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Cerebrovascular Reactivity Mapping Using Resting-State BOLD Functional MRI in Healthy Adults and Patients with Moyamoya Disease

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See also the editorial by Wolf and Ware in this issue.

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Background: Cerebrovascular reserve, the potential capacity of brain tissue to receive more blood flow when needed, is a desirable marker in evaluating ischemic risk. However, current measurement methods require acetazolamide injection or hypercapnia challenge, prompting a clinical need for resting-state (RS) blood oxygen level–dependent (BOLD) functional MRI data to measure cerebrovascular reactivity (CVR).

Purpose: To optimize and evaluate an RS CVR MRI technique and demonstrate its relationship to neurosurgical treatment.

Materials and Methods: In this HIPAA-compliant study, RS BOLD functional MRI data collected in 170 healthy controls between December 2008 and September 2010 were retrospectively evaluated to identify the optimal frequency range of temporal filtering on the basis of spatial correlation with the reference standard CVR map obtained with CO_2 inhalation. Next, the optimized RS method was applied in a new, prospective cohort of 50 participants with Moyamoya disease who underwent imaging between June 2014 and August 2019. Finally, CVR values were compared between brain hemispheres with and brain hemispheres without revascularization surgery by using Mann-Whitney *U* test.

Results: A total of 170 healthy controls (mean age ± standard deviation, 51 years ± 20; 105 women) and 100 brain hemispheres of 50 participants with Moyamoya disease (mean age, 41 years ± 12; 43 women) were evaluated. RS CVR maps based on a temporal filtering frequency of [0, 0.1164 Hz] yielded the highest spatial correlation (r = 0.74) with the CO_2 inhalation CVR results. In patients with Moyamoya disease, 77 middle cerebral arteries (MCAs) had stenosis. RS CVR in the MCA territory was lower in the group that did not undergo surgery (n = 30) than in the group that underwent surgery (n = 47) (mean, 0.407 relative units [ru] ± 0.208 vs 0.532 ru ± 0.182, respectively; P = .006), which is corroborated with the CO_2 inhalation CVR data (mean, 0.242 ru ± 0.273 vs 0.437 ru ± 0.200; P = .003).

Conclusion: Cerebrovascular reactivity mapping performed by using resting-state blood oxygen level–dependent functional MRI provided a task-free method to measure cerebrovascular reserve and depicted treatment effect of revascularization surgery in patients with Moyamoya disease comparable to that with the reference standard of CO_2 inhalation MRI.

Online supplemental material is available for this article.

An essential task in the diagnosis of cerebrovascular diseases is to evaluate the ischemic risk of brain tissue. Currently, ischemia is clinically detected by examining the cerebral blood flow in the brain with CT, MRI, or SPECT. However, the brain has a compensatory mechanism, known as autoregulation, that aims to maintain constant blood flow but paradoxically makes ischemia harder to detect with use of cerebral blood flow as a marker. Therefore, a more sensitive approach to detect ischemic risk in a vulnerable brain is to measure the cerebrovascular reserve, the potential of the brain tissue to receive more blood flow when demands call for it. Cerebrovascular reserve is a useful marker in various cerebrovascular conditions such as arterial stenosis (1,2), stroke (3), and small-vessel disease (4,5),

However, it is cumbersome to measure cerebrovascular reserve by using the current methods. In clinical and research studies, measurement of cerebrovascular reserve requires a vasoactive challenge to the patient by injecting certain drugs, such as acetazolamide, or having the patient inhale CO_2 gas or perform breath holding. Therefore, it is highly desirable to use resting-state (RS) MRI data to assess cerebrovascular reactivity (CVR) by exploiting natural variations in respiration and blood CO_2 level. Although several proof-of-principle studies have been reported in small study samples (6–9), this imaging technique has not been subject to systematic optimization and clinical testing in a large cohort of healthy controls and patients with Moyamoya disease.

Abbreviations

BOLD = blood oxygen level–dependent, CVR = cerebrovascular reactivity, MCA = middle cerebral artery, RS = resting state

Summary

Cerebrovascular reactivity mapping performed with resting-state blood oxygen level–dependent functional MRI provided a task-free method for measuring cerebrovascular reserve in both healthy adults and patients with Moyamoya disease and is sensitive to revascularization surgery.

Key Results

- Cerebrovascular reactivity (CVR) maps created by using resting-state (RS) blood oxygen level–dependent functional MRI with a temporal filtering frequency of [0, 0.1164 Hz] yielded the highest spatial correlation (r = 0.74) with the reference standard CO_2 inhalation MRI.
- With use of this optimum frequency range, 96% of healthy controls and 88% of participants with Moyamoya disease had an r value greater than 0.4.
- RS CVR in the middle cerebral artery territory was lower in the nonsurgery group than in the surgery group (P = .006), which is corroborated by the CO_2 inhalation CVR data (P = .003).

