Original research

Microvascular reperfusion during endovascular therapy: the balance of supply and demand

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ABSTRACT

Background Endovascular therapy (EVT) has revolutionized the treatment of acute stroke, but large vessel recanalization does not always result in tissue-level reperfusion. Cerebral blood flow (CBF) is not routinely monitored during EVT. We aimed to leverage diffuse correlation spectroscopy (DCS), a novel transcranial optical imaging technique, to assess the relationship between microvascular CBF and post-EVT outcomes.

Methods Frontal lobe CBF was monitored by DCS in 40 patients undergoing EVT. Baseline CBF deficit was calculated as the percentage of CBF impairment on pre-EVT CT perfusion. Microvascular reperfusion was calculated as the percentage increase in DCS-derived CBF that occurred with recanalization. The adequacy of reperfusion was defined by persistent CBF deficit, calculated as: baseline CBF deficit − microvascular reperfusion. A good functional outcome was defined as 90-day modified Rankin Scale score ≤2.

Results Thirty-six of 40 patients achieved successful recanalization, in whom microvascular reperfusion in itself was not associated with infarct volume or functional outcome. However, patients with good functional outcomes had a smaller persistent CBF deficit (median 1% (IQR −11%–16%)) than patients with poor outcomes (median 28% (IQR 2–50%)) (p=0.02). Smaller persistent CBF deficit was also associated with smaller infarct volume (p=0.004). Multivariate models confirmed that persistent CBF deficit was independently associated with infarct volume and functional outcome.

Conclusions CBF augmentation alone does not predict post-EVT outcomes, but when microvascular reperfusion closely matches the baseline CBF deficit, patients experience favorable clinical and radiographic outcomes. By recognizing inadequate reperfusion, bedside CBF monitoring may provide opportunities to personalize post-EVT care aimed at CBF optimization.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite the remarkable clinical benefit of endovascular thrombectomy (EVT), large vessel recanalization does not always result in microvascular reperfusion. Incomplete microvascular reperfusion is associated with poor clinical outcome, but in current practice microvascular cerebral blood flow (CBF) is not routinely monitored.

WHAT THIS STUDY ADDS

⇒ Non-invasive optical CBF monitoring identifies patients with inadequate microvascular reperfusion, which is correlated with larger infarct volume and poor outcome. The adequacy of reperfusion is best defined not by CBF augmentation, but rather by the degree to which CBF augmentation closely matches the baseline CBF deficit.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In characterizing microvascular reperfusion at the bedside, optical CBF monitoring presents an opportunity to (1) personalize acute stroke care aimed at CBF optimization and (2) enrich future clinical trials by identifying patients likely to benefit from neuroprotectants or EVT-adjuvant therapies.

INTRODUCTION

Endovascular therapy (EVT) has changed the landscape of acute stroke treatment in the context of large vessel occlusion (LVO).[1 2] Procedural success of EVT is currently determined based on the degree of large vessel recanalization.[3] Although the vast majority of patients achieve successful recanalization, approximately half of these patients suffer a poor functional outcome.[1 4] Interestingly, post-EVT advanced imaging has also shown that large vessel recanalization does not always result in successful microvascular reperfusion.[5 6] Thus, opportunities remain to refine acute stroke treatment in conjunction with EVT. A bedside cerebral blood flow (CBF) monitor would provide opportunities to recognize inadequate reperfusion in real time, and thereby facilitate the development of new approaches for CBF optimization in the angiography suite. The emergence of EVT has revived the study of a range of adjuvant therapies, including neuroprotectants,[7 8] but recognizing the adequacy of microvascular reperfusion may be critical to enriching clinical trial populations and demonstrating a benefit of new therapies.

