Original Contribution

Tissue-Selective Salvage of the White Matter by Successful Endovascular Stroke Therapy

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Background and Purpose—White matter (WM) is less vulnerable to ischemia than gray matter. In ischemic stroke caused by acute large-vessel occlusion, successful recanalization might therefore sometimes selectively salvage the WM, leading to infarct patterns confined to gray matter. This study examines occurrence, determinants, and clinical significance of such effects.

Methods—Three hundred twenty-two patients with acute middle cerebral artery occlusion subjected to mechanical thrombectomy were included. Infarct patterns were categorized into WM^- (sparing the WM) and WM^+ (involving WM). National Institutes of Health Stroke Scale–based measures of neurological outcome, including National Institutes of Health Stroke Scale improvement or National Institutes of Health Stroke Scale worsening, good functional midterm outcome (day 90-modified Rankin Scale score of ≤2), the occurrence of malignant swelling, and in-hospital mortality were predefined outcome measures.

Results—WM^- infarcts occurred in 118 of 322 patients and were associated with successful recanalization and better collateral grades ($P<0.05$). Shorter symptom-onset to recanalization times were also associated with WM^- infarcts in univariate analysis, but not when adjusted for collateral grades. WM^- infarcts were independently associated with good neurological outcome (adjusted odds ratio, 3.003; 95% confidence interval, 1.186–7.607; $P=0.020$) and good functional midterm outcome (adjusted odds ratio, 8.618; 95% confidence interval, 2.409–30.828; $P=0.001$) after correcting for potential confounders, including final infarct volume. Only 2.6% of WM^- patients, but 20.5% of WM^+ patients exhibited neurological worsening, and none versus 12.8% developed malignant swelling ($P<0.001$), contributing to lower mortality in this group (2.5% versus 10.3%; $P=0.014$).

Conclusions—WM infarction commonly commences later than gray matter infarction after acute middle cerebral artery occlusion. Successful recanalization can therefore salvage completely the WM at risk in many patients even several hours after symptom onset. Preservation of the WM is associated with better neurological recovery, prevention of malignant swelling, and reduced mortality. This has important implications for neuroprotective strategies, and perfusion imaging-based patient selection, and provides a rationale for treating selected patients in extended time windows. **(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.117.017903.)**

Key Words: gray matter ■ infarction ■ stroke ■ thrombectomy ■ white matter

Mechanical thrombectomy (MTE) is clinically effective in stroke caused by large-vessel occlusion (LVO),[1–3] but associated risks are not negligible. Some patients will not benefit, and methods to reliably identify such patients before treatment are desirable.

After the large trials of systemic thrombolysis,[4–6] patient selection for acute recanalizing therapies in LVO stroke has traditionally been based on fixed time limits for symptom onset to treatment times. However, time limits do not account for individual differences in the time dependency of tissue viability, which relate to, for example, different degrees of collateralization.[7,8] Consequently, computed tomography (CT)– or magnetic resonance imaging (MRI)–based measurements of tissue perfusion have been developed to discriminate cores of already infarcted tissue from a critically ischemic surrounding penumbra, which is still viable and potentially salvageable, but predicted to progress to irreversible infarction in case of persisting vessel occlusion.

The conceptual foundations of these approaches, however, also contain simplifications. Specifically, they usually apply uniform parameter thresholds for gray matter (GM) and white matter (WM) that do not account for the different metabolic demands and hence different ischemic tolerance[9,10] of these tissues. Experimental evidence shows that the fate of ischemic

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tissue depends on both time and hypoperfusion: with more severe hypoperfusion, penumbra progresses to infarction more rapidly.[9] In LVO stroke, WM may thus remain viable for longer than GM, which implies that recanalizing therapies could sometimes have tissue-selective effects,[11] by salvaging WM, but not GM.

This study, performed in a large cohort of patients with acute occlusion of the middle cerebral artery treated with MTE, is the first to examine the occurrence, time dependency, and clinical benefits of such effects. We hypothesized that successful recanalization would promote infarctions confined to GM, and that such MTE-related preservation of WM would be associated with better outcome.

Patients and Methods

Patient Sample

All consecutive patients (n=409) who were subjected to angiography with the intention to treat an isolated middle cerebral artery occlusion in our center between March 2008 and June 2016 were retrospectively assessed. Eighty-seven of these had to be excluded because of

1. unavailability of adequate follow-up imaging (either postinterventional MRI or postinterventional CT>18 hours after symptom-onset) to assess infarct patterns (because of, eg, early transfer back to the referring hospital, n=72),
2. preexisting neurological deficits that interfered with the assessment of infarct severity of the incident stroke (n=12), and
3. large parenchymal hemorrhage precluding accurate assessment of infarct location and extent (n=3).

The final study population thus consisted of 322 patients.

Endovascular Therapy

Systemic thrombolysis with intravenous r-tPA (recombinant tissue-type plasminogen activator) was used as bridging in all eligible patients (64.0%, n=206). MTE was performed by 1 of 8 experienced neurointerventionalists, almost always with stent retrievers or with direct aspiration with large lumen aspiration catheters (n=296) using standard techniques. Procedures were performed under conscious sedation or with the use of general anesthesia at the discretion of the neurointerventionalist.

Imaging and Clinical Assessment

Preinterventional ASPECTS (Alberta Stroke Program CT Score) was determined in all patients presenting directly to our institution (mothership hospital, n=185), but not in referred patients for whom preinterventional CTs were available from the primary hospital only, to avoid any confounding impact of transport-associated delays. Collateral supply was graded using a 4-step scale as applied by the MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) investigators, with 0 corresponding to 0%, 1 to 0% to 50%, 2 to 50% to <100%, and 3 to 100% filling of the territory distal to the occlusion.[1,12] To ensure technical homogeneity, only patients with high-quality single-phase CT-angiography acquired at the mothership hospital were graded (n=176).