Blood oxygen level–dependent (BOLD) functional MRI signal has a complex mechanism. Therefore, a critical task in RS-based CVR estimation is to identify the optimal temporal frequency range in which the reactivity-related signal component is most reliable. In this study, using a lifespan cohort of healthy controls, we determined the optimal temporal filtering window for RS CVR mapping by comparing it with reference standard CO_2 inhalation CVR. We then evaluated its performance in a large group of participants with Moyamoya disease. Finally, we studied the clinical utility of RS CVR in assessing neurosurgical treatment by comparing hemispheres with and hemispheres without revascularization surgery. The overall goal of this study was therefore to optimize and evaluate an RS CVR MRI technique and demonstrate its relationship to neurosurgical treatment.

Materials and Methods

Participants

The institutional review board approved this Health Insurance Portability and Accountability Act–compliant study, and all data were obtained with participants' written informed consent. Two participant cohorts were studied. First, a group of healthy controls was part of the cohort of the prospective, longitudinal Dallas Lifespan Brain Study, enrolled between December 2008 and September 2010. These participants underwent extensive health screening, had no contraindications to MRI, and were generally of good health, with no serious or unstable medical conditions. Next, MRI data sets from participants with Moyamoya disease were collected prospectively and consecutively between June 2014 and August 2019. A small subset of these participants (n = 12) has been reported previously to demonstrate the initial feasibility of CVR mapping by using RS functional MRI (8,10). In both cohorts, each participant must have undergone an RS BOLD scan and a gas-inhalation scan. Figure 1 summarizes the participant recruitment.

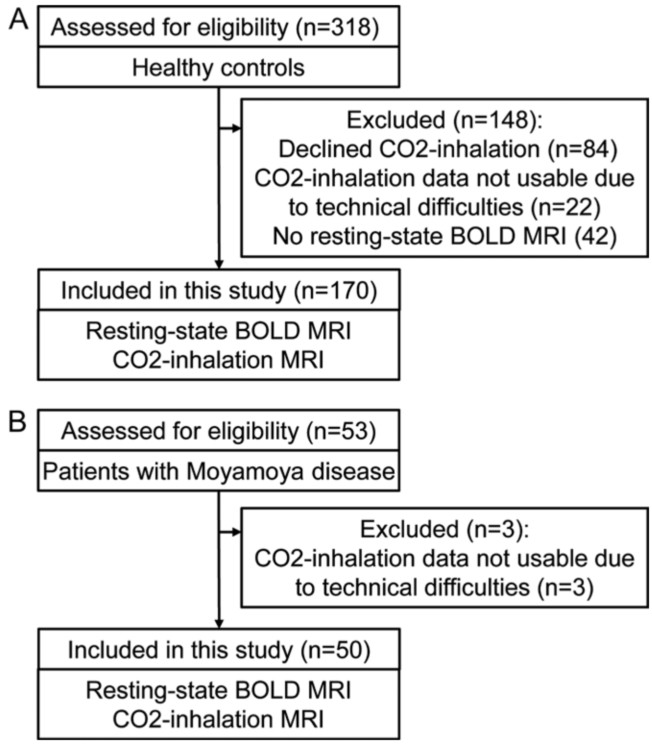

Figure 1: Flowcharts show inclusion and exclusion criteria for, *A*, healthy controls and, *B*, patients with Moyamoya disease. BOLD = blood oxygen level–dependent.

MRI Protocols

All MRI examinations were performed with a 3-T machine (Achieva, Philips Medical Systems). The healthy controls underwent both a 5-minute RS examination and a 7-minute gas-inhalation examination, with identical BOLD imaging parameters (repetition time msec/echo time msec, 2000/25). The participants with Moyamoya disease underwent both a 9-minute RS examination and a 9-minute gas-inhalation examination (1510/21). In participants with Moyamoya disease, a time-of-flight MR angiogram was also obtained (25/3.45). See Appendix E1 (online) for details.

Data Processing

For data processing, we used Statistical Parametric Mapping (SPM12, University College London) and in-house Matlab (version 2013a, MathWorks) scripts. The processing pipeline for RS CVR data is illustrated in Figure 2 and detailed in Appendix E1 (online).

For data from participants with Moyamoya disease, RS CVR maps were obtained by using the optimal frequency range determined from the healthy controls. The processing steps were similar to those used in healthy controls except that, in participants with Moyamoya disease, the cerebellum was used to yield the reference signal time course. This was done because posterior circulation territories are typically unaffected in Moyamoya disease, whereas the anterior circulation territories are often compromised.

