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FULL PAPER

Defining reperfusion post endovascular therapy in ischemic stroke using MR-dynamic contrast enhanced perfusion

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Objectives Cerebral blood flow (CBF) measurements after endovascular therapy (EVT) for acute ischemic stroke are important to distinguish early secondary injury related to persisting ischemia from that related to reperfusion when considering clinical response and infarct growth.

Methods We compare reperfusion quantified by the modified Thrombolysis in Cerebral Infarction Score (mTICI) with perfusion measured by MRI dynamic contrast-enhanced perfusion within 5 h of EVT anterior circulation stroke. MR perfusion (rCBF, rCBV, rTmax, rTO) and mTICI scores were included in a predictive model for change in NIHSS at 24 h and diffusion-weighted imaging (DWI) lesion growth (acute to 24 h MRI) using a machine learning RRELIEFF feature selection coupled with a support vector regression.

Results For all perfusion parameters, mean values within the acute infarct for the TICI-2b group (considered clinically good reperfusion) were not significantly different from those in the mTICI <2b (clinically poor reperfusion). However, there was a statistically significant difference

in perfusion values within the acute infarct region of interest between the mTICI-3 group *versus* both mTICI-2b and <2b ($p = 0.02$). The features that made up the best predictive model for change in NIHSS and absolute DWI lesion volume change was rTO within acute infarct ROI and admission CTA collaterals respectively. No other variables, including mTICI scores, were selected for these best models. The correlation coefficients (Root mean squared error) for the cross-validation were 0.47 (13.7) and 0.51 (5.7) for change in NIHSS and absolute DWI lesion volume change.

Conclusion MR perfusion following EVT provides accurate physiological approach to understanding the relationship of CBF, clinical outcome, and DWI growth.

Advances in knowledge MR perfusion CBF acquired is a robust, objective reperfusion measurement providing following recanalization of the target occlusion which is critical to distinguish potential therapeutic harm from the failed technical success of EVT as well as improve the responsiveness of clinical trial outcomes to disease modification.

INTRODUCTION

Endovascular therapy (EVT) is now the standard of care for acute ischemic stroke (AIS) for large vessel intracranial occlusion.^{1–4} Correct assessment of successful reperfusion following recanalization of the target occlusion after EVT is important to distinguish potential therapeutic harm (*i.e.* injury due to reperfusion) from the failed technical success of EVT (*i.e.* injury related persistent ischemia), as well as

improve the responsiveness of clinical trial outcomes to disease modification.

The modified Thrombolysis in Cerebral Infarction Score (mTICI), assessed on the last run of the EVT procedural digital subtraction angiography (DSA), is the most common scoring system to assess reperfusion, in which successful treatment adjudicated by some to be mTICI-2b, and by others as mTICI-3.⁵ However, studies investigating differences in clinical outcome and infarct growth between

the mTICI-2b and mTICI-3 reperfusion subgroups are limited and inconsistent in their conclusion.⁵⁻¹² The mTICI classification is limited by its subjective nature and arbitrary classification of reperfusion within medium- to large-sized arteries, but not the microcirculation. Therefore, there is a pressing need to quantify the return of cerebral blood flow to the capillary bed of the ischemic region following EVT to obtain a more objective assessment of ischemic injury as opposed to injury that occurs predominantly after reperfusion.

MR dynamic contrast-enhanced (DCE) perfusion acquired within the first few hours after EVT to measure the quality of reperfusion may broaden our knowledge of the interplay between persisting ischemic infarction with injury that occurs when blood flow is fully restored, commonly referred as 'reperfusion injury'. This quantitative CBF measurement may capture distal emboli, target reocclusions, persisting hypoperfusion, e.g. related to no reflow phenomenon, and even hyperperfusion not observed on the DSA last run post-EVT.