Successful recanalization was defined as Thrombolysis in Cerebral Infarction (TICI) 2b or 3 referring to the original TICI-scale[13] (TICI 2b: reperfusion in ≥2/3 of the initially involved territory). Infarctions were assessed on postinterventional unenhanced CT (NECT; n=160) or MR diffusion–weighted imaging (DWI) and associated apparent diffusion coefficient maps (n=162). Two infarction patterns (IPs), derived from preliminary observations, were predefined (Figure 1): (1) infarctions confined to the GM of the cortex (Figure 1A and 1B), the basal ganglia (Figure 1D), or both (Figure 1C), that is, sparing the subcortical or deep WM, except for (possibly) small numbers (≤5) of disseminated lesions not exceeding 3 mm in maximal diameter (WM$^-$), and (2) infarctions involving both GM and WM (WM$^+$; Figure 2). In addition, postinterventional images (NECT or, in cases with MRI, fluid attenuated inversion recovery-images) were assessed for malignant swelling, defined as swelling of the infarction zone causing midline shifts of ≥10 mm, or prompting hemicraniectomy. Hemorrhagic transformations were rated according to the ECASS criteria (European Cooperative Acute Stroke Study). Infarct volume was assessed on postinterventional diffusion-weighted imaging sequence using the open source software ITK-Snap and a threshold-based algorithm. Resulting segmentations were manually refined where necessary. Images were first assessed independently by 2 experienced neuroradiologists blinded to clinical and MTE-related data and digital subtraction angiography images. A consensus read was performed in cases of discrepant judgments to obtain a unified data set for subsequent analyses.

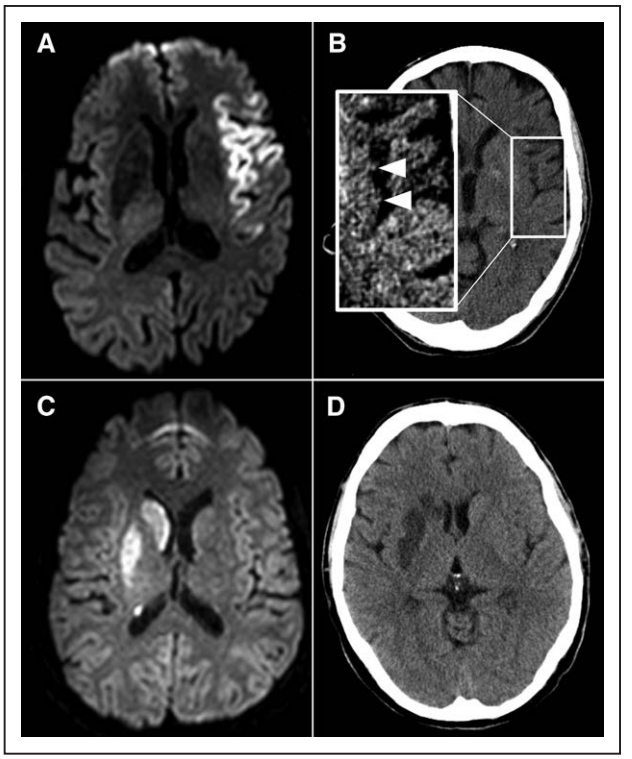

Figure 1. Sample images illustrating patterns of infarctions confined to gray matter (GM), that is, sparing the white matter (WM$^-$). **A** and **B**, Postinterventional diffusion-weighted magnetic resonance imaging (DWI, **A**) and unenhanced CT (NECT) from the same patient (67-year-old man, successfully recanalized with TICI 2b 297 min after symptom onset), illustrating purely cortical (gyral) infarction of the insular cortex and the adjacent frontal operculum. NECT obtained ≈20 hours after symptom onset shows hypoattenuation of the involved cortex, clearly visible in the magnified view (arrows, inset), without recognizable involvement of the WM. **C** and **D**, Postinterventional DWI (**C**) from a 77-year-old woman patient (TICI 3 190 min after symptom onset), and NECT (**D**) from a 61-year-old man (TICI 3 257 min after symptom onset), illustrating WM$^-$ infarctions confined to the GM of the striatum and the cerebral cortex (**C**), or the striatum only (**D**), not involving the internal capsule or other WM in between.

Clinical Outcome Measures

National Institutes of Health Stroke Scale scores at presentation and at discharge from our hospital (NIHSS-PRE, NIHSS-DIS) were assessed by qualified neurologists. A score of 42 was assigned to patients who died during the hospital stay. NIHSS-DIS≤5 was prespecified as a dichotomous measure of good neurological outcome.