To study CVR in disease-affected flow territories, the RS CVR maps were normalized to the MNI space. Region-of-interest CVR values were obtained from the perfusion territories

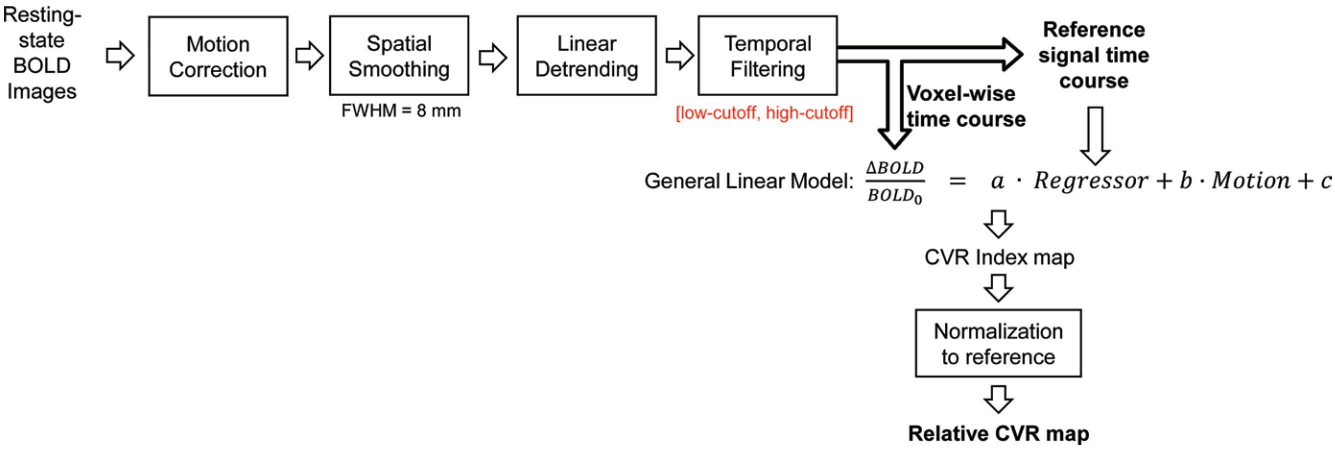

Figure 2: Diagram shows analysis steps for the resting-state cerebrovascular reactivity (CVR) mapping method. BOLD = blood oxygen level–dependent, FWHM = full width at half maximum.

of the middle cerebral artery (MCA) based on a perfusion atlas (11). In this study, we focused on MCA territories because revascularization procedures typically aim to recover perfusion in these regions.

We further examined which voxels contributed to the differences in CVR between the hemispheres that underwent revascularization surgery and those that did not. Additional analyses were conducted (see Fig E1 [online] for an example), in which voxels with the highest or lowest CVR values were identified and their values were averaged. We studied eight indexes, specifically the top 1%, 5%, 10%, and 50% voxels and the bottom 1%, 5%, 10%, and 50% voxels.

Stenosis Grading of MCAs

The stenosis grade of MCAs of each participant with Moyamoya disease was rated independently by a neuroradiologist (M.P., with >10 years of experience) who was blinded to the CVR results and clinical records; ratings were made by using a previously published angiographic scoring system adapted to MR angiography (12).

Statistical Analysis

All statistical analyses were performed by using Matlab scripts (version R2013, Mathworks). Results are reported as means ± standard deviations. Pearson correlation coefficients (*r* values) were computed to evaluate the spatial correlation between RS CVR and CO_2 CVR maps. The band-pass filter that yielded the highest *r* value was identified as the optimal frequency range. The distribution of spatial correlation coefficient between RS CVR and CO_2 CVR was investigated in both healthy controls and participants with Moyamoya disease. The association between RS CVR and MCA stenosis grade was evaluated by using linear regression in participants who did not undergo revascularization surgery. Mann-Whitney *U* tests were performed to compare CVR values between hemispheres that underwent revascularization surgery and those that did not. $P < .05$ was considered to indicate a statistically significant difference. For histogram-based indexes, the *P* value threshold was .006 (0.05/8) to account for multiple comparisons.

Results

Participant Characteristics

The study sample consisted of 170 healthy controls (mean age ± standard deviation, 51 years ± 20 [range, 20–88 years]; 105 women) and 50 participants with Moyamoya disease (mean age, 41 years ± 12 [range, 18–72 years]; 43 women). Demographic information for all participants is shown in the Table.