In this study, we use a T_1 weighted MR-DCE imaging technique to measure cerebral blood flow within 5 h of EVT for treatment of acute ischemic stroke recruited to REPERFUSE (Recanalization following Endovascular treatment and Imaging of Perfusion, Regional Infarction and Atrophy to Understand Stroke Evolution) study. We hypothesize that: (1) there will be variable MR perfusion values (*i.e.* hyper/normo/hyperperfused) within ischemic brain that is successfully reperfused, defined by mTICI $\geq 2b$, and 2) post-EVT MR perfusion measurements will show a higher correlation with clinical improvement (change in NIHSS) and early DWI growth (absolute change in the DWI lesion volume from 5 to 24 h post-EVT) when compared to mTICI defined reperfusion, the reperfusion metric currently used in the ESCAPE-NA1 clinical trial (NCT02930018).¹³

METHODS AND MATERIALS

Participants

This study was approved by the University of Calgary local ethics committee. We analyzed the EVT subset of the REPERFUSE study, recruited between May 2013 and December 2017 ($n = 17$). All patients had an EVT target occlusion of the MCA M1 or M2 segment or ACA A1 segment causing hemispheric stroke of the anterior cerebral circulation observed on the baseline CT angiography, were ≥ 18 years, had MR imaging, including diffusion-weighted imaging (DWI) and perfusion-weighted DCE performed within 5 h and at 24 h after acute stroke treatment [EVT alone, EVT + alteplase (human recombinant single chain tissue plasminogen activator)]. The patient or their surrogate provided written informed consent. Clinical characteristics and demographics, medical history, and workflow timing (last seen normal, imaging times, recanalization) were collected prospectively. Reading of anonymized scans was performed blinded to all demographic data, mTICI and functional outcome. Each imaging modality was read independently and at different times. The study was approved by our institutional research ethics board (Conjoint Health Research Ethics Board).

Imaging acquisition

Admission imaging

Standard non-contrast CT (NCCT) and multiphase CT angiography (mCTA) were acquired at admission to score early ischemic change using ASPECTS, localizing the EVT target occlusion, and determining leptomeningial collateral status, respectively.¹⁴⁻¹⁶ All phases of the mCTA were taken into account for the collateral scoring. Once EVT was complete, a final DSA run was acquired in both frontal and lateral views, making sure to include the vascular territory supplied by the target occlusion.

Post-EVT MRI

Patients were stabilized and carefully positioned into a 3.0 T clinical MR scanner (Discovery 750; General Electric Healthcare, Waukesha, WI) within 5 h of EVT (acute) and at 24 h post-EVT, under the supervision of a nurse and neurologist. DWI was performed at both time points using a spin-echo echoplanar imaging (SE-EPI) sequence. Acquisition details were: repetition time (TR) = 9000 ms; echo time (TE) = 94.3 ms; field of view (FOV) = 250–350 mm; number of signals averaged (NSA) = 1; acquisition matrix = 144×144 ; and slice thickness = 5 mm with no gap with diffusion sensitizing gradients ($b = 1000 \text{ s/mm}^2$) applied in 15 directions, and without diffusion weighting ($b = 0 \text{ s/mm}^2$). At the < 5 h time point only, axial perfusion-weighted DCE imaging was performed using a T_1 weighted time-resolved imaging of contrast kinetics (TRICKS) spoiled gradient-echo (SPGR) sequence.¹⁷ This sequence has been optimized to increase the contrast-agent induced signal difference in tissues with low blood volume (*i.e.* in ischemic tissue). Acquisition details were: scan time 3:01 min; temporal phases = 48; temporal resolution = 3.5 s; TR = 8.0 ms; TE = 3.0 ms; FOV = 240–350 mm; flip angle = 30° ; NSA = 1; acquisition matrix = 144×144 ; and slice thickness = 5 mm without gap. The Gadovist (Bayer, Germany) bolus contrast was given at 5 ml s^{-1} . The total amount of contrast injected was 10 ml followed by 20 ml of saline.

Image analysis

DSA post EVT

The mTICI score was used to score the degree of reperfusion within the arterial tree distal to the target EVT occlusion.¹³ The score was defined as follows: 0 = no perfusion; 1 = penetration, but no distal branch filling; 2a = perfusion with incomplete ($< 50\%$) distal branch filling; 2b = perfusion with incomplete ($> 50\%$) distal branch filling; and 3 = full perfusion with filling of all distal branches.