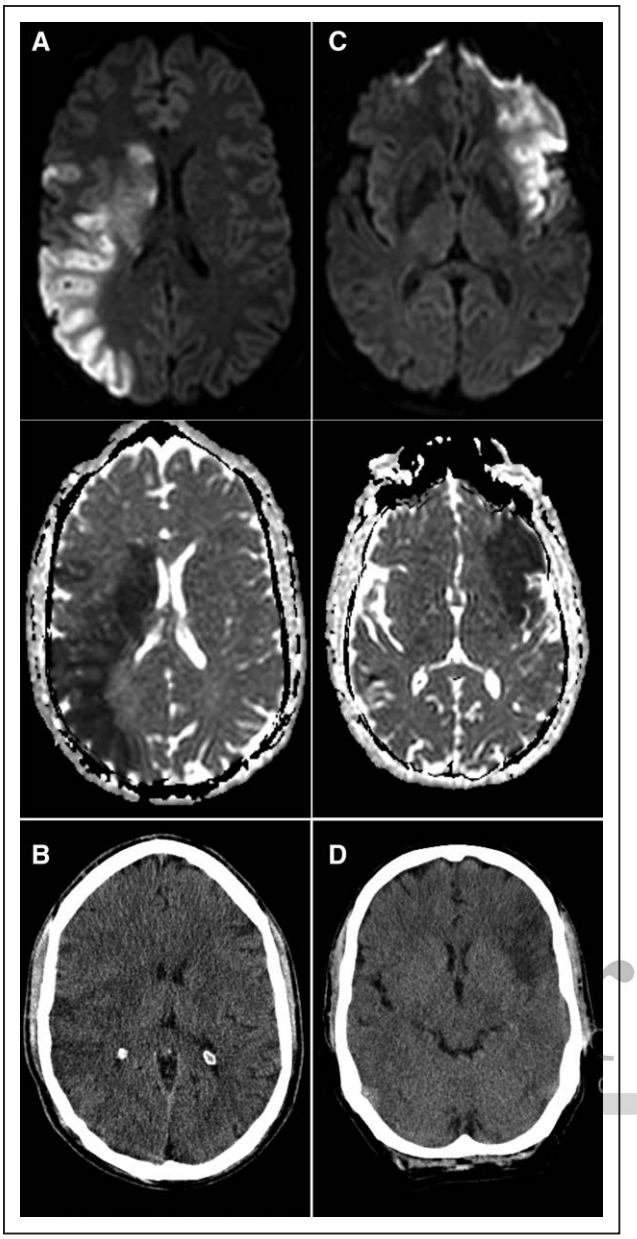

Figure 2. Sample images illustrating infarctions involving both gray matter (GM) and white matter (WM⁺). **A**, Postinterventional diffusion-weighted MRI (DWI) and corresponding apparent diffusion coefficient (ADC) map, and (**B**) unenhanced CT (NECT) from a 36-year-old man patient (TICI 2b 365 min after symptom onset) showing infarctions in the cortical GM and subcortical WM of the temporal and posterior insular cortex, and in the basal ganglia, also involving the anterior limb of the internal capsule. A small purely cortical infarction in the frontal operculum can also be seen. **C**, Postinterventional DWI and ADC-map, and (**D**) NECT from a 65-year-old man patient (TICI 2b 333 min after symptom onset) show infarcts of the cortex and subcortical WM in the frontal lobe and insular region, not involving the basal ganglia.

Δ-NIHSS (NIHSS-PRE–NIHSS-DIS), and dichotomized measures of strong neurological improvement (Δ-NIHSS≥8), and of neurological worsening (Δ-NIHSS<0), respectively, were defined as measures of the postinterventional neurological course. Dichotomized modified Rankin Scale (mRS) score of ≤2 assessed at discharge, available for 292 patients, and on day 90 (d90), available for 217 patients, were defined as good short- and midterm functional outcome, respectively. Occurrence of malignant swelling, as defined above, and in-hospital mortality were prespecified as further outcome parameters.

Statistical Analysis

Interrater agreement was assessed by Cohen κ. A subset of 50 patients with available postinterventional CT and MRI were designated for the evaluation of intermodality agreement. Normally distributed continuous variables were assessed with Welch *t* test, non-normally distributed data with the Mann–Whitney *U* test, and categorical variables with Fisher exact test. Data are displayed as mean±SD if normally distributed, and as median (interquartile range [IQR]) -if non-normally distributed. Binary logistic regression was used for candidate variables with $P<0.1$ in univariate analyses to assess independent determinants of IPs and dichotomized good neurological and midterm functional outcome measures. Results of logistic regression models are shown as adjusted odds ratio (aOR) and 95% confidence interval (CI). To assess improvement of model fit on incorporation of WM involvement, analysis of deviance tables were computed and 5-fold cross-validated receiver operating characteristic curves for both models (with and without WM involvement, respectively) were plotted. Logistic regression was not performed for the prespecified outcome parameters malignant infarction and in-hospital mortality because of small subsample sizes. All statistical analyses were performed with SPSS release 23.0 (IBM Corporation).

All procedures were in accord with the 1964 declaration of Helsinki and its later amendments and approved by the local ethics committee. Written informed consent of individual patients for this anonymized retrospective study was waived according to institutional guidelines.

Results

The mean age of the 322 patients included was 71.9±14.5 years (median, 73.1 years; range, 18–96 years). Median NIHSS-PRE was 14 (IQR, 11–18). Successful recanalization was achieved in 80.4% (n=259). The median symptom-onset to recanalization time (SORT) in substantially recanalized patients (≥TICI 2a) was 269 minutes (IQR, 214–320 minutes).

Infarction Patterns

Interrater agreement as to IPs was excellent (overall κ=0.88), and virtually identical for MRI and NECT-derived ratings (κ_{MRI}=0.88 and κ_{NECT}=0.87), respectively. Intermodality agreement between MRI and NECT was substantial (κ=0.620). According to consensus reads, 13 patients had virtually no recognizable infarcts, and 105 patients had infarcts confined to the GM (of the cortex, of the basal ganglia, or both). As there were no significant differences on candidate determinants between these patients, they were pooled, yielding 2 groups for subsequent analyses: 118 patients (36.6%) with infarcts sparing the WM (WM⁻) and 204 patients (63.4%) with infarcts involving (parts of) the WM (WM⁺).