Diffuse correlation spectroscopy (DCS) is a promising non-invasive method for continuous bedside monitoring of microvascular CBF in patients with

stroke.[9–11] DCS uses temporal fluctuations of light scattered by moving red blood cells to measure a signal decay rate that is proportional to CBF.[12 13] DCS can non-invasively measure microcirculatory CBF and has been validated against Xenon CT,[14] arterial spin-labeled MRI,[15] velocity mapping MRI,[16] invasive laser Doppler,[17] and ^{15}O positron emission tomography.[18] A small case series previously demonstrated the feasibility of DCS monitoring during EVT.[19] Near infrared spectroscopy (NIRS) is a more widely available optical technique and is often used as a surrogate of CBF,[13 20 21] but NIRS requires several assumptions, most notably a constant arterial oxygen saturation and cerebral oxygen metabolism,[22] which may not hold true in acute stroke. Indeed, a study of 33 patients who underwent NIRS monitoring during EVT found no baseline asymmetry in the NIRS signal and no change in the NIRS signal associated with recanalization,[21] thus emphasizing the need for more direct CBF monitoring.

We deployed DCS during EVT to assess the relationship between microvascular reperfusion and outcomes after EVT. We further aimed to quantify a personalized metric that estimates the adequacy of reperfusion (ie, that estimates how well reperfusion matches the baseline CBF deficit), and its correlation with outcomes. Specifically, we operationalized perfusion demand in acute stroke due to LVO as the percent deficit in CBF in the affected territory based on CT perfusion imaging, and we operationalized supply as the percent increase in CBF following EVT (ie, reperfusion) measured intraprocedurally by DCS. Using these new parameters, we show that variance in outcome may be predicted by the relationship between supply and demand rather than by CBF change alone.

METHODS

Participants

Eligible patients had a diagnosis of acute ischemic stroke with unilateral occlusion of the internal carotid artery (ICA) or first segment of the middle cerebral artery (MCA) at the Hospital of the University of Pennsylvania. Patients were treated with EVT within 24 hours of stroke onset. Patients were excluded if they had an intracranial mass, bilateral infarcts, or a skull defect that would interfere with optical monitoring. The study was approved by the University of Pennsylvania Institutional Review Board (protocol #828249) and informed consent was provided by each subject (or legally authorized surrogate). The study conformed to the STROBE guidelines for observational research.

Optical instrumentation and analysis

The custom DCS system (online supplemental figure S1) used for this study contained 16 single-photon counters (SPCM-AQ4C, Pacer) connected to a fast software correlator[23] and two long-coherence-length source lasers emitting light at 785 nm (DL785-100-SO, CrystaLaser). A detailed technical description has been previously reported.[19] In brief, optical fibers coupled a source laser and seven detectors to the head via a 2 cm × 5 cm rubber probe (one probe for each hemisphere). The light source and detectors were positioned 2.5 cm apart, which provides sufficient sensitivity to CBF.[19 24] The temporal fluctuations of the collected light are quantified by the light intensity temporal autocorrelation function. These autocorrelation functions are fit to a semi-infinite model of the head to detect and quantify variations in microvascular blood flow.[12 13]

After the patient was situated on the procedure table, the optical probes were placed bilaterally on the lateral aspect of the forehead. To optimize the optical signal, care was taken with probe placement to avoid hair and frontal sinuses. The probes were fixed to the head with double-sided tape and an elastic bandage. Hemodynamic data were collected throughout the course of EVT. Procedural steps were annotated in the optical data record, along with recanalization scores associated with each pass of the clot retrieval catheter. The optical probes were removed from the patient's head after completion of the procedure, when the patient was moved from the procedural table to a stretcher.

