Stroke

ORIGINAL CONTRIBUTION

Perfusion Abnormalities on 24-Hour Perfusion Imaging in Patients With Complete Endovascular Reperfusion

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BACKGROUND: Perfusion abnormalities in the infarct and salvaged penumbra have been proposed as a potential reason for poor clinical outcome (modified Rankin Scale score >2) despite complete angiographic reperfusion (Thrombolysis in Cerebral Infarction [TICI3]). In this study, we aimed to identify different microvascular perfusion patterns and their association with clinical outcomes among TICI3 patients.

METHODS: University Hospital Bern's stroke registry of all patients between February 2015 and December 2021. Macrovascular reperfusion was graded using the TICI scale. Microvascular reperfusion status was evaluated within the infarct area on cerebral blood volume and cerebral blood flow perfusion maps obtained 24-hour postintervention. Primary outcome was functional independence (90-day modified Rankin Scale score 0–2) evaluated with the logistic regression analysis adjusted for age, sex, and 24-hour infarct volume from follow-up imaging.

RESULTS: Based on microvascular perfusion findings, the entire cohort (N=248) was stratified into one of the 4 clusters: (1) normoperfusion (no perfusion abnormalities; n=143/248); (2) hyperperfusion (hyperperfusion on both cerebral blood volume and cerebral blood flow; n=54/248); (3) hypoperfusion (hypoperfusion on both cerebral blood volume and cerebral blood flow; n=14/248); and (4) mixed (discrepant findings, eg, cerebral blood volume hypoperfusion and cerebral blood flow hyperperfusion; n=37/248). Compared with the normoperfusion cluster, patients in the hypoperfusion cluster were less likely to achieve functional independence (adjusted odds ratio, 0.3 [95% CI, 0.1–0.9]), while patients in the hyperperfusion cluster tended to have better outcomes (adjusted odds ratio, 3.3 [95% CI, 1.3–8.8]).

CONCLUSIONS: In around half of TICI3 patients, perfusion abnormalities on the microvascular level can be observed. Microvascular hypoperfusion, despite complete macrovascular reperfusion, is rare but may explain the poor clinical course among some TICI3 patients, while a detrimental effect of hyperperfusion after reperfusion could not be confirmed.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cerebrovascular circulation ■ perfusion ■ reperfusion ■ stroke ■ thrombolytic therapy

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Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
aOR	adjusted odds ratio
CBF	cerebral blood flow
CBV	cerebral blood volume
CT	computed tomography
IQR	interquartile range
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
TICI	Thrombolysis in Cerebral Infarction
Tmax	time to maximum

Current guidelines recommend achieving complete reperfusion (Thrombolysis in Cerebral Infarction [TICI3]) for all patients undergoing endovascular therapy, as the degree of reperfusion is one of the strongest modifiable predictors of a good clinical outcome.[1,2] Yet, in more than one-third of all TICI3 patients, recovery and overall prognosis are poor.[3] Potential reasons for achieving poor clinical outcome despite complete reperfusion have been attributed to a large ischemic core on admission, hemorrhagic transformation, poor collaterals, neuroinflammation, or an altered microvascular perfusion status.[4–6]

Postinterventional changes in perfusion status have been observed in both animal and clinical studies. Intricate pathophysiological processes on both macro- and microvascular levels seem to be driving these perfusion alterations.[7] Parameters like cerebral blood flow (CBF) and cerebral blood volume (CBV) can be used to assess relative changes in perfusion status.[8,9] Prior studies have reported inconsistent results on the impact of microvascular reperfusion status on tissue and clinical outcome.[10–15] Microvascular hyperperfusion was initially associated with a good outcome and even suggested as a desirable postinterventional status.[10–12] However, other studies have reported microvascular hyperperfusion as harmful and associated with increased hemorrhage risks.[13–15]

Another perfusion finding that might be of relevance is microvascular hypoperfusion, that is, the no-reflow phenomenon. No-reflow has been reported as being independently associated with worse clinical outcomes.[16] However, the prevalence of no-reflow is still a matter of debate, partially because different definitions for no-reflow have been used in previous studies.[7,16] Additionally, it remains unknown if no-reflow is an epiphenomenon of already infarcted tissue or a biomarker of tissue destined for infarction because studies using serial imaging acquisitions are lacking. A recent review outlined that there are presently no studies evaluating the impact of impaired microvascular reperfusion on functional outcome among patients with complete macrovascular reperfusion.[17] Therefore, we aimed to identify different microvascular reperfusion patterns on 24-hour follow-up imaging and report their association with clinical outcomes among patients with complete macrovascular reperfusion (TICI3).

METHODS

Study Design

This is a retrospective analysis of a single institution's prospective stroke registry for all patients admitted between February 2015 and December 2021. This study received ethics committee approval (KEK ID 231/14 and 2020-01696) and has been conducted according to the outlines of the Declaration of Helsinki. Patient consent was obtained through a general consent form, with a study nurse subsequently offering participants the option to withdraw it. The article follows Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines. Study data are available from the corresponding authors upon request with presented research plan and clearance by the ethics committee.

