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ORIGINAL RESEARCH

Quantification of Cerebrovascular Reactivity by Blood Oxygen Level–Dependent MR Imaging and Correlation with Conventional Angiography in Patients with Moyamoya Disease

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BACKGROUND AND PURPOSE: BOLD MR imaging combined with a technique for precision control of end-tidal pCO_2 was used to produce quantitative maps of CVR in patients with Moyamoya disease. The technique was validated against measures of disease severity by using conventional angiography; it then was used to study the relationship between CVR, vascular steal, and disease severity.

MATERIALS AND METHODS: A retrospective analysis comparing conventional angiography with BOLD MR imaging was performed on 11 patients with Moyamoya disease. Iso-oxic cycling of end-tidal pCO_2 between 2 target values was performed during BOLD MR imaging. CVR was calculated as the BOLD signal difference per ΔpCO_2. CVR was correlated with the presence of Moyamoya or pial collaterals and the degree of Moyamaya disease as graded by using a modified Suzuki score.

RESULTS: A good correlation between mean CVR and Suzuki score was found for the MCA and ACA territories (Pearson correlation coefficient, −0.7560 and −0.6140, respectively; $P < .0001$). A similar correlation was found between mean CVR and the presence of pial and Moyamoya collateral vessels for combined MCA and ACA territories (Pearson correlation coefficient, −0.7466; $P < .0001$). On a voxel-for-voxel basis, there was a greater extent of steal within vascular territories with increasing disease severity (higher modified Suzuki score). Mean CVR was found to scale nonlinearly with the extent of vascular steal.

CONCLUSIONS: Quantitative measures of CVR show direct correlation with impaired vascular supply as measured by the modified Suzuki score and enable direct investigation of the physiology of autoregulatory reserve, including steal phenomenon, within a given vascular territory.

ABBREVIATIONS: ACA = anterior cerebral artery; AFNI = analysis of functional neuroimages; AIF = arterial input function; ANOVA = analysis of variance; BOLD = blood oxygen level–dependent; CBF = cerebral blood flow; CVR = cerebrovascular reactivity; CO_2 = carbon dioxide; $\Delta SpCO_2$ = difference per change in end-title carbon dioxide; f = fraction; ICA = internal carotid artery; MCA = middle cerebral artery; neg = negative; PCA = posterior cerebral artery; pCO_2 = partial pressure of carbon dioxide; PET = positron-emission tomography; pO_2 = partial pressure of oxygen; pos = positive; SE = standard error; SPECT = single-photon emission CT; TIA = transient ischemic attack

Moyamoya disease is a vasculopathy affecting the proximal circle of Willis vessels characterized by progressive narrowing and formation of secondary collaterals. Blood flow distal to these stenotic vessels is thought to be maintained by a drop in vascular resistance mediated by small artery and arteriolar vasodilation. As the disease progresses, however, the ability of this autoregulatory system or CVR to preserve adequate perfusion is lost when compensatory arteriolar dilation reaches a maximum. Further increases in vascular resistance at the stenosis ultimately lead to tissue oligemia and possible ischemia. Measurements of CVR can provide valuable information for planning surgical revascularization, assessing the success of such a procedure postoperatively, and predicting the recurrence of focal neurologic symptoms.[1]

CO_2 is a potent vasodilator of the cerebrovasculature and can be used to test the responsiveness of the autoregulatory system in patients with Moyamoya disease. Measurements of regional CBF in response to changes in end-tidal pCO_2 have been accomplished with a number of imaging modalities, including PET,[2] SPECT,[3] CT perfusion,[4] and MR imaging. BOLD MR imaging measurement of CVR, in particular, has recently been shown to be highly correlated with CBF in patients with steno-occlusive disease caused by atherosclerosis or Moyamoya disease.[5]

Blood flow manipulation is typically achieved by acetazolamide stress, breath-hold techniques, or steady-state CO_2 administration via a face mask. These methods produce inconsistent changes in blood flow. Recently, we have implemented a method for precision control of end-tidal pCO_2 and pO_2,[6] permitting accurate correlation of changes in pCO_2 with the BOLD MR imaging signal-intensity response.