Clinical data and neuroimaging analysis

Patient demographics and baseline characteristics, including admission NIH Stroke Scale (NIHSS) score and time of stroke onset, were abstracted from the electronic health record. Pre-EVT CT head details were collected, including the Alberta Stroke Program Early CT Score (ASPECTS). The pre-EVT CT angiogram was reviewed to confirm the vessel occlusion and laterality. The occlusion was categorized as ICA, first segment of MCA, or tandem (ie, both ICA and MCA). Pre-EVT CT perfusion imaging was reviewed for infarct core and penumbra volumes, as calculated by RAPID (RapidAI, Menlo Park, California, USA), in which the core is interpreted as rCBF <30%, and the penumbra is interpreted as Tmax >6 s. Recanalization was classified according to the modified Treatment in Cerebral Infarction (mTICI) score based on the angiographic appearance after recanalization.[3] Post-EVT brain imaging was reviewed to identify hemorrhagic complications, if present. Symptomatic intracerebral hemorrhage (ICH) was classified according to the European Cooperative Acute Stroke Study II (ECASS-2) criteria: any hemorrhage on post-treatment brain imaging associated with at least a 4-point worsening of the NIHSS score at 24 hours post-EVT. Infarct volume was assessed based on neuroimaging performed 24–72 hours following EVT. If MRI was available, infarct volume was assessed on diffusion weighted imaging, but if MRI was not performed, the last CT within the 24–72 hour window was used. A trained physician reviewed the imaging with ITK-SNAP and performed manual segmentation of the infarct in order to quantify the volume. Infarct volume was categorized by tertiles (<10 mL, 10–25 mL, or >25 mL). The NIHSS score and discharge disposition (home, acute rehabilation, skilled nursing facility) were assessed at the time of hospital discharge. Long-term functional outcome was assessed by the modified Rankin Scale (mRS) 90 days after the stroke, and an mRS score of ≤2 was considered a good outcome.

Hemodynamic parameters

Baseline CBF deficit was quantified based on CT perfusion imaging (CTP) performed prior to EVT. CTP data were processed using syngo.via (Siemens Medical Solutions, Malvern, Pennsylvania, USA). CBF was measured within a 2 cm circular region of interest (ROI) under the optical probe in the frontal lobe ipsilateral to the LVO. The optical probe location was determined based on the distance from midline and distance above the brow. CBF was also measured in another 2 cm ROI in the contralateral unaffected hemisphere (symmetrical across the midline), and baseline CBF deficit was calculated as the percent difference between the contralateral and ipsilateral CBF at baseline (ie, the percent increase in CBF needed to restore normal flow, see online supplemental figure S2A).

Microvascular reperfusion was quantified to reflect the change in DCS-derived CBF that occurred during recanalization. More specifically, baseline CBF was calculated as the average value over a 2 min epoch, 5 min prior to recanalization. Post-EVT CBF was calculated as the average value over a 2 min epoch, 5 min after

recanalization. Microvascular reperfusion was calculated as the percent increase in CBF, comparing baseline and post-EVT CBF (online supplemental figure S2B). As a control, the analogous change in DCS-derived contralateral CBF was also computed.

Persistent CBF deficit, expressed as a percentage, contextualizes the adequacy of reperfusion relative to each patient's baseline hemodynamic impairment as measured in the optical probe ROI:

$$\text{Persistent CBF deficit (\%)} = \text{baseline CBF deficit (\%)} - \text{microvascular reperfusion (\%)}$$

Statistical analysis

Summary statistics are presented using means and SD for continuous variables, medians and interquartile ranges for ordinal or non-parametric variables, and proportions for categorical variables. In comparing those who achieved a good versus poor functional outcome, CBF metrics were compared using Wilcoxon Mann–Whitney tests. Univariate logistic regression identified factors associated with good functional outcome. A multivariable logistic model quantified the association between CBF metrics and functional outcome, adjusting for age, baseline NIHSS score, and any factors in the univariate analysis at $p<0.10$. In analyzing radiographic outcomes, CBF metrics were compared across infarct volume tertiles using Kruskal–Wallis tests. Univariate ordinal logistic regression identified factors associated with infarct volume, and a multivariable model quantified the association between CBF metrics and infarct volume, adjusting for age, baseline NIHSS score, reperfusion metrics (percent change in CBF and persistent CBF deficit), and any factors in the univariate analysis at $p<0.10$. Finally, to assess whether the CBF metrics are more sensitive to outcomes when the optical probe location overlaps with the RAPID-defined penumbra, the above comparisons were repeated in two patient subsets: (1) patients with a RAPID-defined penumbra under the probe; and (2) patients with no RAPID-defined penumbra under the probe. All statistical analyses were performed in STATA/SE version 15.1 (StataCorp, College Station, Texas, USA). A sample of 40 subjects provided 87% power (setting alpha to 0.05) to detect a 10% difference (assuming 10% SD in each group) in reperfusion metrics when comparing patients with a good and bad outcome.