Study Population

All consecutive acute ischemic stroke patients who were admitted during the study period were considered for eligibility. Only patients fulfilling the following criteria were included in the final analysis: (1) undergoing endovascular therapy, (2) TICI3 reperfusion at the end of an intervention (see details on Reperfusion Grading section below), and (3) undergoing follow-up computed tomography (CT) or magnetic resonance imaging (MRI) perfusion imaging 24 hours after endovascular therapy. Patients with vessel re-occlusion, tandem occlusions, hemorrhagic infarct transformation, and failed perfusion postprocessing on follow-up were excluded from the final analysis (Figure S1). These pathologies were excluded because they may impact the interpretability of susceptibility-weighted perfusion imaging.[7,8] To distinguish between hemorrhage and contrast staining on noncontrast CT, we used time to peak (TTP) and time to maximum (Tmax) perfusion maps, following previously outlined methodology for hemorrhage confirmation on perfusion maps.[8,18]

Neuroimaging

All patients received perfusion imaging on admission and at the 24-hour follow-up, per institutional protocol. Patients underwent either a CT (SOMATOM Definition Edge; Siemens, Erlangen, Germany) or an MRI (1.5/3T MRI Avanto, Avanto fit, Aera, Verio, Skyra fit, and Vida; Siemens). Perfusion postprocessing was performed with syngo.via (Siemens) for CT or Olea Sphere Software (Olea Sphere v2.3; Olea Medical, La Ciotat, France) for MRI. From both software, the following perfusion maps were generated: Tmax, TTP, mean transit time, CBV, and CBF. Volume of radiologically defined infarct on admission and follow-up MRI was calculated on diffusion-weighted imaging using an established nnUNet segmentation algorithm

and after cross-checking by a trained neuroradiologist. The nnUNet algorithm has been benchmarked on a recently published multicenter data set,[19] with the manual correction of the segmentation labels. Volume of radiologically defined infarct on admission and follow-up CT was automatically calculated with syngo.via software using relative CBF <30%. Area of tissue at risk (ie, infarct penumbra) was defined as Tmax >6 seconds on both MRI and CT. For sensitivity purposes, values of Tmax >10 seconds and hypoperfusion intensity ratio for infarct penumbra are also reported.

Reperfusion Grading

Macrovascular reperfusion grading was performed on anteroposterior and lateral digital subtraction angiography images obtained at the end of an intervention. Reperfusion status was graded according to the expanded TICI scale.[20] Microvascular reperfusion status was evaluated on CBV and CBF perfusion maps within the area of radiologically defined infarct on the 24-hour follow-up imaging.[8,9] This was done in 3 consecutive steps. First, noncontrast CT or diffusion-weighted imaging MRI from the 24-hour follow-up examination was used to check the territory of the radiologically defined infarct area. In the second step, the infarct area from these images was coregistered to the corresponding area on CBF and CBV perfusion maps. Lastly, microvascular reperfusion status was assessed qualitatively by comparing reperfusion status in the radiologically defined infarct area to the contralateral homologue in the unaffected hemisphere (Figure S2). Preinterventional CT and MRI images, including perfusion imaging, were screened to exclude cases with pathologies that could potentially confound microvascular reperfusion grading (eg, chronic stenosis, prior infarct, and parenchymal defect). These pathologies have likely altered microvascular status and do not reflect the true microvascular disruption that is seen in acute ischemic stroke.[8,9]

Based on the reperfusion status within the area of radiologically defined infarct on the 24-hour follow-up imaging, microvascular reperfusion was graded as either normal (normoperfusion), increased (hyperperfusion), or decreased (hypoperfusion) when compared with the contralateral side. Grading was performed separately for CBV and CBF maps. For the secondary analysis, we performed microvascular reperfusion grading on the 24-hour follow-up imaging, which was restricted only to the area of initial hypoperfusion (ie, the area of salvageable penumbra from the admission imaging while excluding the area of tissue ischemia predictive of likely infarction, ie, the infarct core). Meaning, this secondary analysis evaluated microvascular reperfusion in oligemic tissue that did not turn into radiologically defined infarct at 24 hours. Again, microvascular reperfusion was stratified into the same clusters as described above. Both macrovascular (on digital subtraction angiography maps with expanded TICI scale) and microvascular (on CBV and CBF perfusion maps) reperfusion grading was done by an independent core laboratory that was not involved in patient treatment and was blinded to clinical outcomes.

Primary and Secondary Outcome

Primary outcome was functional independence, defined as the modified Rankin Scale (mRS) score 0 to 2 at 90 days after the index event. The mRS score was assessed by a neurologist during a scheduled 90-day follow-up examination or by an independent research nurse via a structured telephone interview. Secondary outcomes included changes in the National Institutes of Health Stroke Scale (NIHSS) score and long-term survival. NIHSS score was graded by a qualified neurologist on admission and during routine clinical checkup. Delta NIHSS (ΔNIHSS) was calculated as the difference between NIHSS at discharge and admission, where ΔNIHSS ≥8 was defined as early neurological improvement.[21] Information on long-term survival was extracted from the Swiss Population Registry, which records Swiss residents' vital status and is updated on a monthly basis.[22] For the survival analysis, follow-up time was defined as the time from the index ischemic stroke to the latest update in the registry, or date of death, as captured in the registry. For sensitivity purposes, we have grouped all clusters with perfusion abnormalities together and compared the demographic characteristics and study outcomes between these grouped clusters to the normoperfusion cluster (ie, abnormal versus normal microvascular perfusion).