In the present work, we used BOLD MR imaging in combination with precise iso-oxic changes in end-tidal CO_2 to

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Clinical and angiographic characteristics of 11 patients[a]

Case No.	Age (yr)	Sex	Clinical Presentation	Suzuki		Collaterals ACA		Collaterals MCA		Collaterals PCA	
				Left	Right	Left	Right	Left	Right	Left	Right
1	48	F	Headache	0	III	0	0	0	2	0	0
2	36	M	Headache	0	III	0	0	0	2	0	0
3	45	M	TIA (left weakness)	II	IV	2	2	0	2	0	0
4	39	F	TIA (right weakness)	II	0	0	0	2	0	0	0
5	33	F	Headache	II	II	2	1	1	1	0	0
6	35	F	TIA (left weakness)	IV	IV	2	2	1	1	1	1
7	44	M	Right facial, arm numbness, slurred speech	IV	0	0	0	2	0	0	0
8	41	M	TIA (right weakness)	IV	III	0	1	2	2	0	0
9	10	F	Asymptomatic	IV	0	1	0	2	0	0	0
10	11	F	TIA (right hand weakness)	IV	IV	2	2	2	2	0	0
11	33	F	Asymptomatic	III	II	2	2	2	2	0	1

[a] 0 indicates no collaterals (M−P−); 1, Moyamoya collaterals only (M+P−); 2, pial and Moyamoya collaterals (M+P+).

produce quantitative maps of CVR in patients with Moyamoya disease. To validate this technique, we correlated measurements of CVR with a modified Suzuki score, which is a measure of disease severity determined by using conventional angiography. The measures of CVR were also correlated with the extent of steal within a vascular territory, providing insight into the physiology of autoregulatory reserve.

Materials and Methods

Patient Selection and Angiographic Scoring

A retrospective analysis was performed on patients with Moyamoya disease undergoing cerebrovascular reactivity measurements before surgical revascularization at our institution. Ethics approval was obtained through our research institute's ethics committee and written consent was given by all participants. Patients without structural brain disease such as ischemic or hemorrhagic stroke and those with a prior conventional angiogram with 6-vessel injection obtained within 6 months before the CVR study were included in the study. A total of 11 patients who underwent a CVR study between October 2005 and June 2007 were evaluated.

The degree of Moyamoya disease as visualized on conventional angiography was scored by a neuroradiologist (D.J.M.) using a modified Suzuki score[7]: stage 0, no evidence of vessel disease; stage I, mild-to-moderate stenosis around the carotid bifurcation with absent or slightly developed ICA Moyamoya disease (almost all of both ACA and MCA branches are opacified in antegrade fashion); stage II, severe stenosis around the carotid bifurcation or occlusion of either the proximal ACA or MCA with well-developed ICA Moyamoya disease (either the ACA or MCA branches or both are clearly defective, but at least several of the ACA or MCA branches remain opacified in antegrade fashion); 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).

Each vascular territory was also assessed for the presence of Moyamoya or leptomeningeal collaterals. For the purpose of scoring these collaterals, a simple binary system was used (M−P− to indicate the absence of Moyamoya or pial collaterals, M+P− to indicate the presence of Moyamoya collaterals but the absence of pial collaterals, M+P+ to indicate the presence of Moyamoya and pial collaterals). The Table summarizes the demographic data and angiographic scoring for the 11 patients included in the study.

