Table 3 Multivariable logistic regression with favorable clinical outcome (mRS ≤ 2) as dependent variable

Site of occlusion	Anterior circulation ($N = 116$)		Exclusion of M2- and isolated ICA occlusion ($N = 103$)		Isolated ACM M1 ($N = 62$)	
	OR (CI)	p value	OR (CI)	p value	OR (CI)	p value
Age	0.96 (0.92–1.00)	0.036	0.94 (0.90–0.99)	0.010	0.94 (0.88–1.00)	0.047
Recanalization	5.54 (1.80–17.02)	0.003	6.45 (1.82–22.79)	0.004	18.47 (1.99–172)	0.010
NIHSS on admission	0.90 (0.82–1.00)	0.045	0.89 (0.80–1.00)	0.050	Excluded by backward LR elimination ($p = 0.65$)	
Symptom-onset-to-treatment time (min)	0.96 (0.94–0.99)	0.006	0.96 (0.93–0.99)	0.008	0.97 (0.94–1.00)	0.087
DWI volume (per 10 mL)	0.68 (0.49–0.94)	0.021	0.64 (0.44–0.93)	0.019	0.48 (0.22–1.06)	0.068
Mildly elevated CTH (per 10 mL)	1.17 (1.03–1.33)	0.019	1.17 (1.01–1.36)	0.035	1.32 (1.00–1.72)	0.047

All variables with $p < 0.25$ in the univariate analysis were included in this analysis; variable elimination according to the backward elimination method based on likelihood ratio tests (with a threshold of $p > 0.1$) yielded the stated results. Analysis was conducted for all patients with anterior circulation stroke, as well as for the more homogeneous subgroups (a) with exclusion of M2- and isolated ICA occlusions or (b) with isolated occlusion of the ACM M1 segment

Table 4 Results of the univariate analysis for the occurrence of an intracranial hemorrhage

	ICH $N = 50$ (38%)	No ICH $N = 81$ (62%)	p value
Age	73 (66–78)	70 (59–79)	0.197
Female gender	29 (58%)	41 (51%)	0.411
Treatment mode (IVT + ET)	32 (64%)	60 (74%)	0.221
Recanalization	33 (66%)	55 (68%)	0.822
Favorable clinical outcome	9 (18%)	40 (49%)	< 0.001
Risk factors			
• Hypertension	40 (80%)	53 (65%)	0.074
• Diabetes	12 (24%)	8 (10%)	0.029
• Hyperlipoproteinemia	14 (29%)	23 (28%)	0.983
• Current smoker	6 (13%)	16 (20%)	0.332
• Previous stroke	9 (18%)	13 (16%)	0.733
• Coronary heart disease	9 (19%)	20 (25%)	0.448
• Peripheral vascular disease	2 (4%)	6 (8%)	0.454
• Atrial fibrillation	22 (44%)	24 (30%)	0.094
NIHSS on admission	19 (15–20)	17 (15–20)	0.097
Symptom-onset-to-treatment time (min)	353 (268–520)	336 (206–476)	0.016
DWI volume (mL)	18 (9–36)	12 (4–21)	0.022
Mildly elevated CTH (mL)	55 (34–76)	65 (35–88)	0.101
Mildly elevated CTH/*T*max mismatch ratio	0.53 (0.35–0.76)	0.68 (0.49–0.88)	0.026

Data are shown as median (IQR) or *n* (%). All variables with a p value below 0.25 in the univariate analysis were included in a multivariable logistic regression; the alpha-level in the multivariable analysis was determined to be 0.05

Moreover, statistics are again confirmed by sensitivity analysis where volumes with mildly elevated CTH were varied randomly up to ± 5% (see above) with OR 0.84 (0.73–0.96, $p = 0.011$).

As the definition of mildly elevated CTH was chosen based on theoretical assumptions, we also tested other definitions for mildly elevated CTH as a sensitivity analysis (10–25 s; 10–30 s). The prediction of a favorable outcome and the occurrence of an ICH were found to be robust and statistically significant in multivariable analysis independent of the applied thresholds (see supplementary material). Examples for the effect of mildly elevated capillary transit time heterogeneity can be found in Figs. 1 and 2.