Statistical Analysis

All results are reported as median (interquartile range [IQR]) or n (percentage, %). Categorical variables were handled with the Fischer exact test and continuous variables with Mann-Whitney *U* test. Interrater agreement for macro- and microvascular reperfusion grading is reported with Krippendorff's alpha coefficient (α). Patient clustering was based on the microvascular reperfusion status of CBV and CBF maps. Clustering was determined with k-means cluster analysis (Methods S1).[23,24]

A complete case analysis was performed. Logistic regression analyses for primary and secondary outcomes were performed for different patient clusters, such that patients without any perfusion abnormalities (ie, patients in the normoperfusion cluster) served as the reference category. Cox regression was performed for the long-term survival analysis. All regression analyses were adjusted for age, sex, and infarct volume from 24-hour follow-up imaging. Analyses on mRS and long-term survival were additionally adjusted for the NIHSS score on admission. ΔNIHSS assumes that admission NIHSS is linearly related to discharge NIHSS, which might not reflect clinical reality.[25] To overcome this limitation of ΔNIHSS and reduce reporting bias in observational studies, we used the ANCOVA model to assess the difference in NIHSS at discharge between the perfusion clusters.[25] Dependent variable was NIHSS at discharge, and the model was adjusted for age, sex, 24-hour infarct volume, and NIHSS score on admission. Results from logistic and cox regression analyses are reported as adjusted odds ratios (aORs) or adjusted hazard ratios (aHRs) with the corresponding 95% CIs. Statistical handling of the outcome variables was as follows: functional independence (mRS, 0–2 versus 3–6) and early neurological improvement (ΔNIHSS <8 versus ≥8 points difference). All statistical analysis and data visualization were performed in R, v4.3.0.

RESULTS

Two hundred and sixty-six patients were included in the analysis (Figure S3). The mean age of the final cohort was 75 (IQR, 63–82) years, 49.2% were female, 85.7% had MRI on admission, and 84.6% had MRI on

follow-up. Compared with patients without perfusion imaging on follow-up, those with perfusion imaging were on average younger and presented with less comorbidities (Table S1).

Based on the microvascular reperfusion status in the 24-hour follow-up infarct, all patients were grouped into one of the 4 clusters: normoperfusion, hyperperfusion, hypoperfusion, and mixed cluster (Figure 1). The normoperfusion cluster included patients who showed no perfusion abnormalities on neither CBV nor CBF (Figure 1A). The hyperperfusion cluster included patients who had hyperperfusion on both CBV and CBF (Figure 1B). Correspondingly, the hypoperfusion cluster included patients who had hypoperfusion on both CBV and CBF maps within the established infarct area (Figure 1C). All patients who had discrepant ratings (eg, hypoperfusion on CBV and hyperperfusion on CBF) were classified into the mixed cluster (Figure 1D). Silhouette Index of 0.8 suggested good classification within- and discrimination between-clusters (Figure S4). Interrater agreement for expanded TICI evaluation and clustering was very good (α=0.90 [95% CI, 0.85–0.92] and 0.92 [95% CI, 0.88–0.94], respectively). Agreement was also good on individual assessments of CBV and CBF maps (α=0.98 [95% CI, 0.95–0.99] and 0.93 [95% CI, 0.90–0.94], respectively).

Baseline and interventional characteristics across different clusters are presented in the Table. In comparison with the other clusters, patients in the hyperperfusion cluster were less likely to have hypertension, had lower ASPECTS and lower NIHSS on admission, were more likely to have an M1 occlusion, and had received intravenous thrombolysis. The mean Tmax >6 seconds volume was 82 mm^3 (IQR, 43–121), Tmax >10 seconds was 38