Optimization of Temporal Filtering Frequency in Healthy Controls

Figure 3, *A*, shows group-averaged (n = 170) *r* values between RS CVR and CO_2 CVR maps as a function of band-pass filter frequency cutoffs. The highest spatial correlation (r = 0.74) was obtained by using a band-pass filter with a frequency of [0, 0.1164 Hz], although the performances were not very sensitive to the high-cutoff threshold between 0.0745 and 0.01164 Hz (<1% [0.73/0.74] difference) (Fig 3, *B* and *C*). With this optimum frequency range, the histogram of *r* in all healthy controls is shown in Figure 4, *A*. The *r* value did not show significant dependence on age (β = −0.0008, *P* = .10) or association with sex (β = 0.0302, *P* = .15). Of the 170 healthy controls, 164 (96%) showed an *r* value greater than 0.4, 160 (94%) showed an *r* value greater than 0.5, and 152 (89%) showed an *r* value greater than 0.6. To illustrate how the *r* value is related to CVR image quality, Figure 4, *B*, shows RS CVR maps (averaged over four controls) as a function of *r* values.

Evaluation of RS CVR Mapping in Patients with Moyamoya Disease

Figure 5, *A*, shows RS CVR maps in three representative participants with Moyamoya disease with variable degrees of arterial stenosis. Figure 5, *B*, shows the histogram of spatial correlations in all participants with Moyamoya disease. Of the 50 participants in this typical clinical cohort, 44 (88%) had an *r* value greater than 0.4, 37 (74%) had an *r* value greater than 0.5, and 25 (50%) had an *r* value greater than 0.6. In the 21 participants imaged without revascularization surgeries, RS CVR values of all 42 MCA territories showed no significant correlation with the MR angiogram–based stenosis

Participant Characteristics

Characteristic	All Participants	Women	Men
Healthy controls			
No. of participants	170	105	65
Age range (y)	20–88	20–88	20–86
Mean age ± SD (y)	51 ± 20	51 ± 19	50 ± 21
Patients with Moyamoya disease			
No. of participants	50	43	7
No. of participants who underwent unilateral revascularization surgery	18	15	3
No. of participants who underwent bilateral revascularization surgeries	11	8	3
Age range (y)	18–72	18–72	31–53
Mean age ± SD (y)	41 ± 12	41 ± 12	41 ± 9

Note.—SD = standard deviation.