Cerebrovascular Reactivity by BOLD MR imaging

MR imaging was performed on a 3T Signa HD clinical MR imaging scanner (GE Medical Systems, Milwaukee, Wisconsin) equipped with 40 mT/m gradient coils and a standard head coil. A standard single-shot BOLD protocol with a spiral readout (TE, 40 ms) was used. The imaging time was 12 minutes for a total acquisition of 320 volumes. Each volume contained 28 sections with a resolution of $3.75 \times 3.75 \times 4.5$ mm. High resolution T1-weighted images were obtained to provide anatomic coregistration. Patients breathed via a tight-fitting mask that was attached to a circuit consisting of a 3 valve manifold and reservoirs for externally supplied gas and exhaled gas. The valves are configured such that external gas is inhaled first and, if the breath size exceeds the gas flow entering the circuit, the balance of inhaled gas is made up with the previously exhaled gas (i.e., rebreathing). External gas is supplied by a custom built computer-controlled gas blender (Respiract; Thornhill Research, Toronto, Canada). It supplies O_2, and mixtures of CO_2 and N_2 (nitrogen) with O_2, to achieve target end-tidal CO_2 and end-tidal O_2 independent of breathing pattern.[8] This resulted in near square wave transitions (within 1–3 breaths) and precise, sustained end-tidal gas levels. We used this approach to cycle end-tidal CO_2 between 40 and 50 mmHg in 90 sec cycles while keeping end tidal O_2 at 100 mmHg during BOLD signal acquisition.

Data Analysis

Image analysis was performed by using AFNI, an open-source environment used for processing and displaying functional MR imaging data. BOLD MR imaging data were transformed onto the Talairach coordinate system, and the BOLD data were temporally shifted and correlated with the patient's CO_2 waveform. A least-squares regression analysis of the BOLD signal intensity versus the CO_2 waveform for each voxel was calculated. For each vascular territory (ACA, MCA, PCA), the CVR for positively and negatively reacting voxels was determined. CVR for each voxel was calculated according to the following:

$$CVR_{voxel} = \Delta S \div \Delta pCO_2,$$

where ΔS is the change in MR signal intensity for a given voxel that occurs between peak and trough CO_2 levels and ΔpCO_2 is the change in end-tidal CO_2 in mmHg. In healthy brain, CVR is positive, reflect-