IPs depended strongly on recanalization success. WM⁻ patterns were observed in 113 of 259 successfully treated patients (43.6%) but in only 5 of 63 (7.9%) after failed recanalization ($P<0.001$) and were associated with shorter SORTs (median, 251 versus 278 for WM⁻ versus WM⁺), better collateral grades (2 [IQR, 1–2] versus 2 [IQR, 1–3]; $P=0.033$), and higher median ASPECTS scores in preinterventional CT imaging (8 versus 9; $P=0.003$). Table 1 summarizes these results. Successful recanalization (aOR, 6.739; 95% CI, 1.974–23.007; $P=0.002$) and better collaterals (aOR, 1.55; 95% CI, 1.019–2.358; $P=0.041$) were associated with the occurrence of WM patterns also in logistic regression models, whereas SORTs were significant

Table 1. Impact of Baseline Characteristics on Infarct Patterns (White Matter⁻ Versus White Matter⁺)

	WM⁺ (n=204)	WM⁻ (n=118)	*P* Values	LR 1 aOR (95% CI) n=272	LR 2 aOR (95% CI) n=147
Age, y	71.5±13.8	72.7±15.7	0.473	…	…
Sex (women)	51.0% (104)	59.3% (70)	0.164	…	…
Intravenous r-tPA bridging	60.8% (124)	69.5% (82)	0.120	…	…
Baseline NIHSS (n=313)	15 (11–18)	14 (10–17)	0.175	…	…
CTA-collateral grade (n=176)	2 (1–2)	2 (1–3)	0.033	…	1.550 (1.019–2.358), *P*=0.041*
SORT, min (n=275)	278 (233–335)	251 (195–300)	0.006†	0.996 (0.993–1.000), *P*=0.024*	0.997 (0.992–1.001), *P*=0.167
Successful recanalization	71.6%	95.8%	<0.001†	6.739 (1.974–23.007), *P*=0.002†	8.403 (1.030–68.563), *P*=0.048*
Diabetes mellitus	16.8%	19.7%	0.546	…	…
Hypertension	75.2%	76.1%	0.893	…	…
Atrial fibrillation	53.0%	53.0%	1.000	…	…
History of stroke or TIA	15.3%	23.1%	0.098	1.361 (0.727–2.546), *P*=0.335	0.773 (0.336–1.779), *P*=0.545

Hierarchical logistic regression models (LR1, LR2), in which LR1 omits, and LR2 includes collateral grade as covariate. WM⁻ denotes infarcts sparing the WM; and WM⁺, infarcts involving WM. aOR indicates adjusted odds ratio; CI, confidence interval; CTA, CT-angiography; LR, logistic regression; NIHSS, National Institutes of Health Stroke Scale; r-tPA, intravenous recombinant tissue-type plasminogen activator; SORT, symptom-onset to recanalization time; TIA, transient ischemic attack; and WM, white matter.

*P<0.05; †P<0.01.

only as long as collaterals were not taken into account (Table 1, compare logistic regression model 1 versus model 2).

Neurological Outcome

WM involvement had strong impact on all prespecified neurological outcome measures (Table 2). In WM⁻ patients, median NIHSS-score improvement (Δ-NIHSS) was 8 (IQR, 5.25–12), as compared with 4 in WM⁺ patients (IQR, 0–8; P<0.001), they had a much higher rate of strong neurological improvement (55.2% versus 28.2%; P<0.001) and, accordingly, much higher rates of good neurological outcome (60.2% versus 20.6%; P<0.001). Similarly, the rate of good functional short- and midterm outcomes was higher in these patients (mRS score of <2 at discharge 23.1% versus 57.3%; P<0.001 and

Table 2. Factors Associated With Good Neurological Outcome (National Institutes of Health Stroke Scale <5)

	No Good Neurological Outcome (n=209)	Good Neurological Outcome (n=113)	*P* Values	LR aOR (95% CI)	LR (including FIV) aOR (95% CI)
Age, y	73.2±13.7	69.6±15.7	0.042*	0.982 (0.963–1.001), *P*=0.067	0.975 (0.949–1.003), *P*=0.077
Sex (women)	53.6% (112)	54.9% (62)	0.907	n.i.	…
Intravenous r-tPA bridging	58.9% (123)	73.5% (83)	0.011*	1.870 (0.989–3.535), *P*=0.054	1.243 (0.460–3.361), *P*=0.668
Baseline NIHSS	16 (13–19)	12 (9–15)	<0.001†	0.797 (0.743–0.855), *P*<0.001†	0.812 (0.729–0.904), *P*<0.001†
SORT, min	289 (236–340)	247 (199–286)	<0.001†	0.994 (0.990–0.998), *P*=0.005†	0.997 (0.991–1.003), *P*=0.348
Successful recanalization	71.8% (150)	96.5% (109)	<0.001†	7.163 (2.280–22.562), *P*=0.001†	2.922 (0.404–21.142), *P*=0.288
WM⁻	22.5% (47)	62.8% (71)	<0.001†	5.353 (2.907–9.858), *P*<0.001†	3.003 (1.186–7.607), *P*=0.020*
FIV, mL	36 (18–88)	10 (4–24)	<0.001†	n.i.	0.980 (0.963–0.997), *P*=0.019*

WM⁻ denotes infarcts sparing the WM. aOR indicates adjusted odds ratio; CI, confidence interval; FIV, final infarct volume; LR, logistic regression; n.i., not included; NIHSS, National Institutes of Health Stroke Scale; r-tPA, recombinant tissue-type plasminogen activator; SORT, symptom-onset to recanalization time; and WM, white matter.