Discussion

In particular in prolonged OTT [2, 3], adequate imaging strategies are required to identify patients potentially benefiting from ET. Traditionally, the classification of potentially salvageable tissue and infarct core is based on net perfusion parameters (as *T*max, MTT and CBV, or CBF). While *T*max

Table 5 Results of the multivariable logistic regression for the occurrence of an intracranial hemorrhage considering variables with $p < 0.25$ in the univariate analysis

	Anterior circulation ($N = 116$)		Exclusion of M2- and isolated ICA occlusion ($N = 103$)		Isolated ACM M1 ($N = 62$)	
	OR (CI)	p value	OR (CI)	p value	OR (CI)	p value
Atrial fibrillation	2.69 (1.10–6.57)	0.030	2.48 (0.98–6.29)	0.056	3.72 (1.02–13.63)	0.047
NIHSS on admission	1.10 (1.01–1.19)	0.030	1.10 (1.01–1.20)	0.026	Excluded by backward LR elimination ($p = 0.155$)	
DWI volume (per 10 mL)	1.51 (1.17–1.19)	0.002	1.53 (1.17–2.00)	0.002	2.47 (1.34–4.54)	0.004
Mildly elevated CTH (per 10 mL)	0.83 (0.73–0.96)	0.009	0.81 (0.69–0.94)	0.006	0.71 (0.54–0.94)	0.015

Again, variable elimination according to the backward elimination method based on likelihood ratio tests (with a threshold of $p > 0.1$) yielded the stated results. As for the prediction of a favorable clinical outcome, analysis was conducted for all patients with anterior circulation stroke, as well as for the more homogeneous subgroups (a) with exclusion of M2- and isolated ICA occlusions or (b) with isolated occlusion of the ACM M1 segment

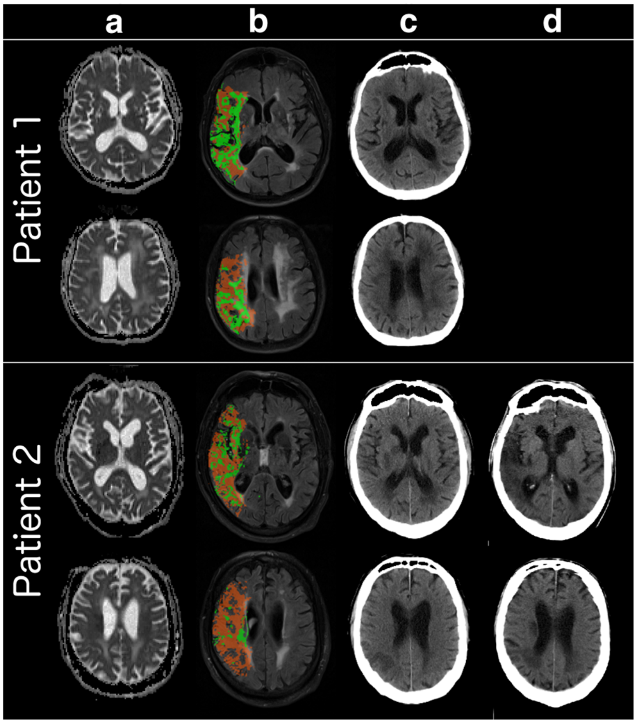

Fig. 1 ADC maps (column a), CTH maps with mildly elevated CTH depicted in green and hypoperfused tissue (*T*max > 4 s) depicted in orange overlaid on T2-imaging (column b), follow-up NECT at day 1 (column c) and at 2-month follow-up (only available for patient 2, column d) on the level of the basal ganglia and above the basal ganglia for two patients with acute M1 occlusion who underwent successful mechanical recanalization. Patient 1 had a substantially larger portion of the right M1 territory exhibiting mildly elevated CTH than patient 2, lower initial and post-treatment NIHSS scores (patient 1 with initial and post-treatment NIHSS scores of 10 and 1 vs. patient 2 with NIHSS scores of initially 17 and post-treatment 10) and better clinical outcome at day 90 (favorable outcome of patient 1 vs. unfavorable outcome of patient 2). The follow-up NECT at day 1 shows no significant infarct demarcation for patient 1, while beginning infarction within the basal ganglia and in the superior posterior MCA territory is visible for patient 2. The additional follow-up NECT after 2 months exhibits the full extent of infarction within the left MCA M1 territory for patient 2

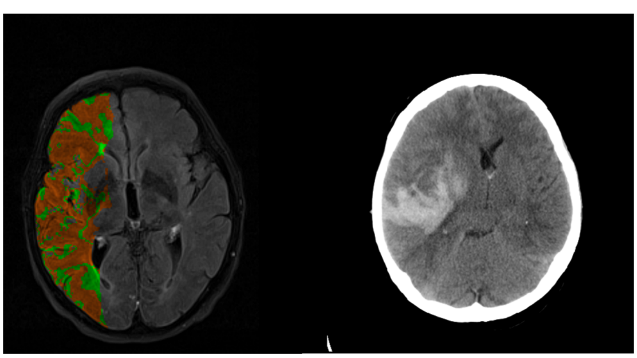

Fig. 2 CTH map (left) and follow-up CT scan (right) of a patient with acute M1 occlusion and symptomatic intracranial hemorrhage on follow-up imaging. CTH map shows only a small portion of the right M1 territory with mildly elevated CTH (depicted in green), whereas a large portion exhibits either severe heterogeneity or homogenization (depicted in orange)

