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Relationships between hypercarbic reactivity, cerebral blood flow, and arterial circulation times in patients with Moyamoya Disease

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Abstract

Purpose—To evaluate the correlation between angiographic measures of Moyamoya disease and tissue-level impairment from measurements of tissue perfusion and cerebrovascular reactivity (CVR).

Materials and Methods—The relationship between perfusion-weighted arterial spin labeling (ASL) and hypercarbic blood oxygenation-level dependent (BOLD) CVR and time-to-peak (TTP) were compared with angiographically measured risk factors including arterial circulation time (ACT) and modified Suzuki Score (mSS) in patients (n=15) with Moyamoya disease.

Results—Hemodynamic contrasts provided information not apparent from structural or angiographic imaging. Mean z-statistics demonstrate that BOLD is significantly ($P=0.017$) higher in low mSS hemispheres ($z\text{-statistic}=5.0\pm 2.5$) compared to high mSS hemispheres ($z\text{-statistic}=3.7\pm 1.7$), implying that regions with less advanced stages of Moyamoya disease have higher reactivity. After correcting for multiple comparisons, a strong trend for a direct relationship ($R=0.38$; $P=0.03$) between BOLD TTP and ACT was observed, and a significant inverse relationship between CBF and ACT ($R=-0.47$; $P=0.01$) was found, demonstrating that BOLD and ASL contrasts reflect DSA measures of vascular compromise in Moyamoya disease, albeit with different sensitivity.

Conclusion—Correlative measures between angiography and hemodynamic methods suggest that BOLD and ASL could be used for expanding the diagnostic imaging infrastructure in Moyamoya patients and potentially tracking tissue response to revascularization.

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Keywords

CBF; BOLD; reactivity; Moyamoya disease; stroke; stenosis

Introduction

Moyamoya disease is characterized by progressive stenosis of the distal internal carotid arteries (ICA) and ICA branches with unknown etiology. The most frequent presentation for Moyamoya patients in North America and Europe is ischemic stroke or transient ischemic attack (TIA) (1). Secondary stroke risk may be as high as 10% per year in this debilitating disease (2), which most commonly affects women in their 3rd or 4th decade. The extent of intracranial vascular stenosis and the presence or absence of collaterals has traditionally been used as surrogates for disease severity and stroke risk. These macrovascular changes are measured with digital subtraction angiography (DSA), which is the gold standard for staging Moyamoya disease. However, it is unclear how arterial stenosis translates to parenchymal impairment at the tissue level. This question is fundamental, as large vessel disease and related collateralization do not directly relate to hemodynamic compromise at the tissue level: collaterals may either reflect aggressive, unstable disease or alternatively adequate protective compensatory mechanisms (3). MRI holds promise for elucidating this relationship and providing a complementary or alternative diagnostic technique to DSA, which has significant vascular risks and contrast-related complications.

Noninvasive MRI techniques and analysis strategies for assessing hemodynamic impairment have been proposed, yet a lack of cross-modal validation studies with standardized radiological measurements and clinical scores has precluded routine clinical implementation. Here, we aim to characterize the relationship between DSA metrics of disease severity and multiple spatial and temporal signal characteristics of two relatively promising, yet sparsely clinically utilized, noninvasive MRI methods for assessing tissue hemodynamics: cerebral blood flow (CBF)-weighted arterial spin labeling (ASL) and blood oxygenation level-dependent (BOLD) hypercarbic MRI.

Physiologically, BOLD signal is an indirect marker of tissue function, arising from complex metabolic and hemodynamic modulations (4,5). During hypercarbia, BOLD contrast derives from a large increase in CBF and moderate increase in cerebral blood volume (CBV), with little or no change in the cerebral metabolic rate of oxygen consumption (CMRO₂) (6). A smaller increase in CBF relative to CBV will lead to a smaller BOLD response, and a slower increase in CBF relative to CBV will lead to a delay in the time-to-peak (TTP) of the BOLD signal increase. Importantly, most studies focus only on the magnitude of the BOLD response, with comparatively less information available on temporal signal features.