RESULTS

In total, 40 patients with acute stroke with proximal anterior circulation LVO underwent transcranial optical hemodynamic monitoring during the course of EVT. LVOs were 72% MCA, 15% ICA, and 13% tandem ICA/MCA. Baseline demographics and stroke characteristics are shown in table 1. Successful recanalization, defined as mTICI ≥2b, was achieved in 36 (90%) patients. One subject was removed from the analysis because the baseline CTP imaging was uninterpretable. Therefore, 35 patients were included in the analysis of reperfusion and infarct volume. Two patients were lost to follow-up (ie, no 90-day function outcome assessment), so 33 patients were included in the analysis of CBF and functional outcome.

The baseline CBF deficit was heterogeneous (see online supplemental figure S3A), with a median of 26% (IQR 14–47%). Baseline CBF deficit was correlated with pre-EVT RAPID-calculated infarct core volume prior to EVT (R: 0.46, p=0.006) but not penumbra volume (R: −0.06, p=0.74). Microvascular reperfusion was also heterogeneous (see online supplemental figure S3B) with a median increase in CBF of 12% (IQR 0–26%). Similar to baseline CBF deficit, microvascular reperfusion was correlated with pre-EVT RAPID-calculated infarct core volume (R: 0.36, p=0.05), but not penumbra volume (R: 0.04, p=0.83). In the unaffected hemisphere, the change in DCS-derived CBF (baseline vs post-EVT) was minimal (median +4.7%; IQR −1.0%–9.4%); this change in CBF was smaller than the affected hemisphere (p=0.008). Point estimates raise the possibility that patients with mTICI 3 recanalization experienced a larger increase in CBF than patients with mTICI 2b, but the difference was not statistically significant (median 17% vs 3%, p=0.06). Microvascular reperfusion was similar in patients with first pass recanalization to those without (median 11% vs 9%; p=0.98).

Among the patients who achieved successful recanalization (mTICI ≥2b), the median infarct volume was 11.4 mL (IQR 6.5–49.0 mL). Although infarct volume was derived from MRI in 70% and CT in 30% of the patients, the median infarct volume was similar for each imaging modality (volume by MRI: median 11.4 mL (IQR 5.5–52.1 mL); volume by CT: median 11.5 mL (IQR 7.5–25.7 mL); p=0.74). The presence of any ICH was noted in 10% of the patients based on post-procedure CT,

Table 1 Cohort demographics and baseline clinical characteristics

	Cohort (n=40)
Age, years	71 (17)
Sex, % female	55%
Race, %	
White	60%
Black or African American	32.5%
Asian	7.5%
Baseline NIHSS	16 (8)
Site of occlusion	
Internal carotid artery	15%
Middle cerebral artery	72%
Tandem	13%
Side of occlusion, % left	53%
Baseline ASPECTS	8 (7–9)
tPA, %	38%
Core, mL (based on rCBF <30%)	14 (18)
Penumbra, mL (based on Tmax >6 s)	140 (93)
Time from onset to recanalization, hours	5.0 (3.8–12.0)
mTICI score	
0	7%
1	0%
2a	3%
2b	32%
3	58%
Modified first pass recanalization, %	44%
Endovascular technique	
Stent retriever alone	13%
Aspiration alone	15%
Combination stent+aspiration	73%
General anesthesia, %	88%

Continuous variables are reported as mean (SD), ordinal variables are reported as median (IQR), and categorical variables are reported as proportions.
ASPECTS, Alberta Stroke Program Early CT Score; mTICI, modified Treatment in Cerebral Ischemia (modified first pass recanalization indicates mTICI ≥2b on first pass); NIHSS, National Institutes of Health Stroke Scale; rCBF, relative cerebral blood flow; Tmax, time to maximum.