is a parameter of mainly macrovascular hemodynamics [8], CBF and CBV, as well as their ratio MTT, do only account for voxel-wise net perfusion of the macro- and microvascular compartments. They do not describe intra-voxel heterogeneity of blood flow and hence fail to consider the important role of microvascular distribution of blood [13]. Recently, it was realized that the oxygen extraction fraction for a given oxygen tension depends on the capillary transit time heterogeneity, CTH [15]. This dependency becomes especially important in the case of hypoperfusion, when tissue survival hinges upon an intact microvascular compartment and efficient oxygen extraction to compensate for reductions in CBF [25]. We herein present evidence that CTH helps to predict clinical outcome in patients with acute ischemic stroke who present with a homogenous relevant imaging mismatch and undergo ET. The volume showing a mildly elevated CTH was found to be a positive predictor for a favorable clinical outcome at 3 months and a negative predictor for the occurrence of an intracranial hemorrhage after acute ischemic stroke. The effect was found to be robust and consistent throughout the subgroup and sensitivity analyses.

We point out that, so far, no experimental studies have been conducted, which directly compare CTH computed by PWI-MRI with OEF as measured by the gold standard 15O2 positron emission tomography (PET) [26]. This surely presents a limitation of the method and future research should address this limitation. Still, there is a strong theoretical background indicating the relation between CTH and OEF [15, 27] and their connection was confirmed by several model simulations [21]. Further details on the relation between CTH and OEF can be found in the supplementary material.

In our study, the finding of a predictive value only for the volume of tissue showing a mildly elevated CTH is in accordance with the results of previous studies [13, 17]. In a perfect compliant, passive capillary bed, a decreasing perfusion pressure should lead to a capillary transit time heterogenization which is proportional to the prolongation of the mean transit time, MTT [17, 21]. The resulting longer circulation time ensures sufficient oxygenation of the dependent cerebral tissue [17]. In a second regime with beginning microvascular dysfunction (e.g., due to erythrocyte clogging and fibrin aggregation [28, 29]) and increased levels of oxygen and nitrogen radicals related to the ongoing infarction which leads to a constriction of pericytes [30, 31], CTH becomes more severely affected. The results may be twofold. First, the continuing increase of CTH leads to critical "shunting" of oxygenated blood and affects the distribution of erythrocytes in the capillary bed [13]. Especially in combination with a reduced CBF, this will ultimately lead to a critically reduced oxygen extraction efficacy [25] up to the point at which the metabolic need of resting brain tissue can no longer be met. Secondly, severe CTH could make reperfusion futile if CTH fails to normalize after recanalization. Angleys et al described this phenomenon of malign CTH in which the sudden increase in CBF after recanalization could even lead to reduced net oxygen availability by forcing erythrocytes through the capillaries at transit times that are too fast to allow for sufficient oxygen extraction [27]. Østergaard et al showed that both CBF and CTH must normalize (after recanalization) in order to restore tissue oxygen availability to the pre-stroke level [13]. Presumably, disruption of blood-brain-barrier due to microvascular impairments including ischemia-related damage to the basement membrane and to endothelial cells [32] might also explain the robust prediction of an ICH by CTH in our cohort. Especially if CBF is restored with successful recanalization but CTH fails to normalize, large volumes of blood will be shunted through the impaired microvascular compartment possibly triggering the occurrence of an ICH. Finally, in a third regime, severe capillary transit time heterogeneity should be followed by a regime of decreasing CTH as a result of step-wise capillary occlusions. This process was demonstrated by Engedal et al [17] using simulations of a simplified model of the microvascular compartment and corroborated by reductions in CBV in a cohort of acute stroke patients. At the end, capillary transit time homogenization might represent capillary no-flow which also implies critical reduction of CBF and OEF [17]. We point out that our study is not designed to answer pathophysiological questions on whether this capillary no-flow persists and will ultimately lead to infarction independently from successful recanalization. Although there is evidence for a scenario of capillary *no-reflow* in ischemic tissue [33], recent studies hint at that at least a partial reversibility of capillary no-flow is possible [17, 34]. In such a scenario, severe capillary transit time heterogenization as well as capillary transit time homogenization would entail a higher risk of infarction of the dependent, hypoperfused tissue, whereas mildly elevated CTH represents tissue with a lower risk of infarction and better chances for complete regeneration.