Diffusion-weighted MR imaging

DWI lesion volumes at 5 h and 24 h post-EVT were determined according to Sah et al.¹⁸ Briefly, the mean (μ) and standard deviation (σ) of the DWI intensity values in normal contralateral brain tissue was obtained from each average DWI data set and used to calculate individual relative thresholds (t), where $t = \mu + k \cdot \sigma$, with $k = 0.85$. The absolute and relative (percent change) DWI lesion growth (24 h DWI lesion volume minus the 5 h DWI lesion volume) was calculated. Petechial hemorrhage was included in the follow-up DWI volume.

MR perfusion-weighted imaging

In-plane patient motion was corrected in the x/y-axis. Perfusion hemodynamic functional maps were calculated using delay-insensitive deconvolution using the Johnson-Wilson model.^{19,20} For each study, the dynamic signal time curves were converted to concentration time curves, assuming negligible T2* effects, as is expected in T₁ weighted SPGR sequences with short TE.²¹ The arterial input function was manually selected from the basilar artery or contralateral ICA. Perfusion parameter maps of cerebral blood flow [CBF; in ml·min⁻¹·100g⁻¹], cerebral blood volume [CBV; ml·(100g)⁻¹], start time of the impulse residue function (T₀; seconds), and T_{max} (seconds), which equates to T₀ + 0.5×(MTT) were calculated. Perfusion-weighted anatomical maps (average maps) were created by averaging the serial MR-DCE images (first six 6-time point volumes).

The <5 h and 24 h post-EVT DWI acquisitions were co-registered non-linearly to the MR-DCE dynamic average image to compensate distortion effects using in-house developed software (Calgary Image Analysis and Processing Centre, Calgary, AB) prior to being analyzed using custom perfusion analysis software (IDL, v. 6.3; RSI, Boulder, CO). The DWI lesion volumes from both time points were then superimposed onto each MR-DCE functional map for extraction of mean perfusion values. CBF, CBV, T₀, and T_{max} parameters values were derived from four regions of interest (ROIs), within gray matter tissue only, as defined on the T₁ weighted image: (1) within the 5 h post EVT DWI lesion (*acute infarct ROI*), (2) within tissue surrounding the 5 h post-EVT DWI lesion, consisting of only the 24 h post-EVT DWI lesion (*infarct growth ROI*), (3) ipsilateral tissue within the vascular territory supplied by the target EVT occlusion but outside the 24 h DWI lesion (*Non-infarct ROI*), and (4) contralateral tissue that mirrored the 5 h post EVT DWI lesion – the ROI was flipped about the hemisphere midline and manually corrected if needed. Relative perfusion values for each individual subject were calculated from the contralateral mirror region by division (rCBF, and rCBV) or subtraction (rT₀ and rT_{max}).

Clinical assessment

Clinical outcome was measured by the National Institutes of Health Stroke Scale score (NIHSS; range = 0–42, with higher scores indicating greater stroke severity), assessed at admission and at the 24 h MR time point by a qualified neurologist. For patients who died, a score of 42 was given.

Statistical analysis

The distribution of all variables was characterized using descriptive statistics [means, medians, standard deviations, frequency distributions, interquartile range (IQR)].

For the primary objective of determining MR perfusion heterogeneity within mTICI sub groups, mean relative (normalized to contralateral) perfusion values (rCBF, rCBV, rT₀ and rT_{max}) were determined within mTICI - 3, 2b, and <2b subgroups respectively. An independent *t*-test (normal data) or Mann-Whitney Rank Sum Test (non-normal data) was used to compare individual perfusion parameters within ROIs 1–3 between mTICI-subgroups. A *p*-value < 0.05 was considered significant.