In this study, we first confirm the relationship between two known clinical measures of impairment: (i) DSA-measured arterial circulation time (ACT) and (ii) the modified Suzuki Score (mSS), which accounts for internal carotid, middle cerebral artery (MCA) and anterior cerebral artery (ACA) disease, as well as the presence or absence of lenticulostriate collaterals (7). We hypothesize (Hypothesis 1) that the time-to-peak (TTP) of the BOLD response, which is fundamentally a measure of the time for parenchyma to increase CBF and CBV (8), positively correlates with the angiographic measure of impairment, ACT, and therefore provides a noninvasive marker of hemodynamic compromise. Next, we test the hypothesis (Hypothesis 2) that hypercarbic BOLD responses inversely correlate with ACT. Finally, it is unclear whether baseline hemodynamics are similarly related to angiographic impairment as reactivity measures. To assess this (Hypothesis 3), we implemented an arterial spin labeling (ASL) MRI approach, which has previously been directly compared

with invasive PET and dynamic contrast enhanced (DCE) MRI methods (9), to quantify the extent to which baseline ASL contrast correlates with ACT. Results of this study demonstrate the extent to which temporal features of the hypercarbic BOLD response, and baseline CBF-weighted imaging, collectively or independently reflect similar information as DSA measures of impairment in patients with Moyamoya disease.

Materials and Methods

Subjects

Demographic, clinical, and radiographic data were analyzed from consecutive Moyamoya patients (n=15) referred from an endovascular neurosurgeon for this study. All patients had idiopathic Moyamoya disease, as they did not have risk factors for acquired Moyamoya syndrome (or secondary Moyamoya). Patients were included in the study if conventional angiography, performed for clinical purposes, demonstrated intracranial findings of Moyamoya disease. All patients provided informed, written consent, and Institutional Review Board approval was obtained for these analyses. Two patients underwent indirect revascularization (EDAS) following the initial scan, and these two patients were re-scanned at a six-month follow-up to assess changes in tissue contrast. Patient demographics are summarized in Table 1.

MRI

All patients were scanned using a 3T MRI (Philips Achieva, Best, The Netherlands) between January 2011 and December 2011 using body coil transmission and SENSE-8 array coil reception with a multimodal protocol including: (i) T_1 -weighted (MPRAGE: $1 \times 1 \times 1 \text{ mm}^3$; TR/TE=8.9/4.6 ms; duration=3 min 47s), (ii) T_2 -weighted FLAIR ($0.9 \times 0.9 \times 1 \text{ mm}^3$; TR/TE=11000/120 ms; multishot turbo spin echo inversion recovery; duration=1 min 39s), (iii) CBF-weighted pseudo-continuous ASL (pCASL; $3.4 \times 3.4 \times 5 \text{ mm}^3$; TR/TE/TI=4000/17/1650 ms; 16 slices; bipolar dephasing gradients; duration=6 min) and (iv) hypercarbic BOLD ($3.4 \times 3.4 \times 5 \text{ mm}^3$; TR/TE=2000/35 ms; 30 slices; duration=15 min). For BOLD, a block paradigm of 3/3 min baseline (room air) / 5% carbogen (5% CO_2 ; 95% O_2) breathing repeated twice was used. Patient vitals (heart rate, blood pressure, pulse oximetric saturation and end-tidal CO_2 , EtCO_2) were recorded throughout the scan. The hypercarbic temporal dynamics and baseline perfusion were obtained and processed in approximately one hour. All MRI data were corrected for motion, baseline drift and were co-registered to T_1 and standard space (MNI; 2 mm) using offline registration routines (10).