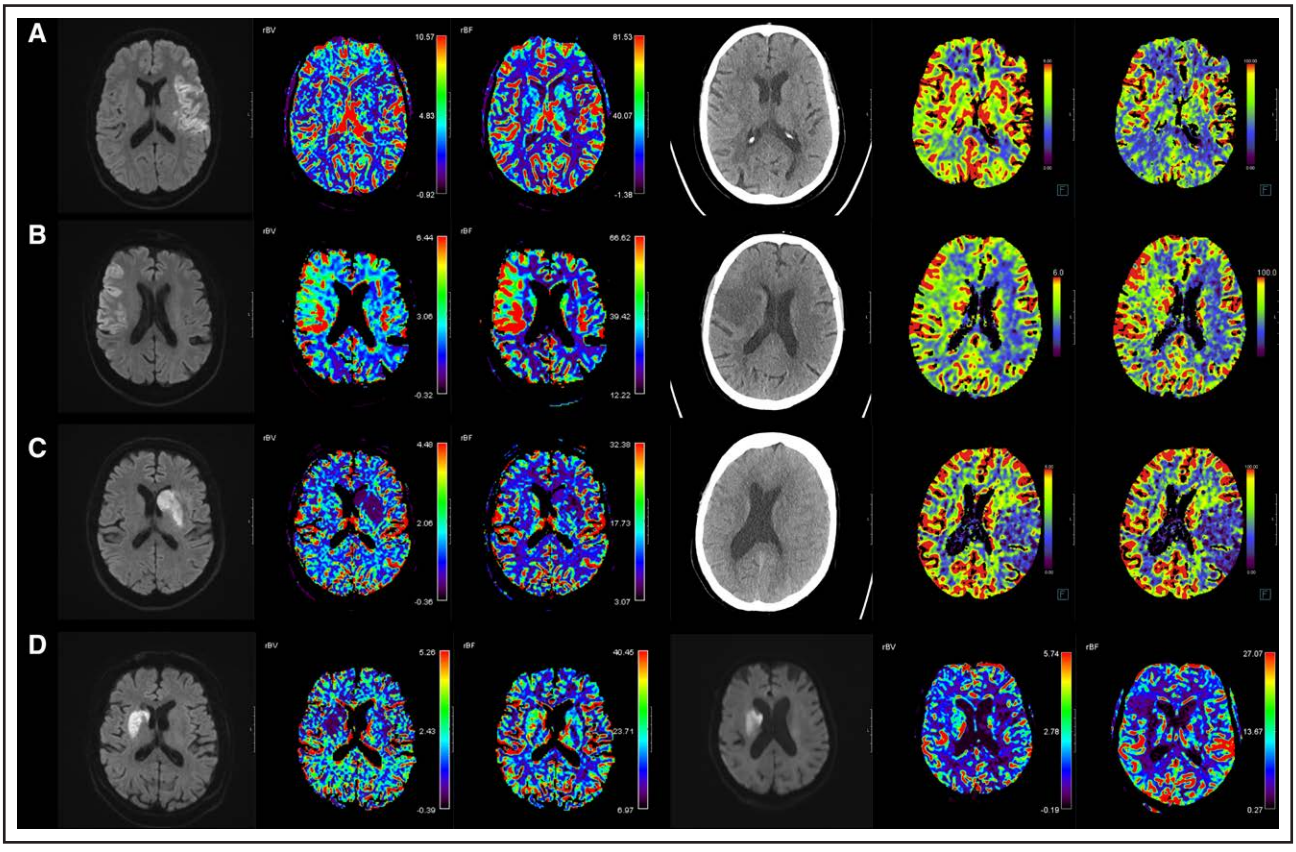

Figure 1. Patient clusters.
A, Normoperfusion cluster. Left side: Follow-up DWI of a patient after a left-side M1 occlusion. Right-side: Follow-up NCCT of a patient after a right-side M1 occlusion. In both cases, there was no discernible increase or decrease of perfusion parameters in the area of radiologically defined infarct on neither CBV nor CBF perfusion maps. **B**, Hyperperfusion cluster. Left side: Follow-up DWI of a patient after a right-side ICA occlusion. Right-side: Follow-up NCCT of a patient after a right-side M1 occlusion. In both cases, there was microvascular hyperperfusion in the area of radiologically defined infarct on both CBV and CBF perfusion maps. **C**, Hypoperfusion cluster. Left side: Follow-up DWI of a patient after a left-side M1 occlusion. Right-side: Follow-up NCCT of a patient after a left-side M1 occlusion. In both cases, there was microvascular hypoperfusion in the area of radiologically defined infarct on both CBV and CBF perfusion maps. **D**, Mixed cluster. Left-side: Follow-up DWI of a patient after a right-side M2 occlusion. On CBV we observe microvascular hypoperfusion, while on CBF we observe microvascular hyperperfusion in the area of radiologically defined infarct. Right-side: Follow-up DWI of a patient after a right-side M2 occlusion. On CBV we observe microvascular hyperperfusion, while on CBF we observe microvascular hypoperfusion in the area of radiologically defined infarct. CBF indicates cerebral blood flow; CBV, cerebral blood volume; CT, computed tomography; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; and NCCT, noncontrast CT.

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Table. Cohort Characteristics