For the secondary objective to determine which reperfusion metric, MR perfusion parameters *versus* mTICI, was better at predicting change in NIHSS (admission to 24 h) and DWI lesion growth (<5 h postEVT to 24 h), we generated a predictive model using a machine learning RRELIEFF feature selection method coupled with a support vector regression (SVR).^{22,23} Specific features (input variables) included were: MRP parameters of rCBF, rCBV, rT₀ and rT_{max} from within the *acute infarct ROI*, the tertiary mTICI score (3, 2b, ≤2a), the binary mTICI score (2b/3 vs. <2b), and clinical demographics including sex, age, onset to reperfusion time, baseline NIHSS, and admission CT ASPECTS. Non-informative features potentially downgrade the accuracy of any machine learning model, therefore, the RRELIEFF feature selection algorithm was used to identify relevant features by detecting dependencies between them and estimating the quality of the features in a regression problem. After feature ranking (establishing order of feature importance), a linear kernel SVR model, was trained based on the ranked attributes. The number of highest ranked features was optimized by iteratively removing the lowest ranked feature from the training and testing. Following a leave-one-out cross-validation approach, the regression performance was determined by comparing the predicted outcome to the real outcome by calculating the root mean square error.²⁴ The regression results obtained using the attribute subset with the lowest root mean square error were used as the final reported regression result and for a subsequent qualitative analysis of the selected features. To determine directionality of the variables in the model with respect to each outcome, a Pearson correlation was performed.

RESULTS

17 patients (6 male and 11 female) with a mean (SD) age of 68 (12) years were included (Table 1). The mean time from stroke onset to first recanalization was 187 ± 117 min, 10/17 received alteplase treatment, one patient had a hemorrhagic transformation (H1-1). Confirmed on the last run of DSA post-EVT, two patients had mTICI <2a, eight patients had mTICI-2b, and seven patients had mTICI-3 reperfusion. Median (IQR) admission and follow-up NIHSS was 16 (11-20) and 8 (1-12) respectively.

For the primary aim of determining the post-EVT perfusion heterogeneity within mTICI subgroups heterogeneity, Figure 1 shows the relative perfusion values (rCBF, rCBV, rT₀, and rT_{max}) shown as median, IQR, and 95% confidence interval (CI) obtained from acute infarct ROI, infarct growth ROI, and the non-infarct ROI. There was a statistically significant difference in perfusion values within the acute infarct ROI between the mTICI-3 group *versus* both mTICI-2b (*p* = 0.02). Figures 2 and 3 show example imaging for two patients with TICI-2b reperfusion.

For the secondary aim of this study, which was to compare the predictive ability of the reperfusion metrics mTICI and post-EVT MRP for change in NIHSS and absolute DWI lesion volume change, respectively, the features that made up the best predictive model for change in NIHSS and absolute DWI lesion volume change was rT₀ within acute infarct ROI and

Table 1. Patient demographics, imaging and clinical outcomes

Age	Sex	Baseline NIHSS	CT ASPECTS	CTA collaterals	tPA (Alteplase)	onset to reperfusion (mins)	mTICI score	Acute rCBF	Acute rCBV	Acute rT0	DWI volume change	NIHSS change
83	M	17	10	19	Yes	245	2a	0.24	0.07	9.00	10.14	-2
59	M	11	10	20	Yes	545	2b	0.67	0.56	-0.40	0.13	10
49	M	19	10	20	Yes	24	2a	1.45	1.52	0.78	4.70	17
72	M	16	10	7	No	71	3	0.71	0.98	1.96	18.37	9
73	M	15	9	20	Yes	188	2b	1.18	1.40	3.00	1.55	10
89	M	17	8	15	Yes	76	2b	0.85	1.37	0.90	-3.10	4
84	M	21	10	20	Yes	169	2b	1.18	1.65	0.40	2.71	9
71	F	21	8	20	No	210	3	1.48	1.44	-0.22	9.80	9
56	M	17	5	10	Yes	110	2b	0.97	0.94	0.10	10.50	6
76	M	21	10	20	Yes	261	2b	0.28	0.21	9.70	1.20	-3
70	F	20	3	10	Yes	279	2b	2.48	1.72	-0.07	54.48	2
80	M	22	9	13	No	218	2b	0.16	0.45	7.60	38.42	-1
44	F	1	10	20	No	240	3	1.20	1.20	0.30	0.26	0
68	F	20	8	18	No	120	3	1.1	1.3	0.2	1.10	19
54	F	13	10	20	Yes	128	3	1	1	0.1	0.10	13
61	M	16	9	17	No	123	3	1.3	1.2	0.2	23.50	16
69	F	13	8	20	No	180	3	1.3	1.6	0.3	5.00	11

CBF, cerebral blood flow; CBV, cerebral blood volume; CTA, CT angiography; DWI, diffusion-weighted imaging; mTICI, modified Thrombolysis in Cerebral Infarction.