*P<0.05; †P<0.01.

Table 3. Factors Associated With Good Functional Midterm Outcome (d90-Modified Rankin Scale Score of ≤2)

	d90-mRS Score of >2	d90-mRS Score of ≤2	*P* Values	LR aOR (95% CI)	LR (including FIV) aOR (95% CI)
Age, y	74.8±12.3	66.1±16.3	<0.001†	0.936 (0.908–0.964), *P*<0.001†	0.940 (0.898–0.984), *P*=0.008†
Sex (women)	58.8% (60)	53% (62)	0.495	n.i.	n.i.
Intravenous r-tPA bridging	59.8% (61)	71.3% (82)	0.086	1.061 (0.504–2.234), *P*=0.876	0.712 (0.208–2.433), *P*=0.588
Baseline NIHSS	17 (14–19)	13 (9–16)	<0.001†	0.824 (0.759–0.894), *P*<0.001†	0.905 (0.806–1.016), *P*=0.090
SORT, min	281 (233–328)	251 (198–307)	0.096*	0.999 (0.994–1.003), *P*=0.498	1.006 (0.997–1.015), *P*=0.213
Successful recanalization	68.6% (70)	93.0% (107)	<0.001†	5.087 (1.777–14.564), *P*=0.002†	2.695 (0.533–13.615), *P*=0.230
WM⁻	21.6% (22)	60.9% (70)	<0.001†	6.729 (3.028–14.954), *P*<0.001†	8.618 (2.409–30.828), *P*=0.001†
FIV, mL	27 (14–82)	13 (6–31)	0.004†	n.i.	0.989 (0.976–1.001), *P*=0.079

WM⁻ denotes infarcts sparing the WM. aOR indicates adjusted odds ratio; CI, confidence interval; FIV, final infarct volume; LR, logistic regression; mRS, modified Rankin Scale; n.i., not included; NIHSS, National Institutes of Health Stroke Scale; r-tPA, recombinant tissue-type plasminogen activator; SORT, symptom-onset to recanalization time; and WM, white matter.

*P<0.05; †P<0.01.

mRS score of <2 at d90 76.1% versus 36.0%; P<0.001, Figure IA in the online-only Data Supplement).

WM remained an independent factor associated with good neurological (aOR, 3.003; 95% CI, 1.186–7.607; P=0.020) and good functional midterm outcome (aOR, 8.618; 95% CI, 2.409–30.828; P=0.001) after adjusting for age, intravenous r-tPA, baseline NIHSS, SORTs, successful recanalization, and final infarct volume (Tables 3 and 4). WM⁻ versus WM⁺ infarct patterns remained significant independent predictors of good neurological and midterm functional outcome also when ASPECTS scores and collateral grades were accounted for as further potential confounders (Tables I and II in the online-only Data Supplement).

Model fit for mRS score of ≤2 at d90 using age, baseline NIHSS, intravenous r-tPA, SORTs, reperfusion grade, and final infarct volume improved significantly when WM involvement was included into the model (Figure I in the online-only Data Supplement). Including the term WM⁺ versus WM⁻ significantly decreased deviance of models (76.987 versus 91.789, P deviance decrease <0.001) and Akaike information criterion (92.987 versus 105.79).

Shorter SORTs were associated with better neurological and functional outcome (Tables 2 and 4). Of note, however, these associations were strong in WM⁻ patients (Spearman ρ for SORT versus NIHSS-DIS: ρ=0.294, P=0.002; for SORT versus Δ-NIHSS: ρ=−0.396, P<0.001; for SORT versus

Table 4. Outcome Data Stratified According to Infarct Patterns (White Matter⁺ Versus White Matter⁻)

	WM⁺ (n=204)	WM⁻ (n=118)	*P* Values
FIV, mL	33 (16–86)	11 (4–28)	<0.001†
NIHSS-DIS	10 (6–15)	3 (1–7)	<0.001†
Δ-NIHSS (NIHSS-PRE–NIHSS-DIS)	4 (0–8)	8 (5.25–12)	<0.001†
Strong NIHSS improvement (Δ-NIHSS≥8)	28.2%	55.2%	<0.001†
Good neurological outcome (NIHSS-DIS<5)	20.6%	60.2%	<0.001†
Malignant infarction	12.8%	0%	<0.001†
Neurological worsening (Δ-NIHSS<0)	20.5%	2.6%	<0.001†
In-hospital mortality	10.3%	2.5%	0.014*
mRS score of <2 at discharge (n=292 patients)	23.1%	57.3%	<0.001†
mRS score of <2 at day 90 (n=217 patients)	36.0%	76.1%	<0.001†

WM⁻ denotes infarcts sparing the WM; WM⁺, infarcts involving WM; NIHSS-PRE, NIHSS scores at presentation; and NIHSS-DIS, NIHSS scores at discharge. FIV indicates final infarct volume; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and WM, white matter.

*P<0.05; †P<0.01.

d90-mRS: ρ=0.227, *P*=0.031), but less stringent in WM+ patients (SORT versus NIHSS-DIS: ρ=0.171, *P*=0.030; SORT versus Δ-NIHSS: ρ=−0.109, *P*=0.24; SORT versus d90-mRS: ρ=0.096, *P*=0.346).