DSA

Four-vessel DSA was performed in the neuroangiography suite using a Philips Allura Xper biplane neuro X-ray system with the patient in the supine position. Selected arterial catheterizations of bilateral internal carotid arteries and bilateral vertebral arteries were performed in multiple projections using nonionic, water-soluble intra-arterial contrast. All injections were performed by hand by the collaborating vascular surgeon using the following volumes and rates: ICA injections—3–4 cc over 0.5s, ECA injections—2–3 cc over 2s, CCA injections—4–5 cc over 0.5s. Digital images were acquired at three frames/second for the first four seconds, then one frame/second for the next eight seconds, and 0.5 frames/second thereafter. Stenosis degree was classified as the ratio of the width of the stenosed lumen to the width of the normal distal vessel. If there was no normal distal vessel, the stenosed lumen was measured against the normal lumen proximal to the stenosis.

ACT

One neuroradiologist, blinded to clinical history and BOLD and ASL results, retrospectively reviewed the DSA images and calculated the ACT; and, in a separate session, determined (mSS) for each internal carotid artery. ACT was modified from that of Milburn et al. (11) and similar to that of Yamamoto et al. (12) ACT was defined as the interval between initial opacification of the ipsilateral cavernous ICA and the maximum capillary blush phase within the regional territory of interest (ACA or MCA). If the ipsilateral ICA was occluded, ACT was defined by the interval between the initial opacification of the predominant collateral feeding artery (either the contralateral cavernous ICA or the external carotid artery) at the cranio-caudal level of the cavernous ICA and the maximum capillary blush phase of the regional territory of interest.

mSS

Suzuki's classification for Moyamoya disease was designed to track vascular changes longitudinally with serial angiograms (13). Modifications of the Suzuki score have subsequently been made so that the score can be applied to individual cases (7). The mSS used for this study has been used previously (14) and includes the following five stages of disease severity: stage 0, no evidence of vessel disease; stage I, mild-to-moderate stenosis around the carotid bifurcation with absent or slightly developed ICA disease; stage II, severe stenosis around the carotid bifurcation or occlusion of either the proximal ACA or MCA with well-developed ICA Moyamoya disease; stage III, occlusion of both the proximal ACA and MCA with well-developed ICA Moyamoya disease (only a few of either the ACA or MCA branches or both are faintly opacified in antegrade fashion through the meshwork of ICA Moyamoya disease); and stage IV, complete occlusion of both the proximal ACA and MCA with an absent or a small amount of ICA Moyamoya disease (without opacification of either the ACA or MCA branches in antegrade fashion).

Analysis

The primary objective of this study was to assess the correlation between the more novel MRI measurements (i.e., BOLD hypercarbia response, TTP, and baseline CBF) and the conventional clinical and imaging measures (i.e., mSS and ACT). The mSS score is derived from a test with very coarse, discrete values (e.g., 0, 1, 2, 3, 4) and therefore correlation testing between these values and those over a more continuous range is suboptimal; therefore, ACT was used for correlation testing in this study. Three hypotheses were tested: Hypothesis 1: BOLD TTP correlated directly with ACT; Hypothesis 2: BOLD signal change correlates directly with ACT; Hypothesis 3: Baseline ASL-measured CBF correlates directly with ACT. For analysis, disease severity, as measured by the mSS, was grouped by cerebral hemispheres. In patients with asymmetric mSS, BOLD and ASL data were oriented using the FMRIB Linear Image Registration Tool (FLIRT) (15) such that radiological right and left were higher and lower mSS, respectively. For BOLD, voxel-by-voxel measurements were made using custom Matlab scripts for: (i) CVR, quantified as mean equilibrated signal in response to hypercarbia (S) normalized by end-tidal CO_2 change (EtCO_2 ; calculated as the difference between the baseline EtCO_2 and carbogen EtCO_2 level); (ii) z-statistic with hypercarbia, indicative of the statistical strength of the BOLD response normalized by the noise (16); and (iii) time-to-peak (TTP), quantified as the time for the BOLD signal to plateau during the hypercarbia periods. Z-statistic maps were used for visualizing reactivity, as is convention, but not directly for correlation testing. The plateau was calculated as the mean signal change of the BOLD signal during the final one minute of carbogen breathing (thereby providing 2 min for signal to reach its stimulus-induced steady state). The standard deviation of this signal plateau (30 data points) was also calculated and the TTP was determined by the time when two subsequent data points were both within one standard deviation of the plateau value. This procedure was found to produce consistent