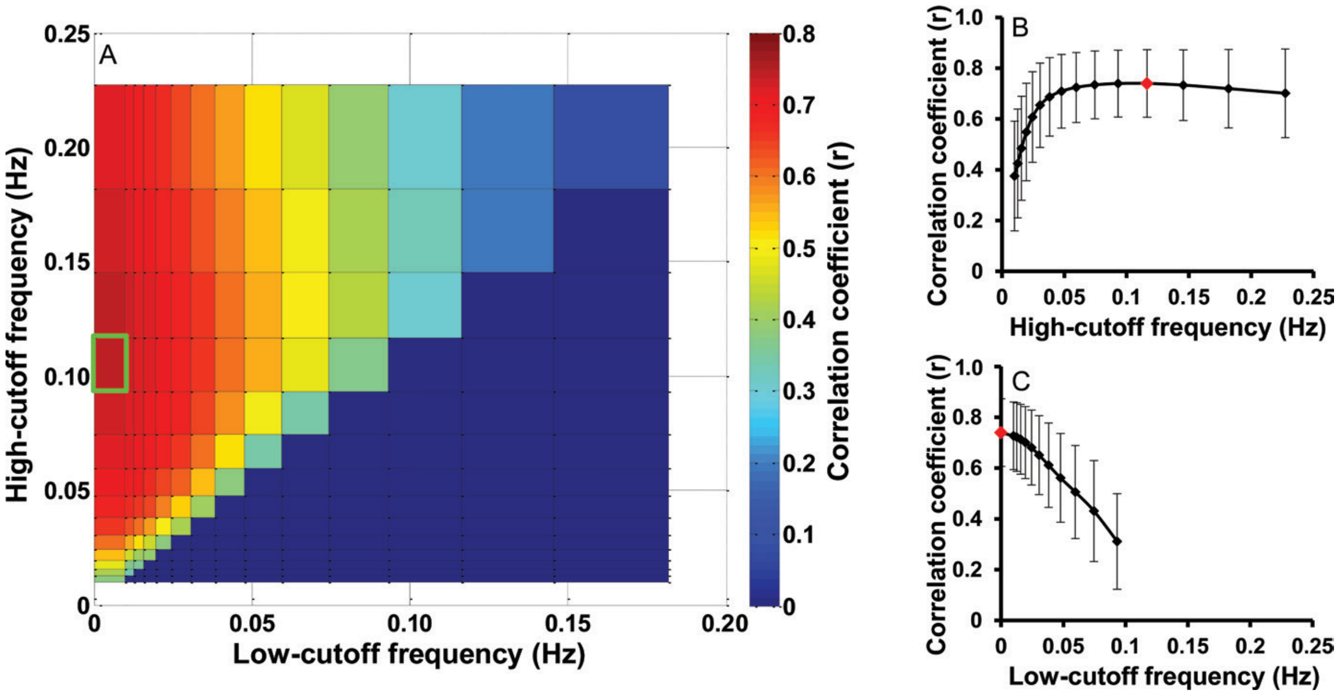

Figure 3: Group-averaged spatial correlation coefficients (*r* values) between resting-state cerebrovascular reactivity (CVR) and CO_2 inhalation CVR maps in healthy controls. *A*, Color plot of group-averaged correlation coefficients using 120 different filtering frequencies. Green box indicates the highest *r* value at a filtering frequency of [0, 0.1164 Hz]. *B*, Two-dimensional plot between correlation coefficients and high-cutoff frequency at a fixed low-cutoff frequency of 0 Hz. *C*, Two-dimensional plot between correlation coefficients and low-cutoff frequency at a fixed high-cutoff frequency of 0.1164 Hz. Red diamonds indicate maximum correlation coefficient values. Error bars indicate standard deviation across healthy controls.

grades (range, 0–3, where 0 is normal) (β = −0.026, *P* = .337); after exclusion of two participants with poor RS CVR quality (ie, $r < 0.4$), however, RS CVR values of the remaining 38 MCA territories revealed a significant correlation with the stenosis grades (β = −0.049, *P* = .03).

The *r* values between RS CVR and CO_2 CVR maps as a function of band-pass filter frequency cutoffs were also examined by using the cerebellum as a reference in both the 170 healthy controls (Fig E2 [online]) and the 50 participants with Moyamoya disease (Fig E3 [online]). The patterns of *r* values associated with different cutoff frequencies were in good agreement with those obtained from healthy controls by using the whole brain as a reference (Fig 3). With use of the cerebellum as a reference, the *r* value peaked at the frequency range of [0, 0.0745 Hz] for both healthy controls (*r* = 0.70) and patients with Moyamoya disease (*r* = 0.56). However, these *r* values were lower than those obtained with use of the whole brain as a reference in healthy controls (*r* = 0.74 for a frequency range of [0, 0.1164 Hz]).

Nonsurgery versus Surgery Groups

Among the 50 participants with Moyamoya disease, 77 MCAs had stenosis; 30 of these MCAs were imaged without revascularization surgery and 47 were imaged after undergoing