	Overall	Normoperfusion	Mixed	Hyperperfusion	Hypoperfusion	*P* value
N	266	142	52	55	17	
Baseline						
Age (median [IQR])	75 [63, 82]	75 [65, 82]	77 [62, 83]	67 [63, 79]	76 [63, 81]	0.32
Female sex, %	131 (49.2)	72 (50.7)	28 (53.8)	25 (45.5)	6 (35.3)	0.532
Atrial fibrillation, %	108 (40.6)	58 (40.8)	22 (42.3)	21 (38.2)	7 (41.2)	0.977
Coronary heart disease, %	38 (14.3)	19 (13.4)	10 (19.2)	9 (16.4)	0 (0.0)	0.245
Diabetes, %	48 (18.0)	27 (19.0)	10 (19.2)	7 (12.7)	4 (23.5)	0.674
Hyperlipidemia, %	175 (65.8)	94 (66.2)	31 (59.6)	37 (67.3)	13 (76.5)	0.613
Hypertension, %	181 (68.0)	97 (68.3)	41 (78.8)	30 (54.5)	13 (76.5)	0.047
Smoking, %*	65 (24.6)	33 (23.4)	15 (28.8)	14 (25.9)	3 (17.6)	0.775
Systolic blood pressure (median [IQR])	155 [133, 174]	156 [138, 172]	153 [131, 189]	155 [130, 173]	150 [128, 158]	0.56
Diastolic blood pressure (median [IQR])	83 [72, 96]	84 [72, 95]	84 [72, 98]	81 [71, 93]	80 [75, 95]	0.854
Antihypertensives prestroke, %	162 (60.9)	90 (63.4)	30 (57.7)	30 (54.5)	12 (70.6)	0.533
Anticoagulants prestroke, %*	48 (18.2)	28 (19.9)	11 (21.2)	6 (10.9)	3 (18.8)	0.469
Antiplatelets prestroke, %	78 (29.3)	42 (29.6)	15 (28.8)	15 (27.3)	6 (35.3)	0.937
mRS prestroke (median [IQR])	0 [0, 1]	0 [0, 1]	0 [0, 1]	0 [0, 0]	0 [0, 0]	0.117
NIHSS on admission (median [IQR])	11 [5, 18]	8 [4, 15]	15 [9, 20]	11 [5, 17]	19 [6, 22]	0.001
Time of symptom onset known (%)						0.527
No	53 (19.9)	28 (19.7)	14 (26.9)	8 (14.5)	3 (17.6)	
Wake up	31 (11.7)	16 (11.3)	5 (9.6)	6 (10.9)	4 (23.5)	
Yes	182 (68.4)	98 (69.0)	33 (63.5)	41 (74.5)	10 (58.8)	
Onset-to-admission time, h (median [IQR])†	2.20 [1.25, 4.27]	2.00 [1.19, 4.10]	2.23 [1.24, 4.84]	2.28 [1.26, 3.49]	3.70 [1.80, 11.13]	0.066
Imaging						
Admission imaging on MRI, %	228 (85.7)	118 (83.1)	47 (90.4)	46 (83.6)	13 (76.5)	0.249
ASPECTS on admission (median [IQR])	9 [8, 10]	9 [8, 10]	8 [7, 9]	9 [8, 9]	8 [8, 9]	<0.001
Tmax >10 s (mm^3; median [IQR])	38 [15–78]	36 [15–73]	70 [22–109]	35 [15–58]	49 [15–92]	0.038
Tmax >6 s (mm^3; median [IQR])	82 [43–121]	75 [39–117]	113 [47–180]	77 [46–116]	82 [45–117]	0.024
Hypoperfusion intensity ratio, mm^3 (median [IQR])	0.50 [0.34–0.63]	0.50 [0.35–0.65]	0.56 [0.34–0.65]	0.47 [0.31–0.54]	0.53 [0.32–0.65]	0.027
Infarct core volume on admission, mm^3 (median [IQR])	6.59 [1.45–24.83]	4.75 [0.53–15.52]	29.94 [5.23–55.42]	7.91 [3.41–22.31]	11.38 [3.41–28.32]	<0.001
Infarct core volume on admission, mm^3 (median [IQR]) MRI patients only (228/266)	5.24 [1.37–20.55]	2.33 [0.34–10.99]	20.82 [5.37–45.20]	6.90 [3.41–15.32]	14.91 [2.55–20.51]	<0.001
Intervention						
Occlusion sites, %*						0.005
ICA	43 (16.3)	16 (11.3)	16 (30.8)	7 (12.7)	4 (25.0)	
M1	113 (42.8)	56 (39.7)	24 (46.2)	28 (50.9)	5 (31.2)	
M2	61 (23.1)	41 (29.1)	9 (17.3)	11 (20.0)	0 (0.0)	
M3	2 (0.8)	1 (0.7)	0 (0.0)	1 (1.8)	0 (0.0)	
A1–A2	2 (0.8)	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	
Posterior circulation	43 (16.3)	25 (17.7)	3 (5.8)	8 (14.5)	7 (43.8)	
Intravenous thrombolysis, %	115 (43.2)	61 (43.0)	15 (28.8)	31 (56.4)	8 (47.1)	0.039
Number of passes (median [IQR])§	1 [1, 2]	1 [1, 2]	1 [1, 2]	1 [1, 2]	1 [1, 2]	0.091
Intervention to follow-up time, h (median [IQR])*	21.43 [17.44, 24.45]	21.42 [17.44, 24.58]	21.47 [18.03, 24.64]	21.65 [17.47, 23.63]	20.87 [14.42, 24.33]	0.936
Outcome						
Follow-up imaging on MRI, %	225 (84.6)	117 (82.4)	46 (88.5)	50 (90.9)	12 (70.6)	0.147

(*Continued*)

Table. Continued

	Overall	Normoperfusion	Mixed	Hyperperfusion	Hypoperfusion	*P* value
Infarct core volume on follow-up, mm³ (median [IQR])†	4.76 [1.00, 14.92]	1.78 [0.43, 6.05]	19.19 [5.79, 42.66]	6.58 [3.11, 11.70]	17.38 [6.54, 37.13]	<0.001
NIHSS at discharge (median [IQR])†	1 [0, 4]	1 [0, 2]	3 [1, 9]	2 [0, 3]	6 [3, 16]	<0.001
90-d mRS (median [IQR])*	1 [0, 3]	1 [0, 3]	2 [1, 4]	1 [0, 2]	3 [2, 4]	0.001
90-d mRS 0–2 (%)*	181 (68.6)	97 (69.3)	32 (61.5)	47 (85.5)	5 (29.4)	<0.001
Long-term mortality, %§	59 (22.8)	30 (21.7)	17 (32.7)	9 (17.3)	3 (17.6)	0.248

ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; IQR, interquartile range; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Data point missing for 2 patients.