Figure 1. Relative perfusion values (CBF, CBV, T0, and Tmax) shown as median, IQR and 95% CI obtained from i) within the 5 h post EVT DWI lesion (acute infarct ROI), ii) within tissue surrounding the 5 h postEVT DWI lesion, encompassing the 24 h post-EVT DWI lesion (infarct growth ROI), and iii) ipsilateral tissue within the vascular territory supplied by the target EVT occlusion but did not contain a DWI lesion (non-infarct ROI). *Significantly different than the TICI-3 group's Acute Infarct ROI perfusion values. #Significantly different than the TICI-3 group's Infarct Growth ROI perfusion values. CBF, cerebral blood flow; CBV, cerebral blood volume; CI, confidence interval; EVT, endovascular therapy; IQR, interquartile range; ROI, region of interest, TICI, Thrombolysis in Cerebral Infarction.

admission CTA collaterals respectively. No other variables were selected for these best models, inclusive of mTICI. The correlation coefficients (Root mean squared error) for the cross-validation were 0.47 (13.7) and 0.51 (5.7) for change in NIHSS and absolute DWI lesion volume change. The Pearson correlation coefficient for rT0 vs change in NIHSS was -0.65 – the shorter the rT0 (*i.e.* arrival time of blood to the tissue of interest) the bigger improvement in NIHSS. The Pearson correlation coefficient for collateral score vs absolute DWI lesion change was -0.64 – the lower collateral score (lower is worse) the larger the DWI growth.

In patients with good reperfusion (mTICI-2b/3; $n = 15$), the mean $\pm$ std absolute and percent DWI lesion growth from 5 h post-EVT to 24 h post-EVT was 13.8 ± 17.5 ml and $120.6 \pm 244.1\%$, respectively. In patients with poor or no reperfusion (mTICI-0/1/2a, $n = 2$), the average $\pm$ std absolute and percent DWI lesion growth from 5 to 24 h post-EVT was 22.4 ± 22.7 ml

Figure 2. 73-year-old female with baseline NIHSS of 15 and left-M2 occlusion with a collateral score of 20 on the (a) multiphase CTA (only the last phase is shown). TICI-2b reperfusion was achieved after EVT as shown on the last run of the (b) DSA. (c) MRP-T0 perfusion map at 4.4 h after the EVT procedure shows minimal perfusion defect in the ischemic territory and a small (d) DWI lesion (5 ml) taken at the same time. (e) DWI taken at 24 h shows slightly a larger DWI lesion (7 ml). 24 h NIHSS was 5. CTA, CT angiography; DWI, diffusion-weighted imaging; EVT, endovascular therapy; TICI, Thrombolysis in Cerebral Infarction.

and $118.8 \pm 146.6\%$, respectively. There was no significant difference between the groups ($p > 0.05$).

DISCUSSION

MRI perfusion techniques have been widely implemented for acute stroke revascularization treatment decision-making.^{25–27} In this work, we acquire and analyze MR-DCE perfusion within 5 h of EVT to provide an objective measurement of reperfusion after revascularization treatment with EVT. Our primary aim was to directly compare the established reperfusion metric mTICI with an objective MR perfusion technique acquired a few hours after EVT. We show that within the mTICI 2b subgroup, accepted clinically as successful EVT reperfusion,

Figure 3. 80 year old female with baseline NIHSS of 22 and left-M1 occlusion with a collateral score of 13 on the (a) multiphase CTA (only last phase is shown). TICI-2b reperfusion was achieved after EVT as shown on the last run of the (b) DSA. (c) MRP-T0 perfusion map at 4.8 h after the EVT procedure shows a large perfusion defect in the ischemic territory but with a small (d) DWI lesion (33 ml) taken at the same time. (e) DWI taken at 24 h shows a larger DWI lesion (71 ml). 24 h NIHSS was 23. CTA, CT angiography; DWI, diffusion-weighted imaging; EVT, endovascular therapy; TICI, Thrombolysis in Cerebral Infarction.

the perfusion values (CBF, CBF, rT0, Tmax) measured within acute and growth DWI lesions are highly variable. Many of these patients continue to show perfusion values below the ischemic threshold.²⁰ As expected, mean values for all perfusion parameters (rCBF, rCBV, rT0, rTmax) within the mTICI-3 group were similar to those in the contralateral normal hemisphere ($p > 0.05$). However, even this group still contained rCBF values well below 1, albeit much less than the mTICI-2b group.