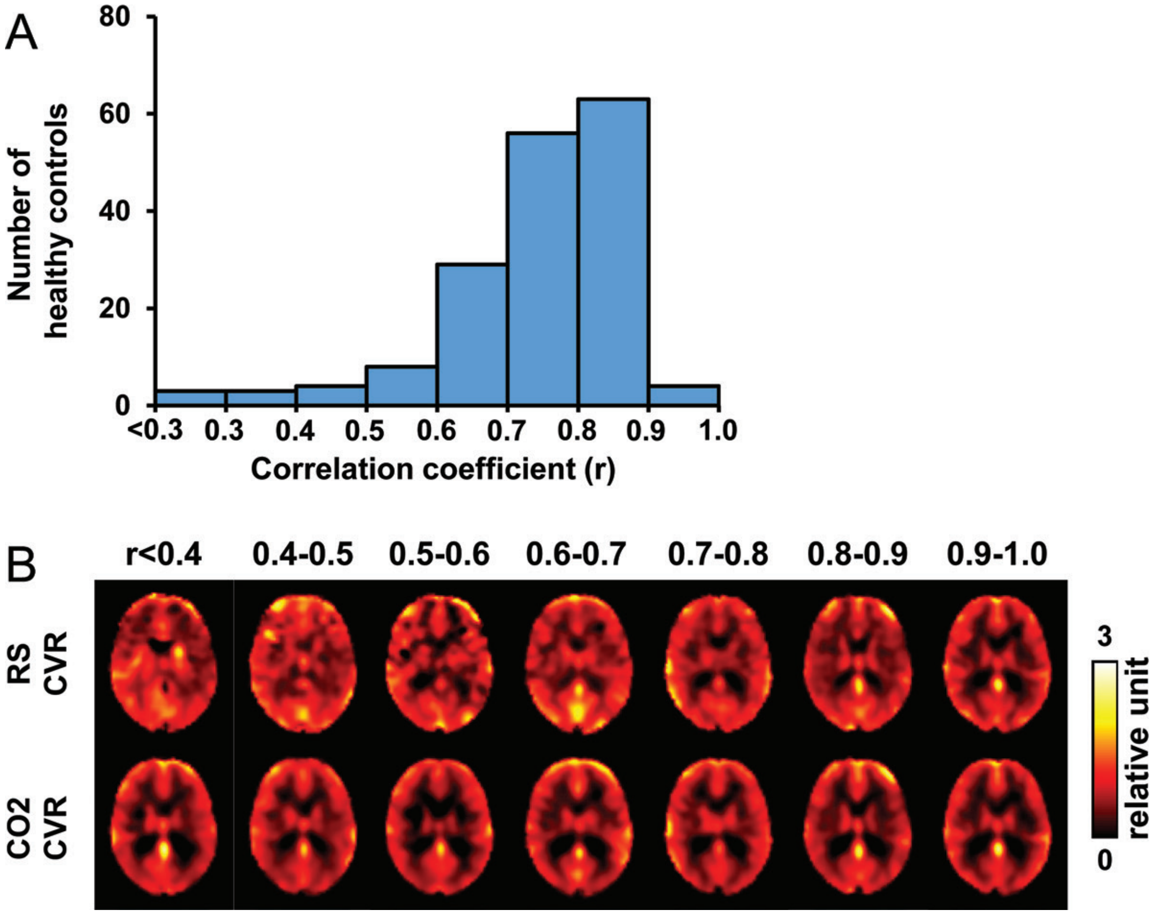

Figure 4: Distributions of spatial correlation coefficient between resting-state (RS) cerebrovascular reactivity (CVR) maps and CO_2 inhalation CVR maps in healthy controls. *A*, Histogram of spatial correlations across 170 healthy controls. *B*, CVR maps stratified according to spatial correlations, listed from low to high. Each map was an average from four controls within a specified range.

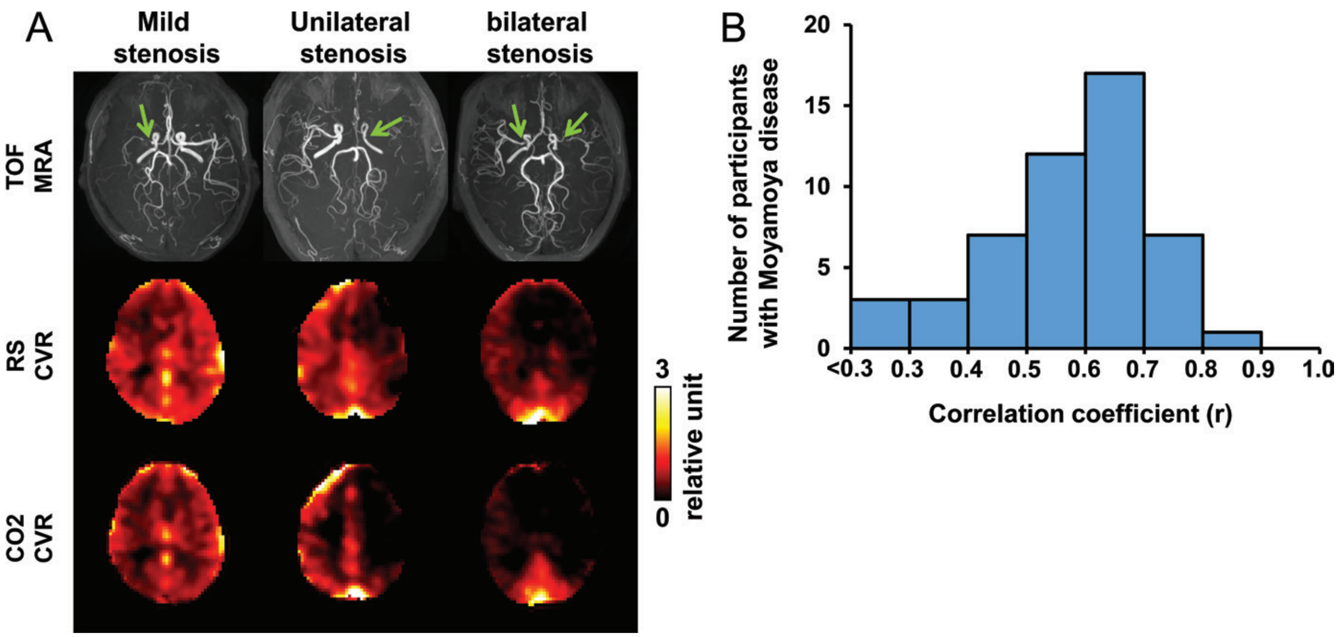

Figure 5: *A*, Resting-state (RS) and CO_2 inhalation cerebrovascular reactivity (CVR) maps and images from time-of flight (TOF) MR angiography (MRA) in three representative participants with Moyamoya disease. Arrows indicate stenotic MCAs. Color bar indicates relative CVR values. *B*, Histogram shows spatial correlations (*r* values) between RS and CO_2 CVR maps in 50 patients with Moyamoya disease.