measurements of TTP and was also less susceptible to noise than if only a single data point was considered for TTP calculations. For signal change detection and z-statistic classification, standard temporal autocorrelation routines from the FMRIB Expert Analysis Tool (16) incorporating a linear model and noise prewhitening were applied to BOLD data, which was pre-smoothed spatially using a Gaussian kernel with full-width-half-max (FWHM)=3 mm (16). For pCASL, all analysis was performed in Matlab. First, label acquisitions were pair-wise subtracted from the control acquisitions and averaged. Subsequently, a single-compartment kinetic model incorporating the flow-modified solution to the Bloch equation was applied to quantify CBF (17), using a constrained nonlinear optimization routine, in absolute units (ml/100g/min) on a voxel-by-voxel basis. ASL images were co-registered to standard space using the non-labeled image as a reference (which is effectively a short TE gradient echo EPI image), recording the transformation matrix, and applying the transformation matrix to the difference image. Finally, values for all parameters were recorded regionally in the high- and low-mSS hemispheres. Territories were defined by applying a separate mask generated from a regional perfusion imaging approach to the atlas-normalized BOLD and ASL data. This mask, which was determined from scans of 24 older adults, using an approach that has been previously assessed for reproducibility (18), with no symptoms consistent with cerebrovascular disease, was used for all patients; therefore, the same region was analyzed in all participants. This mask is shown in Figure 1.

Considerations for outliers were included with outlier criteria being data falling three standard deviations or more beyond the mean. Correlative findings were assessed in terms of Pearson product moment correlation coefficients, with an unadjusted ($P=0.05$) and Bonferroni-adjusted (three comparisons; $P=0.02$) or Sidak-adjusted (three comparisons; $P=0.025$) significance level being required for significance.

Results

No data points met outlier criteria. Adequate co-registration was achieved in 12 of 15 patients, with large infarcts in the remaining three patients preventing co-registration. These three patients were excluded from group analyses. The 12 remaining patients (10 females and 2 males) had a mean age of 46 years (range 28–68 years). One of these 12 patients presented with an intraparenchymal hemorrhage; three presented with TIAs; and eight presented with infarcts. In seven of the eight patients with infarcts, the hemisphere identified as more severely affected by ACT or mSS was the infarcted hemisphere. Six of the 12 patients presented with lateralizing symptoms. Lateralizing symptoms included symptoms which could be referred to the corresponding hemisphere and included numbness and/or weakness on one side of the face or body. Non-lateralizing symptoms included symptoms which could not be localized to one hemisphere, such as headache, psychological symptoms, memory complaints and personality deficits. Half of the cerebral hemispheres studied had been revascularized surgically (12 of 24) with direct EC-IC bypass or indirect bypass (encephalo-duro-arterio-myo-synangiosis (EDAMS) and encephalo-duro-arterio-synangiosis (EDAS)).

First, a strong relationship between ACT and mSS was found ($R=0.51$; $P=0.007$), as expected from the origin of these two measures.

Figure 2 shows mean, co-registered BOLD CVR and CBF maps oriented such that the high (abnormal) mSS hemisphere (mean= 2.5 ± 1.4) is shown on radiological right, whereas the low mSS hemisphere (1.6 ± 1.4) is radiological left. These data depict all patients with asymmetric mSS ($n=8$; Table 1) for identical slices. Both measures of tissue impairment show asymmetric contrast, yet the z-statistic is more visually striking than the baseline CBF.

The mean z-statistics demonstrate that CVR is significantly ($P=0.017$) higher in low mSS hemispheres ($z\text{-statistic}=5.0\pm2.5$) compared to high mSS hemispheres ($z\text{-statistic}=3.7\pm1.7$), implying that regions with less advanced stages of Moyamoya disease by angiography have improved CVR.