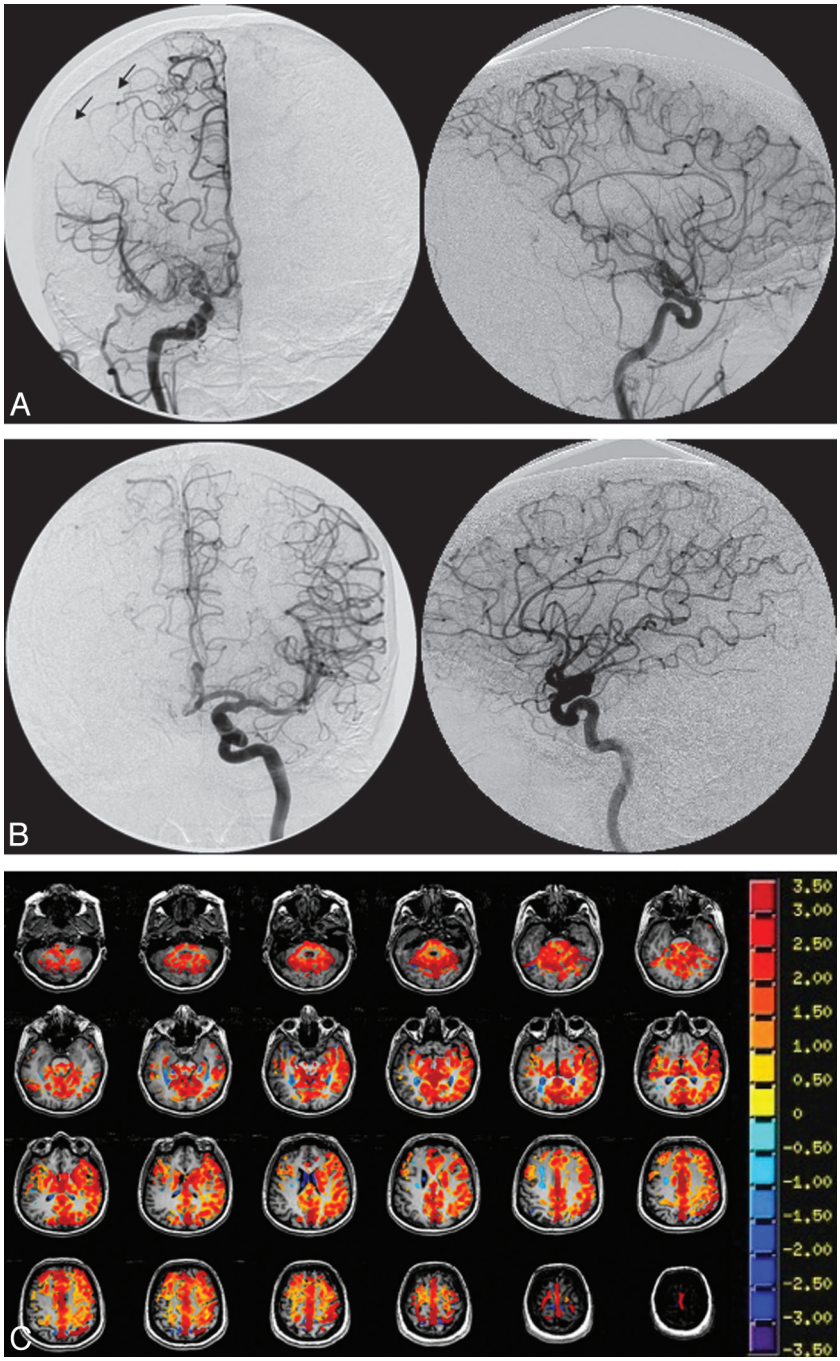

Fig 1. A 48-year-old woman who presented with headache. *A*, There is high-grade stenosis of the main trunk of the right MCA with "puff of smoke" vessels in the region of the stenotic trunk. *B*, The left ICA and branches are normal. Angiography indicates a Suzuki grade II right hemisphere and a Suzuki grade 0 left hemisphere. The arrows indicate surface collaterals extending from the right ACA to the right MCA territory. *C*, The CVR map shows absence of reactivity to the CO_2 stimulus (no color) in the right parietal lobe, corresponding to the region of the angiographic collaterals.

ing an increase in CBF in response to increasing pCO_2. In areas of brain in which blood flow is reduced in response to increasing pCO_2, CVR is negative. Areas of negative CVR are generally thought to be the result of the vascular "steal" phenomenon, whereby hypercapnea leads to diversion of blood from areas of brain where arterioles are maximally vasodilated and vascular resistance is already minimized to areas of the brain capable of decreasing vascular resistance in response to a CO_2 stimulus.[5]

The mean of all positively reacting voxels in a vascular territory (Mean CVR_{pos}) and the mean of all negatively reacting voxels in a vascular territory (Mean CVR_{neg}) were calculated. The Mean $CVR_{combined}$ for a given vascular territory was calculated as a weighted average of negative- and positive-reacting voxels as follows:

$$\text{Mean CVR}_{\text{combined}} = f_{\text{neg}} \times \text{Mean CVR}_{\text{neg}} + f_{\text{pos}} \times \text{Mean CVR}_{\text{pos}},$$

where f_{neg} and f_{pos} are the fraction of negatively and positively reacting voxels respectively.