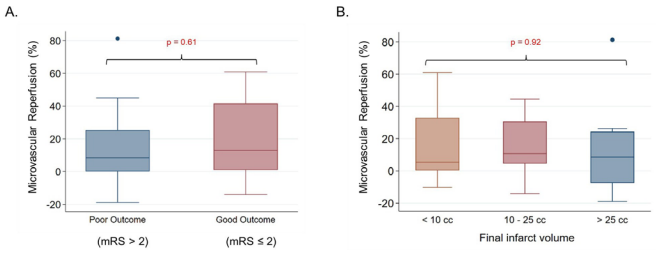

Figure 1 Microvascular reperfusion and outcomes. (A) Functional outcome was assessed by the modified Rankin Scale (mRS) 90 days post-stroke and categorized as good (≤2) or poor (>2). Microvascular reperfusion (percent increase in cerebral blood flow) was similar between the two outcome categories. The p value was calculated by a Wilcoxon Mann–Whitney test. (B) Infarct volume was categorized by tertiles (<10 mL, 10–25 mL, and >25 mL). Microvascular reperfusion (percent increase in cerebral blood flow by diffuse correlation spectroscopy) was similar across infarct volume tertiles. The p value was calculated by a Kruskal–Wallis test.

but only 3% experienced symptomatic ICH. The median 90-day mRS was 3 (IQR 2–4), with 42% achieving a good functional outcome (mRS ≤2). DCS-derived microvascular reperfusion was similar in those who achieved a good versus bad outcome (figure 1A) and was similar across infarct volume tertiles (figure 1B). By contrast, a smaller persistent CBF deficit (ie, more optimal frontal reperfusion) was associated with a favorable functional outcome (figure 2A) and a smaller infarct volume (figure 2B). Point estimates raise the possibility that patients with mTICI 3 recanalization experienced a more favorable persistent CBF deficit, but the difference was not statistically significant (median 3% vs 28%, p=0.17). Point estimates also raise the possibility that first pass recanalization was associated with a smaller, though non-significant, persistent CBF deficit compared with multiple passes (median 2% vs 26%, p=0.14). Intravenous tPA in addition to EVT was also associated with a smaller, but non-significant, persistent CBF deficit compared with EVT alone (median 1% vs 22%, p=0.28).

Univariate logistic regression showed an association between long-term outcome and two baseline factors: (1) age and (2) baseline NIHSS (table 2). A multivariate model indicated that age and larger persistent CBF deficit (ie, suboptimal reperfusion) were independently associated with a poor outcome (table 2). Secondarily, the multivariate model was limited to patients with mTICI 3 recanalization (n=23), which did not meaningfully impact the reported association between persistent CBF deficit and functional outcome (OR 0.45 for the entire cohort; OR 0.49 when limited to mTICI 3). Univariate ordinal logistic regression showed an association between infarct volume and two baseline variables: (1) baseline NIHSS and (2) pre-EVT core infarct volume (table 2). Given the potential correlation between these two factors, a test for interaction was performed but was non-significant (OR for interaction term: 1.00 (95% CI 0.99 to 1.01), p=0.94). A multivariate model indicated that baseline NIHSS and larger persistent CBF deficit (ie, suboptimal reperfusion) were independently associated with a larger infarct volume (table 2). Again, in a secondary analysis, the multivariate model was limited to patients with mTICI 3 recanalization (n=23), which did not meaningfully impact the reported association between persistent CBF deficit and functional outcome (OR 1.89 for the entire cohort; OR 2.18 when limited to mTICI 3).

In 63% of patients the optical probe was overlaying the RAPID-defined penumbra. In these patients, a relatively large baseline CBF deficit was observed (median 33% (IQR 16–72%)); by comparison, in patients in whom there was no RAPID-defined penumbra under the optical probe, the baseline CBF deficit was smaller (median 20% (IQR 1–28%); p=0.04). When the optical probe overlaid the penumbra, a smaller persistent CBF deficit was associated with both a better functional outcome (online supplemental figure S4A) and a trend toward smaller infarct volumes (online supplemental figure S4B). In contrast, when the optical probe did not overlay the RAPID-defined penumbra, a smaller persistent CBF deficit was not associated with functional outcome (online supplemental figure S4C), but there was a trend toward smaller infarct volumes (online supplemental figure S4D). In a secondary analysis, probe location was added to the previously described multivariate models, but probe location was not independently associated with either outcome (functional outcome or infarct volume), nor did its inclusion in the model detract from the association between persistent CBF deficit and outcome. Still, the probe location raises the possibility that DCS may be more informative of reperfusion status in patients with ICA than MCA occlusion. To highlight the ability of DCS to recognize impaired reperfusion, the persistent CBF deficit was compared based on site of occlusion in the subgroup of patients who had a bad outcome. Those with MCA occlusion and a bad outcome had a median persistent CBF deficit of 20% (range 0–33%). In contrast, those with ICA (or tandem) occlusion and a bad outcome had a median persistent CBF deficit of 45% (range 23–99%), p=0.05.