Figure 3 demonstrates (A) a strong trend for a positive correlation between BOLD TTP and ACT (Figure 3A; $P=0.03$), (B) no correlation between the BOLD $\Delta S/\Delta \text{EtCO}_2$ and ACT (Figure 3B; $P=0.39$) and (C) a significant correlation between the ASL-measured CBF-weighted contrast and the ACT (Figure 3C; $P<0.01$). These findings suggest that on average patients with prolonged ACT have delayed hypercarbic TTP and lower baseline CBF, however the ACT has no relevance on the magnitude of the BOLD hypercarbic signal change.

To understand the quality of data on an individual subject level, representative images are included in Figures 4–5. Figure 4 shows an example subject with DSA-confirmed (Figure 4A) Moyamoya disease (mSS of IV on right and mSS of II on left) with unremarkable structural MRI, yet highly asymmetric BOLD reactivity and baseline CBF (Figure 4B). Temporal dynamics of the BOLD timecourse (Fig 4C) corresponds with the asymmetric involvement by DSA staging, revealing periods of high CVR with short TTP in the less severely diseased left hemisphere (green), high CVR with delayed TTP (blue) in the compromised right temporal lobe, and a negative CVR in the right posterior watershed region (red).

Figure 5 shows the potential for BOLD to detect changes in tissue behavior before and after revascularization procedures. Clear increases in BOLD CVR can be seen in both patients for which pre- and post-revascularization data are available.

Discussion

Results of this study demonstrate the extent of concordance between clinical measures of disease severity in Moyamoya patients, quantified from ACT, and more novel measures of ASL-measured CBF and BOLD-measured CVR. The results also demonstrate visible similarity (Figure 2) between noninvasive hemodynamic measures, including hypercarbic BOLD CVR maps and resting CBF, and the correlative findings outline the extent to which each of these measures correlate with DSA measures of impairment. Moyamoya patients with delayed ACT (reflecting more severe angiographic measures of disease) generally had lower baseline CBF and prolonged BOLD TTP compared to Moyamoya patients with less severe angiographic stages of disease. Evaluation of the temporal features of the BOLD response was a key aim of this work. Importantly, TTP is delayed in Moyamoya patients ($\text{TTP}=90\pm27\text{s}$), therefore hypercarbic stimulus duration >2 min are likely required. The correlation between TTP measured with BOLD and ACT measured with DSA have not been previously reported. Prior clinical studies showing this correlation generally focused on mean signal changes with BOLD, with little information describing the rate of changes. *The discrepant correlative findings in Figure 3 also demonstrate that BOLD reactivity cannot be inferred from resting baseline CBF in patients with Moyamoya disease, implying that baseline perfusion is not predictive of cerebrovascular reserve in this population.* These findings are consistent with SPECT studies, which have shown a weaker correlation between the cerebral circulation time and baseline CBF compared to that following acetazolamide challenge (12).

Moyamoya disease is generally considered a surgical disease (2). However, there are no accepted standards to accurately stratify low- and high-risk Moyamoya patients. The large range of BOLD and CBF contrast between Moyamoya patients with intermediate (e.g., 2–3)

mSS suggests non-uniform hemodynamic impairment at the tissue level, which is not reflected by mSS staging. It is assumed that patients with increased hemodynamic compromise are at increased risk for stroke, yet reliable measurements of hemodynamic compromise are likely required with specific sensitivity to tissue impairment and corresponding stroke risk to validate such assumptions. An ongoing longitudinal study evaluating whether increased oxygen extraction is a predictor of subsequent stroke risk in Moyamoya patients (1) may validate treatment stratification based on hemodynamic impairment with PET. Nariai et al also used PET to identify high-risk hemodynamic patterns which placed Moyamoya patients at risk for progression; but emphasized the necessity to build clinically available imaging procedures to measure hemodynamic impairment (19). Nuclear medicine techniques require the administration of radioactive tracers and are limited by poor spatial and temporal resolution. In contrast, noninvasive measurement of hemodynamic impairment with MRI is readily accessible for most treatment centers, due to technical innovations over the past decade, and can be performed and processed within an hour.