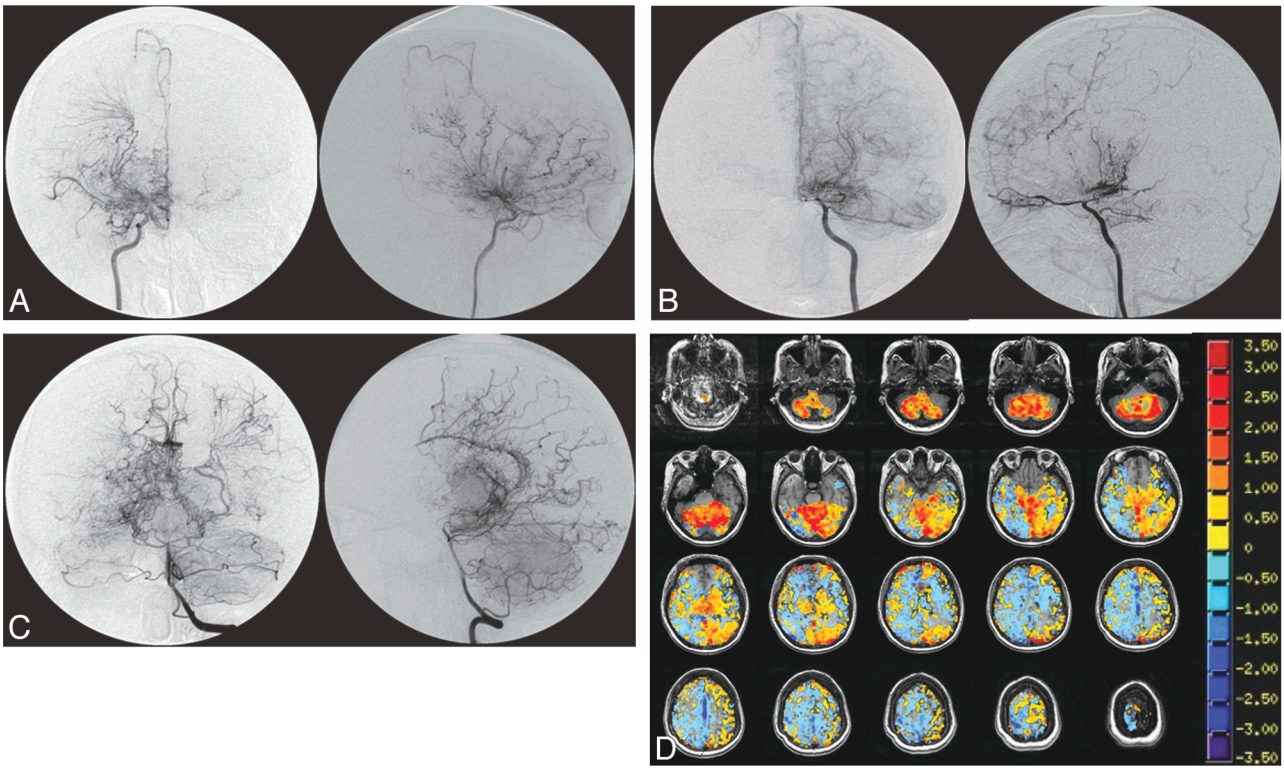

Fig 2. A 35-year-old woman who presented with TIA consisting of left hemiparesis. *A–C,* The angiograms indicate severe stenosis/occlusion of the distal ICAs bilaterally, with extensive Moyamoya vessels consistent with Suzuki grade IV bilaterally. The left vertebral injection (*C*) shows extensive pial collateralization from the posterior circulation to the ACA and MCA territories. However, the right hemisphere is not as well supplied as the left. *D,* This finding is supported by the CVR map, which shows a greater extent of steal phenomena (blue pixels) in the right hemisphere compared with the left. Notice the preservation of reactivity in the relatively well-supplied cerebellum.

Statistical Analysis

Statistical analysis was performed by using Prism (GraphPad Software, La Jolla, California). The correlation between Mean $CVR_{combined}$ for the MCA and ACA territories and the modified Suzuki score, and the correlation between Mean $CVR_{combined}$ for combined ACA and MCA territories and presence of Moyamoya and pial collaterals were calculated with a Pearson correlation coefficient. One-way ANOVA was performed to compare the Mean $CVR_{combined}$ for vascular territories with different Suzuki scores. An unpaired *t* test was used to compare the Mean $CVR_{combined}$ for vascular territories with and without Moyamoya or pial collaterals.

Results

The study group comprised 7 females and 4 males with an age range between 10 and 48 years. Five patients had unilateral disease and 6 patients had bilateral disease. A total of 66 vascular territories were analyzed (11 each of the right and left ACA, right and left MCA, and right and left PCA). CVR maps are shown for 2 patients with varying degrees of Moyamoya disease and the corresponding conventional angiograms for the affected vascular territories (Figs 1 and 2). The CVR maps qualitatively show a correlation between regional changes in CVR and angiographic features of Moyamoya disease.