Neurological Worsening, Malignant Infarction, and Mortality

Postinterventional neurological worsening (NIHSS-DIS worse than NIHSS-PRE) was observed in ≈1 of 5 of WM+ patients, but in only 3 of 118 WM− patients (*P*<0.001). None of the WM− patients developed malignant swelling, but 26 of the 204 (12.8%) with infarctions involving WM did so (*P*<0.001). Malignant swelling was more likely after failed recanalization (22.2% versus 4.6%; *P*<0.001) and associated with longer SORTs (median, 311 versus 265 minutes; *P*=0.004). These associations remained significant when analysis was restricted to WM+ patients (24.1% versus 8.2%, *P*=0.004; median SORTs, 311 versus 271 minutes; *P*=0.017). Also, mortality was substantially lower in WM− than in WM+ patients: 3 of 118 WM− patients, but 21 of 204 WM+ patients died during the hospital stay (2.5% versus 10.3%; *P*=0.014).

Discussion

This study shows that infarctions confined to GM, as far as recognizable with routine clinical diffusion-weighted MRI or NECT, occur frequently after MTE. This cannot be explained by random processes merely biased in favor of the WM−—the reverse pattern (infarctions confined to WM) was never observed—but implies that WM infarction often, if not always, sets in later than GM infarction. As we effectively assessed whether WM infarction had yet commenced, not if it was completed, the average SORTs of WM− patients (median, 251 minutes; IQR, 195–300 minutes) imply that irreversible WM infarction often does not commence until several hours after symptom onset. The present data show that it can therefore sometimes be prevented by successful recanalization, and that this brings clinical benefit.

Early experiments in nonhuman primates have shown that tissue viability in acute middle cerebral artery occlusion depends on both the level of residual perfusion and on the time to restoration of blood flow. This dependency differs in GM and WM, so that WM survives for a longer time than GM at a given degree of hypoperfusion,[9] which may relate to different metabolic demands, and to different neurochemical cascades triggered by the ischemic event.[14,15] More recent positron emission tomography[10] and MRI studies[11,16] have provided evidence for similar differences also in human patients. Accordingly, studies on MR or CT perfusion imaging have determined cerebral blood flow thresholds for irreversible infarction that were lower by ≈40% in WM than in GM.[17,18]

Despite such evidence, the different ischemic tolerance of GM and WM has received little attention in clinical contexts. This may be because of that tissue-selective IPs (confined to GM) could only rarely be observed before the era of thrombectomy. WM− infarctions were observed almost exclusively after successful recanalization, which occurs only rarely with systemic thrombolysis alone in LVO stroke,[19] and only exceptionally spontaneously. In contrast, MTE, as in our study, currently achieves recanalization rates in the order of 80% to 90%, >2.5- to 3-fold higher than systemic thrombolysis,[19] making the different vulnerability of WM and GM a relevant issue.

The better outcome of WM− patients cannot be explained by concomitantly larger GM infarcts associated with WM involvement in WM+ patients: lack of WM involvement was an independent predictor of better outcome also after correcting for total infarct volume. This indicates that WM+ patients, on average, have even worse outcome than WM− patients with infarcts of similar magnitude, suggesting that WM involvement may have additional negative clinical impact, possibly because of disruption of conduction pathways connecting still viable cortex or deep GM.

In addition, patients with salvaged WM never developed malignant infarction. This did not only spare patients secondary damage caused by swelling tissue (reflected in the very low rate of postinterventional neurological worsening observed in this subgroup), and avoided hemicraniectomies (performed in 17/26 patients with malignant WM+ infarctions), but also lowered mortality: more than one third of the in-hospital mortality of WM+ patients (9/24 cases) was directly attributable to malignant swelling, whereas none of the 3 deaths of WM− patients was directly related to the stroke at all. These findings corroborate recent observational data showing a significantly reduced rate of hemicraniectomies after the introduction of MTE with stent retrievers.[20] That salvaging the WM, which comprises ≈40% to 50% of the cerebral tissue volume,[21,22] helps to avert neurological deterioration, malignant swelling, and hemicraniectomies, may seem trivial. However, the important point here is that this potential benefit may often be achievable even by relatively late recanalization.

Recently, updated guidelines recommend endovascular therapy for LVO stroke, but still retain time limits (≤6 hours for the time from symptom onset to start of the procedure), as selection criterion.[23,24] Time limits, however, do not account for variable degrees of hypoperfusion, which modulate the time dependency of tissue damage across patients.[9] Indeed, although our data suggest that WM infarction in middle cerebral artery occlusion often commences only at ≈4.25 to 4.5 hours after symptom onset, there is considerable variability, almost certainly reflecting differences in perfusion and collateralization, and precluding accurate predictions in individual patients. Indeed, the observation that the impact of SORTs on the occurrence of WM− infarct patterns lost significance when adjusting for collateral grades (Table 1) further underpins the importance of collateral supply and is likely to relate to the strongly attenuated impact of time on penumbra loss and clinical outcome in patients with good collaterals reported previously.[7,25] In addition, the less stringent time dependency of outcome parameters in WM+- than in WM− patients suggests that neurological deterioration may slow down at the later stages of infarct evolution also caused by the higher ischemic tolerance of WM, an idea that deserves closer examination in subsequent studies. Overall, this supports the view that rigid time limits are inappropriate criteria for excluding individual patients from MTE, prone to deprive a substantial number of them from potentially beneficial therapy.