A concern may be raised regarding how reproducible the signal changes are between the hypercarbic blocks. We include a representative data set (Figure 4) so that it is possible to gauge the similarity of the response between the stimulus blocks. In this study, we did not find significant (two-tailed; $P > 0.05$) differences between either BOLD reactivity or EtCO_2 between the two stimulus blocks, and independent studies have performed controlled measurements demonstrating the stability of similar paradigms when applied appropriately (20–22).

We have measured a TTP value of 26 ± 9 s in healthy controls ($n=8$; age=18–47 yrs; data not shown) with no known risk factors of cerebrovascular disease, which was less than the mean TTP reported in this study. These measurements were acquired in MCA and VBA artery flow territories, and we found no significant lag in TTP between these regions in the healthy volunteers. Importantly, the delay in the TTP measured in healthy volunteers relative to a typical hemodynamic response function of 3–5 s is attributable to the time for the carbogen gas to reach the mask. Identical tubing length was used in all scans in this study, and therefore while this TTP is a reflection of both the vascular reactivity time and the gas transit time through the tubing, we believe that the latter variable was controlled in all volunteers.

Several limitations of this study should be noted. First, while hypercarbic BOLD has provided important insights into BOLD physiology in healthy volunteers (4,23–26) and patients with ischemic cerebrovascular disease (14,27,28), hypercarbia is not a natural measure of autoregulatory capacity. However, BOLD CVR studies have shown correlations between CVR and disease severity (14), surgical response (29) and cortical thinning (30). Thus, although hypercarbia is not a direct measure of autoregulatory capacity, it carries prognostic potential. A second limitation is our small patient cohort, which reflects the low prevalence of Moyamoya disease (<1 per 100,000). Our sample size is similar to or larger than most studies of cerebral hemodynamics in this population, which typically are performed on 5–20 Moyamoya disease patients and do not incorporate multimodal imaging. Third, ASL contrast is dependent on both CBF and arterial arrival time (AAT). In highly collateralized Moyamoya patients, the AAT may be longer than the blood water T_1 , thereby preventing quantification of CBF at the time the blood reaches capillaries (31). Delayed AAT also creates challenges when using dynamic susceptibility contrast MRI in Moyamoya patients (32). Despite these challenges, other authors have found good correlation between ASL, SPECT and DSA and ASL and acetazolamide SPECT (9). The purpose of the present study was simply to understand whether ASL contrast (which under scenarios of delayed arrival times will provide a mixture of contrast from both arteriolar cerebral blood volume

and perfusion), provides similar or distinct contrast to the arterial circulation time. In our correlation analyses, we observed a strong inverse relationship between the ASL contrast and the ACT. Given the contrast mechanism of ASL, in patients with long ACT this correlation may be driven by blood water that has not yet reached the capillary exchange site, hypoperfusion, or a combination of the two. Fourth, co-registration is always a concern in clinical multi-subject imaging trials. While critical in many applications, non-linear registration is extremely sensitive to small intensity gradients, motion, and unique contrast secondary to spatially localized infarcts, all of which we have found to manifest as confounding complications in stroke patients. Furthermore, the results presented in this study are from relatively non-specific brain regions, broadly defined by the major flow territories (MCA and VBA) that transcend multiple brain lobes and regions. Therefore, we determined that non-linear registration using standard routines was suboptimal for this application.