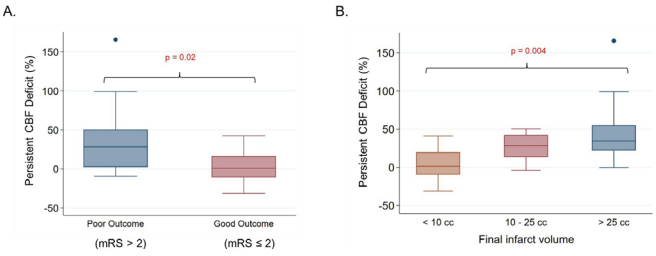

Figure 2 Persistent cerebral blood flow (CBF) deficit and outcomes. (A) Functional outcome was assessed by the modified Rankin Scale (mRS) 90 days post-stroke, and categorized as good (≤2) or poor (>2). The persistent CBF deficit was smaller in those who achieved a good functional outcome. The p value was calculated by a Wilcoxon Mann–Whitney test. (B) Infarct volume was categorized by tertiles (<10 mL, 10–25 mL, and >25 mL). The persistent CBF deficit was different across the infarct volume tertiles. The p value was calculated by a Kruskal–Wallis test.

DISCUSSION

The vast majority of patients with LVO achieve successful recanalization via EVT, based on the current accepted standard of mTICI 2b or greater. However, despite successful recanalization, the increase in microvascular CBF was highly variable and did not correlate with radiographic or functional outcome in our cohort. Using non-invasive monitoring of microvascular CBF during EVT, we show that persistent CBF deficit provides an individualistic characterization of how closely microvascular reperfusion matches the pre-EVT CBF deficit. This work introduces 'persistent CBF deficit' as a novel physiologic biomarker that characterizes the adequacy of reperfusion in real time. Identifying patients with large persistent CBF deficits (ie, inadequate microvascular reperfusion) should provide opportunities to enrich future studies of adjuvant therapies aimed at CBF optimization after EVT.

Table 2 Univariate analysis: factors that impact infarct volume and functional outcome

		Univariate		Multivariate	
Dependent variable	**Factor**	**OR**	**95% CI**	**OR**	**95% CI**
Good functional outcome (Logistic regression)	Age	**0.94**	**0.90 to 0.98**	**0.88**	**0.79 to 0.98**
	Male sex	2.33	0.59 to 9.17		
	White race	1.31	0.32 to 5.43		
	Baseline NIHSS	**0.89**	**0.80 to 0.98**	0.71	0.76 to 1.09
	tPA	2.14	0.54 to 8.51		
	Site of occlusion	0.43	0.13 to 1.36		
	Left sided occlusion	1.80	0.45 to 7.13		
	Baseline ASPECTS	1.58	0.91 to 4.67		
	Pre-EVT core infarct volume (per 10 mL)	0.69	0.43 to 1.05		
	Pre-EVT penumbra volume (per 10 mL)	0.96	0.88 to 1.05		
	Time from onset to recanalization (per hour)	0.96	0.84 to 1.09		
	% CBF increase (per 10%)	1.12	0.81 to 1.54	1.08	0.62 to 1.87
	Persistent CBF deficit (per 10%)	**0.65**	**0.43 to 0.97**	**0.45**	**0.22 to 0.92**
Infarct volume (<10 mL, 10–25 mL, >25 mL) (Ordinal logistic regression)	Age	1.02	0.98 to 1.05	1.05	0.98 to 1.11
	Male sex	1.35	0.39 to 4.66		
	White race	0.35	0.10 to 1.28		
	Baseline NIHSS	**1.11**	**1.01 to 1.21**	**1.14**	**1.01 to 1.31**
	tPA	0.61	0.46 to 1.13		
	Site of occlusion	3.41	0.67 to 9.09		
	Left sided occlusion	1.15	0.34 to 3.92		
	Baseline ASPECTS	0.65	0.33 to 1.12		
	Pre-EVT core infarct volume (per 10 mL)	**1.64**	**1.05 to 2.55**	1.06	0.57 to 1.95
	Pre-EVT penumbra volume (per 10 mL)	1.02	0.95 to 1.09		
	Time from onset to recanalization (per hour)	1.12	0.99 to 1.27		
	% CBF increase (per 10%)	0.95	0.70 to 1.28	0.78	0.54 to 1.12
	Persistent CBF deficit (per 10%)	**1.72**	**1.16 to 2.56**	**1.89**	**1.10 to 3.25**