†Data point missing for 3 patients.

§Data point missing for 5 patients.

mm³ (IQR, 17–78), and the mean infarct core volume was 6.59 mm³ (IQR, 1.45–24.83). On average, patients with hyperperfusion tended to have lower Tmax of >6 and >10 seconds (*P*=0.02), as well as mean infarct volume (*P*<0.001). When all clusters with perfusion abnormalities were grouped together and compared with the cluster with microvascular normoperfusion, patients in the microvascular normoperfusion cluster tended to have lower NIHSS at admission (8; IQR, 4–15 versus 14; IQR, 6–19; *P*=0.001) and more distal occlusions (eg, M2 of 29.1% versus 16.3%; *P*=0.035). Other characteristics, including the choice of follow-up imaging (MRI versus CT), were comparable between the groups (Table S2). When mixed clusters were stratified into subclusters based on different CBV and CBF patterns, there were no differences in baseline and intervention characteristics between these subclusters (Table S3).

Patients in the hypoperfusion cluster were less likely to achieve functional independence (aOR, 0.3 [95% CI, 0.1–0.9]; Figure S5) and tended to have lower rates of early neurological improvement (aOR, 0.5 [95% CI, 0.2–1.5]; Table S4). Conversely, patients in the hyperperfusion cluster had higher odds of being functionally independent (aOR, 3.3 [95% CI, 1.3–8.8]) and having early neurological improvement (aOR, 2.0 [95% CI, 1.1–3.9]; Figure 2). There were no differences in outcomes for the patients in the mixed cluster when compared with the normoperfusion cluster (aOR, 1.8 [95% CI, 0.7–4.9] and 1.5 [95% CI, 0.7–3.2] for mRS 0–2 and Δ NIHSS ≥8, respectively). Comparable results for early neurological improvement were obtained with the ANOCVA model (F value, 7.2; *P*<0.001, for differences between the clusters). For the secondary analysis, we also looked at the outcomes when clusters were stratified according to the microvascular reperfusion status in the area of initial hypoperfusion, that is, salvageable penumbra. When clusters were stratified according to the microvascular reperfusion status in the salvageable penumbra, point estimates across outcomes showed comparable associations as in the main analysis. However, now only the association between microvascular hyperperfusion and functional independence remained significant (aOR, 2.4 [95% CI, 1.1–5.7]; Figure S6).

Long-term survival was comparable between the patients in the hypo-, hyper-, and mixed clusters (aHR, 0.7 [95% CI, 0.2–2.5]; aHR, 0.9 [95% CI, 0.4–1.9]; and aHR, 1.2 95% CI, 0.6–2.5], respectively; Figure S7). There was also no difference in long-term survival when all patients with altered microvascular perfusion status were grouped together and compared with the patients in the normoperfusion cluster (aHR, 0.9 [95% CI, 0.5–1.7]). Results from the sensitivity analysis on microvascular reperfusion status in the salvageable penumbra showed comparable results (Figure S8).

DISCUSSION

This study aimed to identify different microvascular reperfusion patterns among patients with complete macrovascular reperfusion (TICI3). Main findings of this study are as follows: (1) approximately half of patients with complete macrovascular reperfusion demonstrate perfusion abnormalities at the microvascular level; (2) based on microvascular reperfusion status, patients can be classified into one of the 4 distinct clusters: normo-, hypo-, hyperperfusion, and mixed patterns; and (3) patients with microvascular hypoperfusion tended to have a poor prognosis despite complete macrovascular reperfusion, whereas patients with microvascular hyperperfusion had a better overall outcome.

Microvascular Perfusion Patterns

Microvascular reperfusion abnormalities among patients with successful macrovascular reperfusion (≥TICI2b) are not uncommon. Approximately 20% to 50% of all ≥TICI2b patients experience either microvascular hypo- or hyperperfusion on follow-up imaging.[7,10–12] Fluctuation in microvascular reperfusion rates seems to depend on the final reperfusion score (TICI2b, 2c, and 3), perfusion imaging modality used for the evaluation of microvascular reperfusion (CBV, CBF, mean transit time, and Tmax) or time passed from intervention to follow-up imaging (12–72 hours).[7,10–12]