In conclusion, clinical adoption of noninvasive MRI measures of hemodynamic compromise has been hampered by a lack of information regarding prognostic potential and correlation with standard radiographical measures. We have therefore performed correlative measurements between a DSA measure of Moyamoya disease severity (ACT) and hemodynamic measures from MRI, using novel hypercarbic temporal dynamics and perfusion-weighted imaging. Our results suggest that BOLD and ASL, which are generally accessible techniques, provide complementary information to angiography. Whereas ACT and mSS provide only coarse indicators of vascular impairment, BOLD and ASL provide tissue-level information of parenchymal reserves. This study opens the door for clinical trials evaluating the predictive value of these non-invasive hemodynamic contrasts for identifying Moyamoya patients at highest risk for stroke.

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Figure 1. Flow territory mask used in all subjects

The flow territories shown are the mean flow territories obtained from a vessel-encoded arterial spin labeling scan in 24 healthy volunteers. Blue = right internal carotid artery territory; Green = left internal carotid artery territory; Red = basilar artery territory.

Figure 2. Mean BOLD and CBF data in Moyamoya patients with asymmetric mSS (n=8)
 Group-averaged BOLD CVR maps for patients with asymmetric mSS (n=8), with low mSS (low disease) oriented as radiological left and high mSS (high disease) as radiological right. (A) The BOLD z-statistics are visually higher in low mSS hemisphere, a trend that is (B) also apparent in the CBF data (ml/100g/min); however the trend is less visually obvious. Representative slices are shown enlarged in (C).

Figure 3. Correlative information between BOLD, ASL-measured CBF and clinical measures (A) BOLD time-to-peak (TTP) in response to hypercarbia, (B) BOLD normalized signal changes in response to hypercarbia, and (C) baseline CBF correspondence with arterial circulation time (ACT) as measured from DSA.

Figure 4. Multi-modal measurements in Moyamoya disease in a representative patient
 53 yr/F with Moyamoya disease with three TIAs in the month prior to MRI. (A) DSA indicates right cervical ICA occlusion; L ICA injection (left) shows severe left M1 involvement with extensive lenticulostriate collaterals bilaterally (arrows). The right cortical and subcortical MCA territory has delayed transit time, filling on a delayed image (right) primarily via pial collaterals. (B) No impairment can be seen on FLAIR or T₁ MRI, however the right MCA territory has severely reduced hypercarbic BOLD CVR; the same hemisphere has markedly reduced baseline CBF (ml/100g/min) on ASL. (C) The BOLD CVR time course for different regions shows high heterogeneity in response to hypercarbia (gray). This includes regions of normal CVR (green), delayed CVR with delayed time-to-

peak (blue) and even negative CVR (red), indicative of abnormal autoregulation and/or vascular steal phenomenon. Findings imply chronic oligemia or ischemia in the right MCA territory, which cannot respond to hypercapnia. Tissue hemodynamics obtained from BOLD and ASL data provide critical information in this patient at risk for infarct, not provided by structural MRI or DSA.

Figure 5. Demonstration of BOLD reactivity measurement changes six months after surgical revascularization

(A) Patient 1 (Table 1) structural and BOLD reactivity maps before and after EDAS (site of EDAS identified by arrows) Hemispheric reactivity is generally increased unilaterally following EDAS, with focal locations of hyperreactivity pre-EDAS slightly reduced post-EDAS. (B) Patient 2 (Table 1) before and after EDAS. Clear focal increases in reactivity can be seen near the EDAS location, and reductions in hyperreactivity contralateral to EDAS are present on the follow-up scan. All reactivity maps are co-registered to the post-EDAS T1-weighted scan, to allow for direct comparison of spatial regions within the same subject space. Color bar shows BOLD z-statistics with hypercarbia stimulus.

Table (1)

Patient Information

Arterial circulation times (ACT) calculated from dynamic subtraction angiography (DSA).