Functional outcome was defined by the modified Rankin Scale 90 days following the stroke, and a score of ≤2 constituted a good functional outcome. Logistic regression was used to quantify the association between each factor and a good functional outcome.
Infarct volume was categorized by tertiles (<10 mL, 10–25 mL, and >25 mL). Ordinal logistic regression was used to quantify the association between each factor and infarct volume.
In the univariate analyses, parameters that were significantly associated with the outcome measure (p<0.10) were included in the multivariate model. Age, baseline NIHSS score, and reperfusion metrics (% CBF increase and persistent CBF deficit) were pre-specified to be included in the multivariate models.
ASPECTS, Alberta Stroke Program Early CT Score; CBF, cerebral blood flow; EVT, endovascular thrombectomy; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

Optical CBF monitoring revealed a wide range of reperfusion patterns with successful large artery recanalization. However, when accounting for the variability in baseline CBF deficits, the adequacy of reperfusion is more physiologically interpretable and better correlates with radiographic and clinical outcomes than CBF change alone. Ng *et al* reviewed CT or MR perfusion imaging 24 hours following EVT and found impaired CBF in ~25% of patients after successful large vessel recanalization.[25] This was critical in confirming a disconnect between reperfusion and recanalization, but because perfusion imaging was performed 24 hours after EVT, it was not clear if the perfusion deficits led to stroke expansion or vice versa. The temporal relationship between these variables was clarified when Rubiera *et al* performed perfusion imaging immediately following EVT, confirming that post-EVT hypoperfusion is associated with subsequent infarct growth and poor outcome.[5] In the current study we similarly observed both the presence and relevance of inadequate reperfusion but, by using bedside optical imaging, we showed that reperfusion status can be recognized in the angiography suite without the need for additional radiation or contrast agents. A non-invasive prognostic biomarker such as this may help to explain the variability in clinical outcomes after seemingly successful large vessel recanalization.

In addition to its potential prognostic value, DCS-derived reperfusion metrics may contribute to the understanding of no-reflow following EVT, or provide a bedside treatment target with the goal of optimizing CBF after EVT (ie, whether to target CBF augmentation, mitigating reperfusion injury, or personalizing blood pressure goals). Moreover, by identifying patients with impaired microvascular reperfusion, DCS may help to refine clinical trial populations in the study of EVT-adjuvant therapies. For example, adjuvant intra-arterial thrombolysis post-EVT results in better tissue level reperfusion and smaller final infarct volumes.[26] Selective administration based on real-time hemodynamic monitoring may amplify the impact of such an intervention in those who have inadequate reperfusion and avoid the potential risks for those who are already adequately reperfused. In fact, patients in our cohort who received

intravenous thrombolysis had very favorable microvascular reperfusion (median persistent CBF deficit 2%) but, given the small same size, this was not statistically better than those who did not receive intravenous thrombolysis (median persistent CBF deficit 22%).

In contrast to CT or MR perfusion, DCS has the advantage of being a bedside tool that provides continuous monitoring with high temporal resolution.[13] These advantages are particularly evident in the context of EVT.[19] Although CT/MR can provide snapshots before and after EVT, DCS provides data while the interventionalist has arterial access, and thus DCS has particular appeal if selecting patients for intra-arterial treatment trials. Furthermore, DCS can facilitate longitudinal monitoring beyond the angiography suite to detect deleterious changes in cerebral hemodynamics,[11 14 27–29] and in future work it may facilitate CBF-targeted supportive care.