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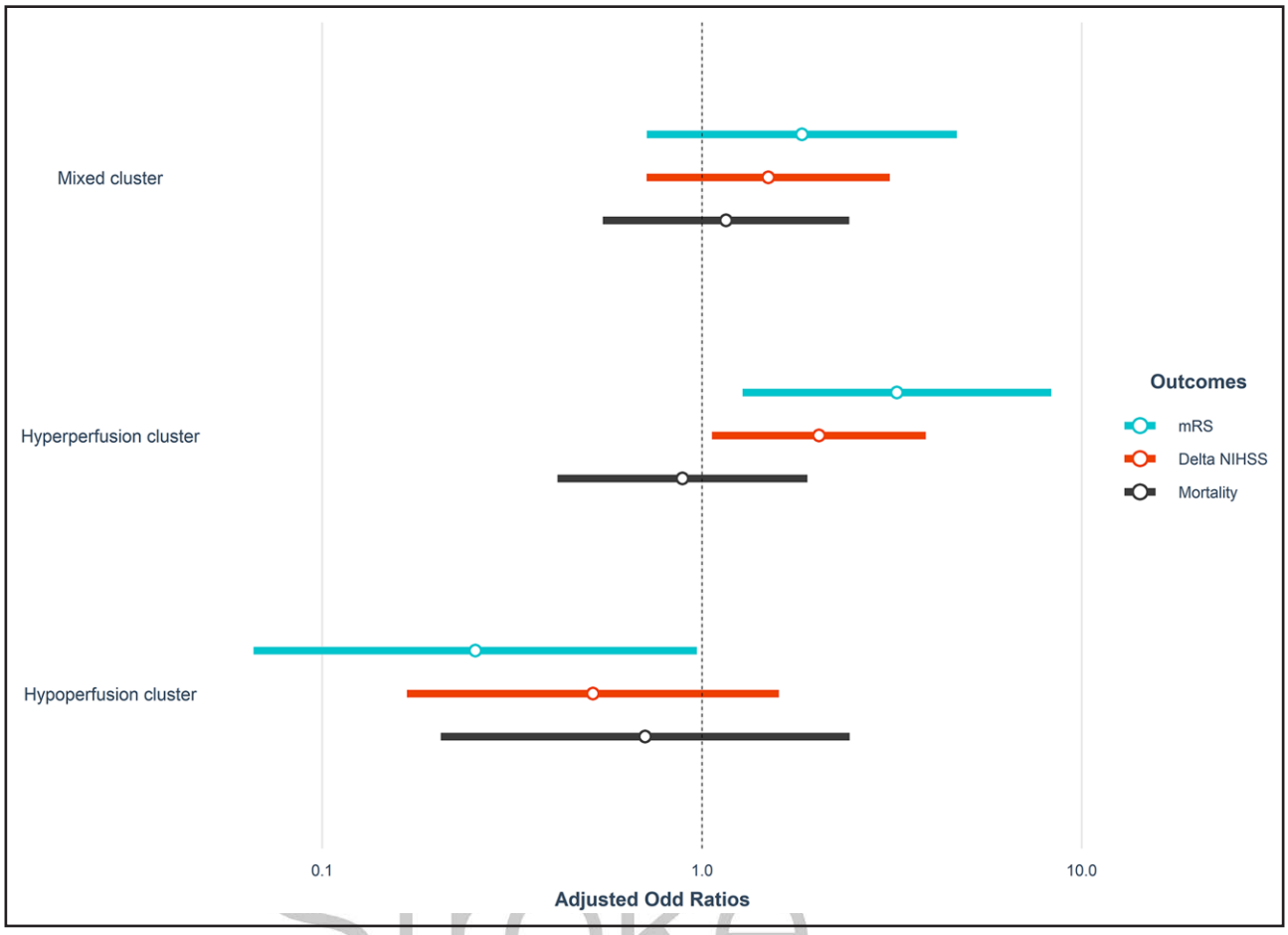

Figure 2. Forest plot for clinical outcomes.
Patients with microvascular hypoperfusion had a lower likelihood for achieving functional independence (mRS 0–2: aOR, 0.3 [95% CI, 0.1–0.9]) and early neurological improvement (Δ NIHSS: aOR, 0.5 [95% CI, 0.2–1.5]). Conversely, patients with microvascular hyperperfusion had a higher likelihood for both functional independence and early neurological improvement (aOR, 3.3 [95% CI, 1.3–8.8] and 2.0 [95% CI, 1.1–3.9], respectively). aOR indicates adjusted odds ratio; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

A recent study reported 3 distinct postischemic microvascular perfusion patterns in an area of established radiologically defined infarct: hypoperfusion, hyperperfusion, and unaffected perfusion pattern.[11] In that study, patients were classified according to the patterns on CBF maps on 24-hour follow-up imaging. We observed similar clustering patterns in our analysis, with the addition of another cluster (mixed) due to the use of 2 different perfusion maps (CBV and CBF) for the evaluation of microvascular reperfusion. Both CBV and CBF maps were used due to their sensitivity in detection of microvascular reperfusion and to mitigate the risk of false-positive ratings when only 1 perfusion map is used.[8,9] Having 4 individual clusters, 3 of which show distinct perfusion abnormalities and 1 with normalized perfusion, may help streamline further clinical management and research efforts in the area of microvascular reperfusion. Imaging outcomes are readily available after the intervention, and depending on when they are performed after the intervention, they may inform acute or postacute patient management.