We wish to emphasize that in a clinical setting, CTH maps are to understand only in combination with the traditional net perfusion maps, such as *T*max, MTT, CBF, and CBV, owing to the inherent interaction of these parameters not only from a modeling point-of-view but also in the pathophysiological process of infarction [13]. We expect that mildly elevated CTH could be used as a supplementary parameter in acute stroke care. It should be of additional value, whenever there is uncertainty whether a patient will benefit from ET (e.g., in patients with large initial infarct size, extended OTT, or higher premorbid mRS). By voxel-wise comparison of CTH:MTT maps to final infarct on follow-up imaging, Engedal et al [17] found that the ratio of CTH:MTT might further help to predict infarction and classify the penumbra by removing the inherent dependency of CTH and MTT. As most of the current studies use *T*max as net perfusion map, we used this parameter to analyze the ratio of microvascular and macrovascular perfusion. Possibly due to our homogeneous cohort (all patients had a relevant PWI/DWI mismatch [12]), in our study, only the absolute volume of tissue experiencing a mildly elevated CTH and not the CTH/*T*max ratio was found to be a significant predictor of a favorable clinical outcome.

Being a monocentric, retrospective study, our study should be interpreted as hypothesis generating, and the predictive capacities of CTH should be tested in a prospective trial before CTH can be implemented in clinical routine. Moreover, though mildly elevated CTH significantly predicted favorable clinical outcome and ICH, no significant correlation was found between volumes of mildly elevated CTH and final infarct size as assessed on follow-up NECT 18–24 h after ET. The reason for this lack of significant correlation may be twofold. Firstly, measuring final lesion size on CT scans is limited by the modality as scattered small infarctions, especially within white matter, may remain undetected on follow-up CT-scans at day 1. Secondly, the time point at 18–24 h after ET is not ideal for measuring final infarct lesion size. Infarct growth and its temporal evolution are yet not fully understood [35], and infarct growth was observed beyond 24 h after symptom onset [36, 37]. Altogether, the association of CTH and final infarct volume would have to be examined with follow-up DWI/FLAIR to obtain reliable results.

We further point out that it was not possible to use symptomatic intracranial hemorrhage for analysis. The relevance of any intracranial hemorrhages is questionable. However, in our cohort, the occurrence of such an ICH (of any kind) was significantly related to an unfavorable outcome. Moreover, finding the optimum thresholds to classify mildly elevated CTH (in our work ≥ 10 s and < 20s) is challenging, and further work on establishing optimum thresholds might be needed. Still, our thresholds are supported by the rational that typical values of MTT within the penumbra [24], and hence for a passive, compliant microvascular compartment also of CTH, should lie in this range. In contrast, CTH values of about 5 s can be found in healthy tissue as well and may represent baseline heterogeneity there [23, 38]. Finally, a generic drawback of the presented method is the need for a time-consuming MRI protocol within the setting of acute ischemic stroke and further research might concentrate on transferring our results to CT-PWI. Nevertheless, our study population has several strengths: with 131 patients, the sample size is rather large, recanalization was performed either with stent retrievers (98%) or aspiration alone (2%), and the study population is comparable to recent trials on ET in terms of the degree of relevant reperfusion (i.e., mTICI 2b/3; 67% in our study vs. 59–88% [1]). Risk factors and rates of symptomatic ICH are comparable to DEFUSE 2 and MR RESCUE [4, 39].

Conclusion

ET has proven to be an effective therapy in acute ischemic stroke [1] and recent trials expand the time window for carefully selected patients in which ET might be applicable up to 24 h [2, 3]. In the light of these studies, the need for an accurate imaging strategy to identify the patients benefiting from ET becomes apparent. Recent findings suggest that the microvascular distribution of blood, which is not shown by traditional net perfusion parameters, directly affects the availability of oxygen within the hypoperfused tissue and should be respected when identifying the potentially salvageable tissue [13, 17]. As such a parameter, mildly elevated capillary transit time heterogeneity was found to be a positive predictor of favorable clinical outcome and a negative predictor of an intracranial hemorrhage in our cohort of patients with acute ischemic stroke and imaging mismatch who underwent ET.

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Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap The study population differs by only eight patients (in whom PWI quality was not sufficient for CTH analysis) from the cohort in a preceding work by Mundiyanapurath et al [7]. While this preceding work concentrated on the effect of perfusion-diffusion mismatch early or late after symptom onset, we now investigated the role of the perfusion index CTH in regard to the prediction of a favorable outcome and the occurrence of an intracranial hemorrhage after endovascular thrombectomy.

Methodology
• retrospective
• diagnostic study
• performed at one institution

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