The Mean $CVR_{combined}$ for MCA and ACA territories was plotted against the degree of Moyamoya disease as observed on conventional angiography and measured by the modified Suzuki score (Fig 3). There was good correlation between

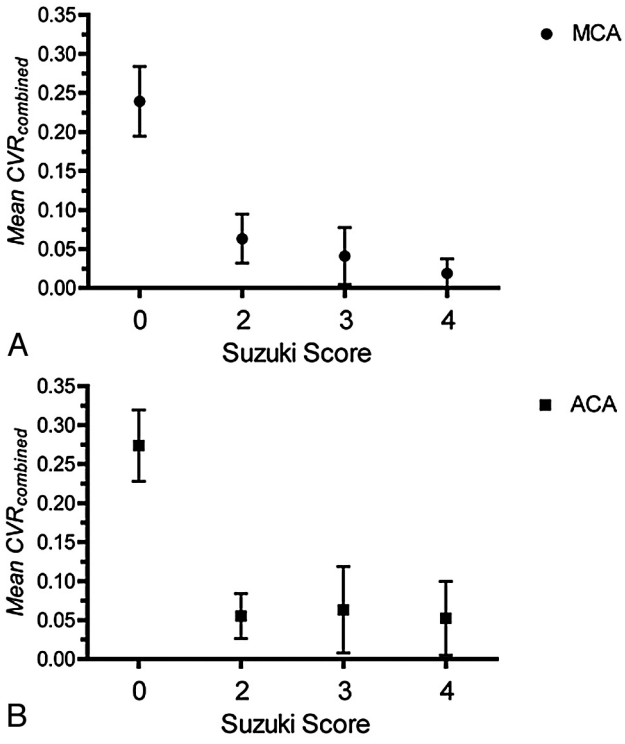

Fig 3. Relationship between Mean $CVR_{combined}$ versus disease severity as measured by the modified Suzuki score. *A,* Mean $CVR_{combined}$ versus the Suzuki score for the MCA territory. *B,* Mean $CVR_{combined}$ versus the Suzuki score for the ACA territory.

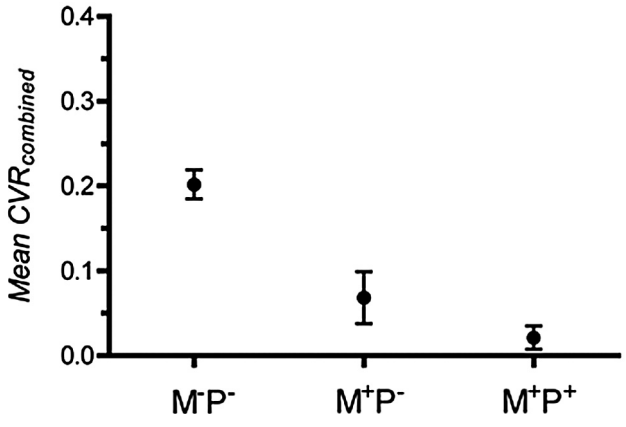

Fig 4. Correlation between Mean $CVR_{combined}$ for MCA and ACA territories and the presence of pial or Moyamoya collaterals. M-P- indicates the absence of Moyamoya or pial collaterals, M+P− indicates the presence of Moyamoya collaterals but the absence of pial collaterals, and M+P+ indicates the presence of Moyamoya and pial collaterals.

Mean $CVR_{combined}$ and Suzuki class for MCA and ACA territories (Pearson correlation coefficient, −0.7560 and −0.6140, respectively); however, the correlation was better for the MCA territory. Vascular territories with Suzuki score >0 had a statistically significant lower CVR score compared with disease-free areas (1-way ANOVA, $P < .0001$ for MCA and ACA territories). There was a decreasing trend of Mean $CVR_{combined}$ with increasing disease score, but the difference was not statistically significant.