Using change in NIHSS and absolute DWI lesion volume change from <5 to 24 h after EVT as the outcomes for the support vector regression models, we show that MRP-rT0 within the acute infarct ROI and the admission collateral

score were the only predictor variables chosen for the best model to predict change in NIHSS and absolute DWI lesion volume change respectively. Neither of the mTICI scores, both binary (*i.e.* 2b/3 vs. <2b – good/bad reperfusion) and tertiary (3, 2b, <2a) were selected for either model. Nevertheless, we admit that the cross-validation correlation coefficients are of moderate strength – increasing sample size and perhaps adding another clinical outcome such as 90 day mRS could improve our model's predictive accuracy. However, our study focuses on the evolution of the acute injury detected by MRI and the associated clinical outcome of change in NIHSS, whereas longer term functional outcome incorporates the complex relationship of the infarct, its location, regenerative mechanisms, and compensatory *versus* adaptive functional recovery.²⁸ Ideally, acute stroke trials, inclusive of new reperfusion treatments or neuroprotective agents, require both early and late clinical and imaging outcomes. Herein, we address the former with respect to the use of MR perfusion parameters to determine early clinical and imaging outcome.

We appreciate that vessel patency of the primary occlusive lesion and the appearance/migration of distal emboli can contribute to the large variance within the mTICI-2b group. It is for these reasons why MR perfusion acquired a few hours post-EVT is crucial for reperfusion quantification not only for clinical trial end point considerations, but also to inform clinicians on whether to use further neuroprotective/thrombolysis treatment. From a technical point of view, MR perfusion captures reperfusion within the whole brain; DSA is typically limited to the vascular territory supplied by the target occlusion. Thus, iatrogenic emboli migrating to other vascular territories can be missed. It is also impossible to adequately quantify reperfusion distal to the target occlusion in patients with partial/no recanalization, as limited antegrade flow would restrict the appearance of DSA contrast agent in the distal arterial vasculature. There have also been attempts to get more objective with the DSA-mTICI 2b subgroup, introducing a 2C category defined as near-complete perfusion except for slow flow in a few distal branches; however, Volny *et al*²⁹ showed only fair to moderate interrater agreement using the subclassification.²⁹

There are several limitations to our study. Firstly, the sample size is small; however, this study is unique with respect to the acute MRI that is acquired early after EVT reperfusion. As a proof of principle, we plan to use the results to inform a neuroprotection clinical trial currently underway.²⁸ Secondly, there are problems with co-registration of two low resolution image sets, the MRP-DSC and DWI. Partial volume averaging exists, especially for smaller stroke lesion volumes. Lastly, we understand that using the binary mTICI stratification, with only two patients in the <2a group, is an issue with respect to the predictive ability of the clinical and radiological outcomes. We have also used the tertiary mTICI classification in our predictive modelling, where 2b and 3 are separated.

We have previously shown that infarcts grow after EVT despite clinically successful reperfusion (*i.e.* mTICI-2b or

3).³⁰ Acquiring MR perfusion early, post-EVT, we can confirm that much of this early infarct growth is likely attributable to ischemia rather than presumed reperfusion injury (*i.e.* cell death caused by restoration of blood flow). Even allowing for the small sample size in this study, we have shown that the measurement of CBF parameters post-EVT provides a powerful physiological approach to understanding the relationship of CBF, clinical outcome, and DWI growth following EVT. It is from this vantage that our data provide a unique perspective regarding CBF measurements following EVT, and categorical evidence that mTICI 2b post-EVT cannot be considered successful reperfusion.

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COMPETING INTERESTS

The authors declare that they have no conflict of interest.

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