Clinical Outcomes

The prognostic value of microvascular reperfusion status has been subject to much debate. Microvascular hypoperfusion has been previously associated with postinterventional infarct expansion and early neurological deterioration,[10,11] while hyperperfusion was considered predictive of favorable clinical outcome.[10,12] However, some studies have also associated hyperperfusion with a higher likelihood of poor outcome and considered it a reflection of extended ischemic damage.[13–15] In the present analysis, we observed that patients with microvascular hyperperfusion had a higher likelihood for a better outcome, while patients with microvascular hypoperfusion tended to do worse. Comparable findings were observed when analyzing the area of salvageable penumbra only. Although the pathophysiological mechanisms of microvascular hyperperfusion are not yet fully understood, it has been hypothesized that it is a response to acute ischemia with loss of autoregulation and subsequent vasodilation.[26,27] This might impact the cellular transport

speed and turnover of inflammatory mediators.[26,27] Microvascular hyperperfusion may therefore be protective and preserve tissue that is not irreversibly damaged (ie, salvageable penumbra). Hyperperfusion might also preserve some tissue within the area of the infarct core that did not yet undergo complete infarction, due to the heterogeneity in tissue vulnerability within the core itself.[28]

Despite the relative benefits of microvascular hyperperfusion, it seems to be of limited value in long-term patient survival. There are several potential explanations for this. We have only included patients with core laboratory-evaluated complete macrovascular reperfusion (TICI3). This might explain high long-term survival rates, as TICI3 patients generally have favorable long-term outcome.[3] By including TICI3 patients only, we have reduced the risk of rating some perfusion abnormalities as changes in microvasculature that may simply be present due to residual vessel occlusions. We have also excluded patients with re-occlusions, tandem occlusions, and hemorrhagic tissue transformation because estimating microvascular reperfusion status among these patients is challenging and perfusion maps alone might not be sufficient for microvascular status evaluation.[7] Posttreatment perfusion imaging findings may reflect preexisting abnormalities. Patients with hyperperfusion tended to have a lower volume of tissue at risk (ie, penumbra) and tissue predictive of likely ischemia (ie, core), which could partially explain the higher likelihood of a better outcome in this cluster. Preinterventional perfusion findings, especially in the penumbra, ought to be considered in studies targeting the postreperfusion period. These preinterventional findings might aid not only in treatment target identification but also modify treatment effect rates of acute interventions.[8,29] Based on the inclusion criteria in the present study, these results could potentially elucidate the true association between microvascular hypoperfusion and poor outcome.

No-Reflow

Several potential pathophysiological mechanisms have been proposed for microvascular hypoperfusion, that is, no-reflow: underlying inflammation, postischemic aggregation of blood elements, or irreversibly injured tissue.[30,31] A recent meta-analysis reported that no-reflow was observed in a quarter of all TICI3 patients (24% [95% CI, 1%–41%]) with substantial between-study heterogeneity (I^2=94.5%) due to the use of different inclusion criteria and measurements for microvascular hypoperfusion.[16] In the present analysis, the percentage of patients with no-reflow constituted only 5% of the entire cohort, or 13% of the cohort with perfusion abnormalities. This is likely because we have included only core laboratory-graded TICI3 patients and have excluded patients with other pathologies, which are commonly attributed to poor outcomes despite complete macrovascular reperfusion (hemorrhagic tissue transformation and large ischemic core on admission).[5,6] Our results are also in line with a recent systematic review, which suggested that rates of no-reflow in TICI3 patients are likely to be sparse, ranging from 0% to 9%.[17] The evidence on true rates of no-reflow is likely to remain inconclusive until a consensus is reached on how to properly define it. Having a standardized set of operational criteria and a robust methodology for defining, measuring, and reporting no-reflow would ensure more reproducible evidence and could streamline scientific efforts in the management of no-reflow.

Limitations

The single-center retrospective study design limits the generalizability of our results. Our study sample is relatively small, owing to the stringent criteria upon which we based our proposal for evaluation of microvascular abnormalities. This is particularly noticeable in the hypoperfusion cluster and subclusters within the mixed cluster with relatively small sample sizes and wide CIs for the clinical outcomes; therefore, we advise caution when extrapolating these results externally. This also might have underpowered our analysis to detect possible changes in long-term survival. TICI3 patients without follow-up perfusion imaging tended to have worse presentation at baseline and most likely a worse outcome. This selection bias could have underestimated true rates of microvascular perfusion abnormalities. Use of different MRI scanners could have influenced the rating of microvascular reperfusion as there may be differences in T2* effects among different protocols. Reported infarct volumes on follow-up imaging are relatively small, which is to be expected given that only core laboratory-graded TICI3 patients were included in this study. Subjective assessment of microvascular reperfusion at a single time point is likely to be insufficient to provide a detrimental effect of microvascular status on clinical outcomes. True evolution of microvascular reperfusion might benefit from a voxel-based evaluation on systematically acquired perfusion maps across several time points, starting immediately postintervention and passing the 24-hour benchmark to more clearly delineate the fate of ischemic tissue.

Conclusions

Around half of patients with complete macrovascular reperfusion experience perfusion abnormalities on a microvascular level. The presence of microvascular hypoperfusion despite complete macrovascular reperfusion is rare and could partially explain reasons for poor prognosis among these patients, while the presence of microvascular hyperperfusion did not seem to negatively affect the clinical outcome.

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Supplemental Material

Methods S1
Tables S1–S4
Figures S1–S8

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