Case	Age (yrs)	Sex	Presentation	Lateralizing Symptoms (Y/N)	Surgery	Vessel (stenosis %)	ACT (s)	mSS	MCA BOLD TTP (s)		MCA BOLD S/ EtCO ₂		MCA CBF (ml/100g/min)	
									R	L	R	L	R	L
1	35	F	Infarct: R ACA R Watershed	Y L Hemisphere TIA	R EDAMS	R MCA (100) R ACA (100) L MCA (100) L ACA (100) R ICA (100) L ICA (100)	2.25 3.25 1.50 1.50	4 4	86	80	0.36	0.35	24	34
2	28	F	IPH: R basal ganglia	Y R Hemisphere IPH	L EC-IC bypass L EDAMS	R MCA (100) R ACA (100) L MCA (100) L ACA (100) R ICA (0) L ICA (100)	1.34 1.34 2.25 2.75	3 4	89	77*	0.13	0.14*	46	42*
3	68	F	TIA: Dizziness Paresthesias	N		R MCA (100) R ACA (0) L MCA (0) L ACA (100) R ICA (79) L ICA (100)	1.00 1.67 1.67 1.00	2 2	94	114	0.24	0.25	50	54
4	59	M	Infarct: Bilateral MCA L watershed	Y L Hemisphere TIA	R EC-IC bypass	R MCA (100) R ACA (100) L MCA (100) L ACA (100) R ICA (100) L ICA (100)	2.25 3.25 3.25	4 3	108*	104	0.11*	0.25	24*	54
5	53	F	Infarct: L caudate	Y R Hemisphere TIA	R EDAS	R MCA (100) R ACA (100) L MCA (100) L ACA (0) R ICA (100) L ICA (0)	3.00 1.25 1.50 0.76	4 2	91*	67	0.20*	0.20	51*	66
6	45	F	Infarct: R watershed	N	R EDAS	R MCA (100) R ACA (80) L MCA (64) L ACA (87) R ICA (52) L ICA (0)	3.00 1.33 1.00 1.00	2 1	90*	50	0.28*	0.32	28*	46
7	50	F	Infarct: R watershed	N	R EDAS	R MCA (46) R ACA (41) L MCA (54) L ACA (100)	2.00 2.50 1.50 2.50	2 2	96	54	0.55	0.55	40	42

Case	Age (yrs)	Sex	Presentation	Lateralizing Symptoms (Y/N)	Surgery	Vessel (stenosis %)	ACT (s)	mSS	MCA BOLD TTP (s)		MCA BOLD S/ EtCO ₂		MCA CBF (ml/100g/min)	
									R	L	R	L	R	L
8	48	F	TIA: R hemisphere	N	R EC-IC bypass R EDAS L EC-IC bypass	R MCA (0) R ACA (100) L MCA (100) L ACA (40) R ICA (46) L ICA (40)	0.66 1.00 1.00 1.00	2 2	53	77	0.18	0.19	48	50
9	46	F	Remote TIA: L hemisphere	N	L EC-IC bypass	R MCA (0) R ACA (0) L MCA (15) L ACA (100) R ICA (52) L ICA (45)	1.34 1.67 1.67 1.34	1 2	120	110 *	0.38	0.33 *	49	44 *
10	49	F	Infarct: L watershed	Y L Hemisphere TIA	L EDAS	R MCA (0) R ACA (0) L MCA (100) L ACA (0) R ICA (0) L ICA (0)	1.00 0.67 1.33 1.67	0 3	92	125 *	0.18	0.15 *	53	49 *
11	33	F	Infarct: L watershed	N	L EDAS	R MCA (0) R ACA (0) L MCA (24) L ACA (51) R ICA (0) L ICA (65)	1.00 1.00 2.00 1.33	0 2	42	63 *	0.26	0.27 *	55	59 *
12	34	M	Infarct: Bilateral watershed	Y R Hemisphere TIA	R EDAS	R MCA (24) R ACA (22) L MCA (100) L ACA (84) R ICA (36) L ICA (42)	1.34 1.34 3.00 2.67	2 2	152	120	0.18	0.19	51	43

* Denotes the hemisphere with higher categorization of disease, as quantified from the mSS.

Other abbreviations: EDAS: encephaloduroarteriosynangiosis; EDAMS: encephalo-duro-arterio-myo-synangiosis; EC-IC: External carotid-Internal carotid; L/R = Left/Right