The Mean $CVR_{combined}$ was calculated for combined ACA and MCA territories with Moyamoya and pial collaterals (M+P+), Moyamoya collaterals alone (M+P−), and no collaterals (M−P−) (Fig 4). There was a good correlation between Mean $CVR_{combined}$ and the presence of collateral vessels (Pearson correlation coefficient, −0.7466). Territories with vessel collaterals had significantly lower Mean $CVR_{combined}$ (Mean $CVR_{combined} \pm SE = 0.068 \pm 0.031$ and 0.021 ± 0.013 for M+P− and M+P+, respectively) compared with territories with no collaterals (Mean $CVR_{combined} \pm SE = 0.20 \pm 0.017$). Territories containing Moyamoya and pial collaterals (M+P+) had a lower Mean $CVR_{combined}$ compared with territories with Moyamoya vessels alone (M+P−), but this difference was not statistically significant ($P = .11$, unpaired t test).

To examine the dependence of CVR on the extent of vascular steal, we generated plots of Mean CVR_{pos}, Mean CVR_{neg}, and Mean $CVR_{combined}$ versus the fraction of negatively reacting voxels (f_{neg}) for all ACA, MCA, and PCA territories. Vascular territories affected by Moyamoya disease (Suzuki >0) have more vascular steal (higher f_{neg}) compared with disease-free territories (Suzuki = 0). A nonlinear decrease in Mean CVR_{pos} with f_{neg} was found (Fig 5*A*). An exponential decay with a plateau of 0 was fitted to the data ($R^2 = 0.45$). A similar trend for Mean $CVR_{combined}$ against f_{neg} (Fig 5*B*) was fitted to an exponential decay with a plateau of −0.09 ($R^2 = 0.72$). Extrapolating from this fit, the x-intercept (Mean $CVR_{combined} = 0$) occurs with $f_{neg} = 0.52$. A plot for Mean CVR_{neg} illustrates the independence of Mean CVR_{neg} over a wide range of f_{neg} values (Fig 5*C*).

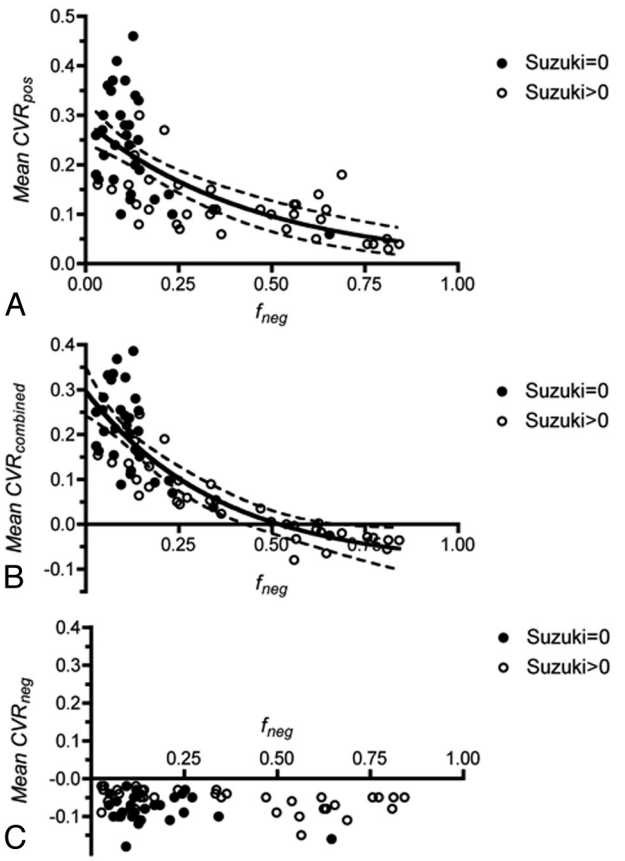

Fig 5. Relationship between Mean CVR_{pos}, Mean $CVR_{combined}$, Mean CVR_{neg}, and the degree of vascular steal (f_{neg}) for all ACA, MCA, and PCA territories. Closed circles represent vascular territories with a Suzuki score of 0, and open circles, Suzuki >0. *A*, Mean CVR_{pos} versus f_{neg}. *B*, Mean $CVR_{combined}$ versus f_{neg}. An exponential decay has been fitted to the data. The dotted lines indicate the 95% confidence band. *C*, Mean CVR_{neg} versus f_{neg}.