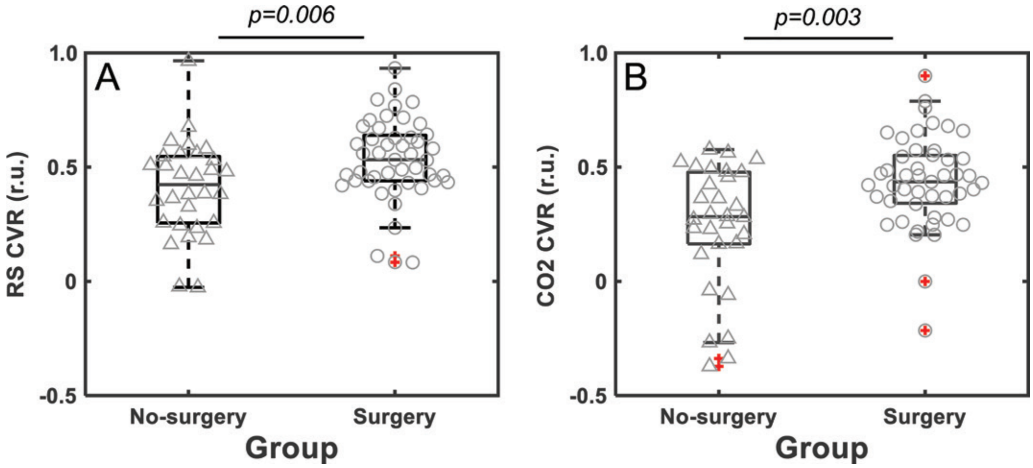

Figure 6: Box plots show, *A*, resting-state (RS) and, *B*, CO_2 inhalation cerebrovascular reactivity (CVR) values between hemispheres with and hemispheres without revascularization surgery. Gray symbols represent individual hemispheres. Central bars and bottom and top edges of the box indicate the medians and 25th and 75th percentiles, respectively. The whiskers indicate the minimum and maximum, excluding outliers. Red crosses indicate outliers. r.u. = relative units.

surgery. In the group that did not undergo surgery, five of the 30 MCAs (17%) had an MR angiogram–based stenosis score of 1, 12 (40%) had a stenosis score of 2, and 13 (43%) had a stenosis score of 3. In the group that underwent surgery, eight of the 47 MCAs (17%) had a stenosis score of 1, 15 (32%) had a stenosis score of 2, and 24 (51%) had a stenosis score of 3. MCA stenosis grades did not significantly differ between the two groups (P = .67). However, the RS CVR values within the MCA territory were lower in the nonsurgery group than in the surgery group (mean, 0.407 relative units [ru] ± 0.208 vs 0.532 ru ± 0.182, respectively; P = .006) (Fig 6, *A*), suggesting that revascularization surgery can effectively improve CVR in the corresponding brain regions. This observation is corroborated with the CO_2 CVR data (mean CO_2 CVR value, 0.242 ru ± 0.273 for the nonsurgery group vs 0.437 ru ± 0.200 for the surgery group; P = .003) (Fig 6, *B*). Upon averaging the left and right MCA territories from the same participants, the RS CVR values in the nonsurgery group (n = 20) remained lower than those in the surgery group (n = 29) (mean, 0.413 ru ± 0.185 vs 0.512 ru ± 0.174, respectively; P = .03); this group difference showed a trend but was not significant for the CO_2 CVR values (mean, 0.289 ru ± 0.209 vs 0.417 ru ± 0.195; P = .07). Further examination of the subset of voxels within the perfusion territories revealed that the peak (ie, higher CVR) voxels showed the greatest differences between the revascularization groups. Specifically, the nonsurgery group had consistently lower values than the surgery group for the top 5% (mean, 1.062 ru ± 0.361 vs 1.338 ru ± 0.362, respectively; P = .002), 10% (mean, 0.932 ru ± 0.329 vs 1.170 ru ± 0.282; P = .001), and 50% (mean, 0.612 ru ± 0.256 vs 0.772 ru ± 0.193; P = .002) voxels. The bottom voxels did not reveal a significant difference. Similar results were observed in the CO_2 CVR data because the nonsurgery group had consistently lower CO_2 CVR than the surgery group for the top 5%, 10%, and 50% voxels. Table E1 (online) summarizes the statistical significance of all indexes examined.

Discussion

With use of CO_2 inhalation MRI as a reference standard, we identified the optimal analysis strategy for resting-state (RS) cerebrovascular reactivity (CVR) mapping by using RS blood oxygen level–dependent (BOLD) functional MRI in a large cohort of healthy controls and applied it in a cohort of patients with Moyamoya disease. CVR maps obtained by using RS BOLD functional MRI with a temporal filtering frequency of [0, 0.1164 Hz] yielded the highest spatial correlation (r = 0.74) with the reference standard CO_2 inhalation MRI. RS CVR maps depicted revascularization treatment effects in the patients. RS CVR in the MCA territory was lower in the nonsurgery group than in the surgery group (P = .006), and this was corroborated with the CO_2 inhalation CVR data (P = .003).