However, DCS has important technical limitations. Most notably, the optical data reported here were limited to small regions in the prefrontal cortex. Our cohort only included patients with occlusion of the ICA and/or the first segment of the MCA to ensure the optical probe was monitoring tissue in the vascular distribution of interest, but the region monitored with DCS included only a small portion of the MCA territory. Among patients who had a bad clinical outcome, we observed a particularly large persistent CBF in patients with ICA (or tandem) occlusion. It is possible that carotid occlusion results in more severe hemodynamic impairment, but it is also possible that the DCS probes are more informative in this subgroup. When the optical probe was overlaying tissue with more significant hemodynamic compromise, optically measured persistent CBF deficit was more clearly associated with clinical outcome. Nevertheless, even when monitoring tissue that is beyond the boundary of what is operationally defined as the penumbra (Tmax >6 s, as per RAPID), persistent CBF deficit may still be informative. For example, the association between the persistent CBF deficit and infarct volume was independent of the probe/penumbra location. Although the DCS probe is only directly informative of the brain tissue within the ROI under the probe, it is possible that patients who achieve successful recanalization have relatively homogenous CBF throughout the MCA (or ICA) territory, in which case the small ROI is indirectly informative of the broader territory. To explore this issue, better spatial coverage with DCS probes is required, but DCS measurements to date have been largely limited to the forehead because hair and hair follicles greatly diminish the DCS signal.[12 13] Multiple groups are addressing this issue to enable DCS monitoring through hair-covered surfaces. With NIRS, hair is less problematic, so this issue has been addressed by whole-head fiber arrangements (eg, NIRS helmet).[13] Finally, the depth of light penetration limits most optical techniques to the superficial cortex. The development of CTP imaging in the angiography suite is appealing as it may resolve logistical barriers, reduce time, and provide the necessary topographic detail,[30] but at the expense of additional radiation and contrast exposure.

Study limitations

The study has some limitations in addition to the technical limitations of DCS outlined above. The sample size is relatively small, which limits statistical power and the number of factors that can reasonably be included in the multivariate model. Still, after including all significant univariate factors, age, and baseline stroke severity, persistent CBF deficit was independently associated with the outcome measures of interest. In the future, a larger cohort might allow for inclusion of additional factors that were not significant in the univariate analysis but have ample evidence of a strong relationship with outcome (eg, time from stroke onset to recanalization). The study included a convenience sample of consecutively recruited subjects, so the extent to which the findings are generalizable is more limited than if the patients were selected at random. In 30% of subjects the infarct volume was calculated on CT rather than MRI. Manual segmentation may be less precise with CT but, reassuringly, infarct volumes were similar in both modalities. Baseline CBF deficit and microvascular reperfusion were measured by two different modalities—CTP and DCS, respectively. This introduces a limitation in calculating the difference between these two metrics but, to mitigate this limitation, each metric was calculated as a percentage (ie, normalized) to simplify the inter-modality comparison. This was necessary because DCS quantified relative CBF over the course of the monitoring session (not absolute CBF). Thus, quantifying a baseline deficit with DCS is particularly challenging. One might consider comparing the DCS signal in the ischemic hemisphere with the unaffected hemisphere to quantify the baseline deficit, but factors like probe position and skin contact may influence the optical signal and render an inter-hemispheric comparison unreliable. This could be overcome in future work by injecting a calibrating intravenous dye to allow for absolute CBF quantification.

CONCLUSION

Persistent CBF deficit is a novel physiologic metric that quantifies the adequacy of microvascular reperfusion based on real-time DCS monitoring during EVT. It characterizes how well microvascular reperfusion (supply) offsets the baseline CBF deficit (demand). This simple personalized approach accounts for the variability in stroke hemodynamics across patients. More adequate reperfusion, quantified as a small persistent CBF deficit, is associated with favorable radiographic and functional outcomes. Thus, CBF monitoring might have prognostic value after EVT and it might also provide a treatment target in which personalized stroke care aims to optimize CBF. Furthermore, consideration of persistent CBF deficits may identify an enriched population for clinical trials evaluating EVT-adjuvant therapies and neuroprotectants.

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