Discussion

Measurement of CVR with BOLD MR imaging and the CO_2 rebreathing circuit used in the current study has a number of advantages over existing methods. Nuclear medicine techniques such as PET and SPECT have poor spatial and temporal resolution and involve the administration of radioactive tracers. Changes in CBF measured with CT perfusion have been shown to correlate well with angiographic scoring of Moyamoya disease.[4] The accurate quantification of CBF by using CT perfusion is dependent on an AIF, which is difficult to define in circulation affected by Moyamoya disease. In addition, studies that rely on breath-hold or acetazolamide stress cannot reproducibly create changes in end-tidal pCO_2 and, therefore, cannot accurately quantify CVR. BOLD MR imaging is a readily accessible technique that can produce quantitative maps of CVR with high temporal and spatial resolution, requires no radioactive tracer, and is not dependent on an AIF. Furthermore, the rebreathing technique used in the current study produces reproducible changes in end-tidal pCO_2, allowing truly quantitative and accurate mapping of CVR.

Using the BOLD MR imaging technique with the rebreathing circuit, we found a good correlation between Mean $CVR_{combined}$ and the Suzuki score. The Mean $CVR_{combined}$ decreases with increasing Suzuki score; however, the difference was not statistically significant between vascular territories for

a Suzuki score of >0. This is not completely unexpected because angiographic scoring of upstream feeding vessels may not adequately reflect the perfusion in downstream tissue. Furthermore, we have shown that the effect on Mean $CVR_{combined}$ is diminished as disease burden increases (Fig 5*B*), so while a significant difference between Mean $CVR_{combined}$ for a vascular territory with a Suzuki score of 0 and a Suzuki score of >0 may be significant, we expect a smaller difference between vascular territories with non-zero Suzuki scores.

The correlation between CVR and the presence of Moyamoya and pial collaterals suggests that the presence of these vessels is associated with poor vascular reactivity that is not adequately compensated by collateralization. Vascular territories with pial and Moyamoya vessels had a nonsignificant but lower Mean $CVR_{combined}$ compared with vascular territories with Moyamoya vessels alone. The presence of pial collaterals may, therefore, represent a more severe disease burden as measured by Mean $CVR_{combined}$; however, further measurements will be needed to clarify this relationship.

Measurements indicate that a nonlinear relationship exists between Mean CVR_{pos} and f_{neg} (Fig 5*A*). For small values of f_{neg}, there is an initial large decrease in Mean CVR_{pos} for small changes in f_{neg}. As f_{neg} increases, the effect on Mean CVR_{pos} is diminished. In contrast, the mean reactivity of negatively reacting voxels (Mean CVR_{neg}) is relatively constant over a range of f_{neg}. The Mean $CVR_{combined}$ is, therefore, predominantly affected by changes in Mean CVR_{pos} for small values of f_{neg}. As the amount of steal increases in a given vascular territory, the decrease in Mean $CVR_{combined}$ is mainly determined by the increasing extent of steal (f_{neg}) and not significantly by decreasing Mean CVR_{pos} or Mean CVR_{neg}. No attempt has been made to mathematically model the relationship between CVR and f_{neg}, but the results presented here demonstrate a reproducible relationship between these parameters in all vascular territories studied and in multiple patients.

There was a decreasing trend between Mean $CVR_{combined}$ and increasing Suzuki score and vessel collateralization, but the difference was not statistically significant. Statistically significant differences may exist; however, the study was limited because of the small number of patients analyzed. Other limitations of this study were the deficiency of patients with mild Moyamoya disease (Suzuki = I) and the retrospective nature of the study.

Conclusions

BOLD MR imaging in combination with precision control of end-tidal pCO_2 and pO_2 is an easily implemented technique that can produce reproducible and quantitative maps of CVR. In the present work, we have demonstrated how this technique correlates well with existing measures of Moyamoya disease burden by using conventional angiography and, therefore, validates the use of BOLD MR imaging for this purpose. However BOLD MR imaging takes this correlation one step further by providing truly quantitative maps of the spatial severity of Moyamoya disease.

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