Perfusion imaging-based patient selection, in contrast, makes inferences about tissue states and tissue fates from

estimates of the hemodynamic situation at the time of imaging. To date, however, studies failed to prove that this would work sufficiently well in individual patients.[26,27] Moreover, numerous competing definitions and criteria have been proposed in the context of perfusion imaging that may lead to contrary treatment allocations in a substantial proportion of patients.[28] Thus, perfusion-based selection criteria, as commonly applied, may have suboptimal accuracy, and the use of uniform criteria for GM and WM, as in all these studies, may be one contributing factor. In addition, our data speak against simplifying pathophysiological concepts that view infarct evolution as a gradual expansion from a centrally located core to a spatially contiguous surrounding penumbra (Figure 1C). These findings strongly support the use of tissue specific parameter thresholds for GM and WM. If this would suffice to make perfusion-imaging based infarct core and penumbra estimates accurate enough to permit sufficiently precise, clinically useful outcome prediction, however, is still unclear and would have to be ascertained by pertinent studies.

Finally, the present data have relevance in the context of neuroprotection.[22] The neurochemical and cellular processes associated with cell death and tissue damage in GM and WM are distinct.[14,29–31] Arguably, neuroprotective agents have to be tissue specific and need to be applied timely enough to exert positive effects on still viable tissue. The present data imply that the time window may close substantially later for WM- than for GM-neuroprotectants.

The study has limitations because of its retrospective design. IPs were in part determined in NECT images, which are less accurate than MRI. We explicitly chose to include these data because not doing so would have resulted in an unrepresentative sample by preferential exclusion of more severely affected patients, in whom MRI is often impracticable. Extensive analyses including intermodality agreement for CT- and MRI-based data ensured that there were no modality-dependent systematic biases. mRS outcome data could not be retrieved for some patients. However, available mRS-based functional outcome data concurred very well with NIHSS-based neurological outcome measures, which were consistently available, and represent an at least equally appropriate measure to assess therapy related effects in acute stroke.[32,33] Perhaps the most important limitation of the study is that routine clinical MRI or NECT may miss microscopic tissue damage and metabolic alterations, which have been revealed by recent [^{18}F]-Fluoromisonidazole-PET and MR spectroscopy studies in the apparently salvaged ischemic penumbra after recanalization.[34,35] The terminology of complete salvage of the WM in the WM$^-$ patients may thus be too optimistic. This, however, does by no means diminish the relevance of the clearly different susceptibility of WM and GM for macroscopically recognizable tissue damage as revealed by the present study.

In conclusion, this study highlights the different vulnerability of WM and GM in ischemic stroke, which should be taken into account in the contexts of perfusion imaging, and neuroprotection, and provides a rationale for endovascular treatment of selected patients in extended time windows. Further research is warranted to elucidate the interplay between perfusion deficit, and time, and its impact on tissue fate in GM and WM in acute LVO stroke. This will help to understand dynamics and determinants of recanalization-associated benefits in this condition.

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Disclosures

None.

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Tissue-Selective Salvage of the White Matter by Successful Endovascular Stroke Therapy

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ONLINE SUPPLEMENT

Tissue-selective salvage of the white matter by successful endovascular stroke therapy

Salvaging the white matter by thrombectomy

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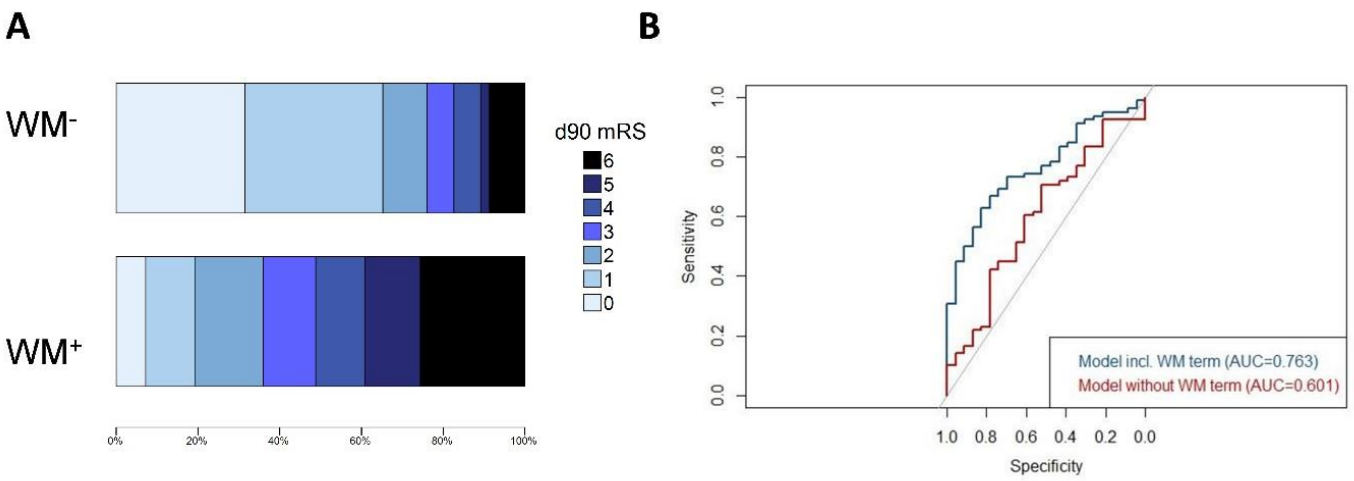
Supplemental Figure I



Supplemental Figure I – Outcome and improvement of model fit according to WM^+ vs WM^-

A) Mid-term functional outcome stratified according to infarct patterns (WM^+ vs WM^-) (n=217) B) 5x cross-validated AUC curves of nested logistic regression models for the endpoint d90 mRS ≤2 with (blue) and without (red) the WM+ vs WM- term. Variables included: Age, baseline NIHSS, IV rtPA, SORTs, reperfusion success and final infarct volume