Conventional CVR mapping techniques require an explicit physiologic maneuver, such as inhalation of CO_2 (13–15), breath holding (3), hyperventilation (16), or acetazolamide injection (17,18), which are cumbersome and may not be feasible in standard clinical settings and in large-scale studies. Unlike these conventional methods, the technique proposed herein uses the natural variations in breathing pattern to measure CVR from typical RS BOLD data without requiring additional challenges.

To use the RS BOLD data for CVR mapping, it is crucial to identify the optimal temporal frequency range in which the reactivity-related signal component is most reliable. The optimal frequency range we identified, 0–0.1164 Hz, is also the typical range used in functional connectivity analysis (19,20). Therefore, our results suggest that spontaneous fluctuations in breathing pattern may play a substantial role in global signal fluctuations in this frequency range. A previous study examined five nonoverlapping frequency bands and showed that the temporal correlation between RS BOLD signal and end-tidal CO_2 time course was the highest at 0.02–0.04 Hz in five healthy controls (8). In our study, we conducted a more systematic search for the optimal frequency range by focusing on spatial correlation in a larger cohort and allowing partially overlapped frequency ranges. When we applied the frequency bands from the previous study (8) to data in our current study, the [0.02, 0.04 Hz] frequency band still yielded a higher spatial correlation than the other frequency bands, demonstrating a general consistency of findings between the two reports.

As a general rule of thumb, the reference region of interest used for RS CVR mapping should be a relatively large brain region that is not affected by the disease. Our results showed that in healthy controls, RS CVR that used the whole brain as a reference revealed higher spatial correlations with CO_2 CVR compared with RS CVR that used cerebellum as a reference.

Although most of the RS BOLD data yielded CVR maps comparable to the CO_2 CVR maps, the cases with small *r* values may be attributed to larger effects of non–CO_2-related factors in the BOLD signals or the lack of spontaneous variations in the breathing pattern during the RS examination. A recent method based on RS with intermittent breath modulation has been proposed to improve the success rate of RS CVR mapping (21); however, it requires an additional, although minor, task.

Moyamoya disease is known to reduce cerebrovascular reserve (2,22–24). Previous studies using the CO_2 inhalation method have shown that effective revascularization surgery can improve cerebrovascular reserve in participants with Moyamoya disease (22). Our RS CVR results are consistent with CO_2 inhalation results from the same cohort and from the previous literature (2,22,23). RS CVR mapping does not require an additional breathing apparatus and patient cooperation. Thus, it may be a convenient and practical tool for the diagnosis and treatment assessment of Moyamoya disease and other cerebrovascular diseases, especially in vulnerable cohorts such as children or unconscious patients when conventional CVR mapping approaches are not feasible.

This study has limitations. First, the RS CVR maps we obtained were in relative units, rather than in absolute units of percentage per millimeter of mercury CO_2. Thus, this method is more suited for diseases in which CVR deficits are regional. Although recording of end-tidal CO_2 during RS BOLD imaging will allow the absolute quantification of CVR, it will add to the complexity of the procedure. Second, we identified an optimal temporal filtering frequency to maximize CO_2-related signal contributions. However, even within this optimal frequency range, there are likely signal sources that are unrelated to CO_2, such as global fluctuations in neural activity (25), individual motion, and heart rate changes. Furthermore, the MCA region-of-interest analyses performed in this study did not distinguish hemispheres from the same patients; this tends to underestimate the standard errors of the mean and overestimate the test statistics and levels of statistical significance.

In conclusion, cerebrovascular reactivity (CVR) mapping using resting-state (RS) blood oxygen level–dependent (BOLD) functional MRI provided a task-free method with which to measure cerebrovascular reserve and depicted treatment effect of revascularization surgery in adults with Moyamoya disease similar to the reference standard of CO_2 inhalation MRI. RS-based CVR mapping may be a useful imaging marker for cerebrovascular diseases. Other data-driven methods, such as deep learning, may be used to further improve the determination of CO_2 contribution in the reference BOLD signal and enhance the specificity of CVR mapping.

Author contributions: Guarantor of integrity of entire study, P.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, P.L., G.L., H.L.; clinical studies, P.L., M.C.P., B.P.T., J.H., B.G.W., H.L.; experimental studies, P.L., G.L., M.C.P., B.P.T., D.C.P.; statistical analysis, P.L., G.L., Z.L.; and manuscript editing, P.L., G.L., M.C.P., B.P.T., D.C.P., B.G.W., H.L.

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