Supplemental Table I

	No Good neurological outcome (n=209)	Good neurological outcome (n=113)	p	LR 1 Adjusted OR (95%-CI)	LR 2 Adjusted OR (95%-CI)	LR 3 Adjusted OR (95%-CI)
Age	73.2+/-13.7	69.6+/-15.7	0.042*	0.982 (0.963-1.001), p=0.067	0.978 (0.952-1.005), p=0.108	0.975 (0.949-1.003), p=0.077
Sex, female	53.6% (112)	54.9% (62)	0.907	n.i.	n.i.	n.i.
IV rtPA bridging	58.9% (123)	73.5% (83)	0.011*	1.870 (0.989-3.535), p=0.054	1.089 (0.426-2.783), p=0.859	1.243 (0.460-3.361), p=0.668
Baseline NIHSS	16 (13-19)	12 (9-15)	<0.001**	0.797 (0.743-0.855), p<0.001**	0.817 (0.737-0.906), p<0.001**	0.812 (0.729-0.904), p<0.001**
SORT (minutes) (n=275)	289 (236-340)	247 (199-286)	<0.001**	0.995 (0.991-0.999), p=0.012*	0.997 (0.991-1.002), p=0.235	0.997 (0.991-1.003), p=0.348
ASPECTS (n=185)	8 (7-9)	9 (8-10)	<0.001**	n.i.	1.364 (0.977-1.904), p=0.069	n.i.
CTA-Collateral grade (n=176)	2 (1-2)	2 (2-3)	<0.001**	n.i.	1.030 (0.588-1.805), p=0.917	n.i.
Successful recanalization	71.8% (150)	96.5% (109)	<0.001**	7.163 (2.280-22.562), p=0.001**	10.505 (0.910-121.286), p=0.060	2.922 (0.404-21.142), p=0.288
WM-	22.5% (47)	62.8% (71)	<0.001**	5.353 (2.907-9.858), p<0.001**	4.537 (1.882-10.936), p=0.001**	3.003 (1.186-7.607), p=0.020*
Final infarct volume, FIV (ml)	36 (18-88)	10 (4-24)	<0.001**	n.i.	n.i.	0.980 (0.963-0.997), p=0.019*
	WM^-, infarcts sparing the WM; LR, logistic regression; OR, Odds Ratio; IV rtPA, intravenous recombinant tissue plasminogen activator; SORT, symptom-onset to recanalization time; FIV, final infarct volume; n.i., not included					

Supplemental Table I – Factors associated with good neurological outcome (NIHSS<5). Hierarchical logistic regression analyses including an additional model (LR 2) that also accounted for ASPECTS scores and collateral grades. WM^- - vs. WM^+ - infarct patterns remained highly significant predictor of good neurological outcome also after correction for these potentially influential factors. The original analyses (LR 1 and LR 3) as shown in the main text are also displayed for comparison.

Supplemental Table II

	d90 mRS90>2	d90 mRS≤2	p	LR 1 Adjusted OR (95%-CI)	LR 2 Adjusted OR (95%-CI)	LR 3 Adjusted OR (95%-CI)
Age	74.8+/-12.3	66.1+/-16.3	<0.001**	0.936 (0.908-0.964), p<0.001**	0.923 (0.884-0.963), p<0.001**	0.940 (0.898-0.984), p=0.008**
Sex, female	58.8% (60)	53.% (62)	0.495	n.i.	n.i.	n.i.
IV rtPA bridging	59.8% (61)	71.3% (82)	0.086	1.061 (0.504-2.234), p=0.876	0.584 (0.164-2.083), p=0.407	0.712 (0.208-2.433), p=0588
Baseline NIHSS	17 (14-19)	13 (9-16)	<0.001**	0.824 (0.759-0.894), p<0.001**	0.851 (0.742-0.976), p=0.021	0.905 (0.806-1.016), p=0.090
SORT (minutes) (n=275)	281 (233-328)	251 (198-307)	0.096*	0.999 (0.9941.003), p=0.498	0.999 (0.993-1.004), p=0.704	1.006 (0.997-1.015), p=0.213
ASPECTS (n=185)	8 (7-9)	9 (8-9)	0.003	n.i.	1.140 (0.771-1.685), p=0.511	n.i.
CTA-Collateral grade (n=176)	2 (1-2)	2 (2-3)	<0.001**	n.i.	1.558 (0.768-3.161), p=0.219	n.i.
Successful recanalization	68.6% (70)	93.0% (107)	<0.001**	5.087 (1.777-14.564), p=0.002**	2.506 (0.370-16.954), p=0.346	2.695 (0.533-13.615), p=0.230
WM-	21.6% (22)	60.9% (70)	<0.001**	6.729 (3.028-14.954), p<0.001**	7.055 (2.138-23.280), p=0.001**	8.618 (2.409-30.828), p=0.001**
Final infarct volume, FIV (ml)	27 (14-82)	13 (6-31)	0.004**	n.i.	n.i.	0.989 (0.976-1.001), p=0.079
	WM⁻, infarcts sparing the WM; LR, logistic regression; OR, Odds Ratio; IV rtPA, intravenous recombinant tissue plasminogen activator; SORT, symptom-onset to recanalization time; FIV, final infarct volume; n.i., not included					

Supplemental Table II Factors associated with good mid-term functional outcome (d90 mRS <= 2). Hierarchical logistic regression analyses including an additional model (LR 2) that also accounted for ASPECTS scores and collateral grades. WM^- - vs. WM^+ - infarct patterns remained highly significant predictor of mid term functional outcome also after correction for these potentially influential factors. The original analyses (LR 1 and LR 3) as shown in the main text are also displayed for comparison.