Evaluation of Cerebrovascular Reactivity and Vessel Wall Imaging in Patients With Prior COVID-19: A Prospective Case-Control MRI Study

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Neuroradiology/Head and Neck Imaging · Original Research

Keywords

arterial wall imaging, cerebral vasoreactivity, COVID-19, perfusion, SARS-CoV-2

Submitted: Jul 13, 2022
Revision requested: Jul 26, 2022
Revision received: Aug 10, 2022
Accepted: Aug 15, 2022
First published online: Aug 24, 2022
Version of record: Nov 9, 2022

Based on a presentation at the American Society of Neuroradiology 2022 annual meeting, New York, NY.

The authors declare that there are no disclosures relevant to the subject matter of this article.

Supported by a University of Colorado Department of Radiology Faculty development seed grant.

BACKGROUND. SARS-CoV-2 infection is associated with acute stroke, possibly caused by viral tropism to the vascular endothelium. Whether cerebrovascular endothelial dysfunction and inflammation persist after acute infection is poorly understood.

OBJECTIVE. The purposes of this study were to assess the association between prior SARS-CoV-2 infection and cerebrovascular reactivity (CVR) and vessel wall imaging (VWI) abnormalities and to explore the association between CVR impairment and post-COVID neurologic conditions.

METHODS. This prospective study included 15 participants with prior SARS-CoV-2 infection (11 women, four men; mean age, 43 years; mean time since infection, 238 days; three with prior critical illness, 12 with prior mild illness; seven with post-COVID neurologic conditions) and 10 control participants who had never had SARS-CoV-2 infection (two women, two men; mean age, 44 years) from July 1, 2021, to February 9, 2022. Participants underwent research MRI that included arterial spin labeling perfusion imaging with acetazolamide stimulus to measure cerebral blood flow (CBF) and calculate CVR. Examinations also included VWI, performed with a contrast-enhanced black-blood 3D T1-weighted sequence. An age- and sex-adjusted linear model was used to assess associations between CVR and prior infection. A *t* test was used to assess associations between CVR and post-COVID neurologic conditions in participants with previous infection. A difference of proportions test was used to assess associations between VWI abnormalities and infection status.

RESULTS. Mean whole-cortex CBF after acetazolamide administration was greater in participants without previous infection than in participants with previous infection (73.8 ± 13.2 [SD] vs 60.5 ± 15.8 mL/100 gm/min; $p = .04$). Whole-brain CVR was lower in participants with previous infection than those without previous infection (difference, –8.9 mL/100 g/min; $p < .001$); significantly lower CVR was also observed in participants with previous infection after exclusion of those with prior critical illness. Among participants with previous infection, CVR was lower in those with than those without post-COVID neurologic conditions, although this difference was not significant (16.9 vs 21.0 mL/100 g/min; $p = .22$). Six of 15 (40%) participants with previous infection versus 1 of 10 (10%) participants without previous infection had at least one VWI abnormality ($p = .18$). All VWI abnormalities were consistent with atherosclerosis.

CONCLUSION. SARS-CoV-2 infection is associated with chronic impairment of CVR. The mechanism is unknown from this study.

CLINICAL IMPACT. Future studies are needed to determine the clinical implications of SARS-CoV-2–associated CVR impairment.

Neurologic sequelae after SARS-CoV-2 infection are widely recognized [1–3]. In its acute phase, SARS-CoV-2 infection is associated with strokes that have features of both vascular inflammation and thromboembolism [4–7]. The putative mechanism of SARS-CoV-2–associated vascular pathology is viral tropism to the endothelium with resultant vascular inflammation, rarefaction, and dysfunction [8, 9]. Histopathologically, viral proteins are found in vascular endothelial cells of the brain; autopsy studies show evidence of vascular endothelial cell destruction in individuals with SARS-CoV-2 infection; and evidence indicates that the main viral protease SARS-CoV-2 M^{pro} mediates widespread vascular en-

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doi.org/10.2214/AJR.22.28267

AJR 2023; 220:257–264

ISSN-L 0361–803X/23/2202–257

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dothelial cell death, capillary rarefaction, and breakdown of the blood-brain barrier [3, 9, 10].

The vascular endothelium, an essential component of the neurovascular unit (NVU), is the principal regulator of the blood-brain barrier and cerebrovascular reserve. Cerebrovascular reactivity (CVR) is a quantitative measure of NVU function. It reflects NVU-mediated changes in cerebral blood flow (CBF) in response to vasoactive stimuli. Impaired CVR is associated with increased risk of stroke in several disease states [11, 12]. For example, impaired CVR in patients with chronic HIV infection is associated with increased risk of stroke despite viral suppression [13, 14].

After the acute phase of SARS-CoV-2 infection, as many as 76% of patients experience persistent neurologic symptoms not attributable to another diagnosis, including headache, difficulty concentrating, vision changes, disequilibrium, and fatigue [15, 16]. The CDC defines post-COVID neurologic conditions as neurologic symptoms that develop during or after SARS-CoV-2 infection and that persist at least 4 weeks after infection [17]. The cause of these symptoms is not yet fully understood, but results of preliminary studies suggest that endothelial and circulatory dysfunction have a role [18, 19].

Arterial vascular inflammation can be detected and characterized with vessel wall imaging (VWI), an MRI technique that affords high-resolution postcontrast visualization of the vessel wall. VWI may help differentiate vasculitic arterial pathology from atherosclerotic pathology on the basis of the length of the involved segment and whether the abnormal enhancement is concentric or eccentric [20–23]. Case studies have shown abnormal findings indicating vascular inflammation on VWI of patients with SARS-CoV-2 infection who present with acute ischemic stroke [24, 25]. However, whether endothelial dysfunction and inflammation persist after acute infection is poorly understood.

The aims of this study were to assess the association between prior SARS-CoV-2 infection and CVR and VWI abnormalities and to explore the association between CVR impairment and post-COVID neurologic conditions.

HIGHLIGHTS

Key Finding

- *Whole-brain CVR was lower in participants with prior SARS-CoV-2 infection than participants without previous infection (difference, –8.9 mL/100 g/min;* p < *.001). Among those with previous infection, CVR was nonsignificantly lower in those with than those without post-COVID neurologic conditions (16.9 vs 21.0 mL/100 g/min;* p = *.22).*

Importance

- *The results support presence of chronic endothelial dysfunction in individuals with prior SARS-CoV-2 infection, reinforcing histopathologic evidence of tropism of SARS-CoV-2 to the vascular endothelium.*

Methods

Study Design

This prospective HIPAA-compliant study received institutional review board approval. All participants provided written informed consent. The study had a case-control design. Individuals with previous SARS-CoV-2 infect and individuals who had never had SARS-CoV-2 infection were recruited. Participant recruitment began on July 1, 2021, and was completed on February 9, 2022. Recruitment was performed through a combination of hospital flyers and newsletters, word of mouth, and proposal to patients by their health care providers (typically when patients received care for COVID-19 or post-COVID-19 symptoms). Potential participants were deemed ineligible on the basis of the following screening criteria: age younger than 18 years, pregnancy, known chronic viral infection (including HIV or hepatitis), known vasculitis or vasculopathy, contraindication to acetazolamide administration, allergy or contraindication to gadolinium-based contrast media, and contraindication to MRI. Individuals with previous infection were required to have had a prior rapid antigen test or polymerase chain reaction test result positive for SARS-CoV-2. Individuals who had never had SARS-CoV-2 infection were defined as those without a prior rapid antigen test or polymerase chain reaction test result positive for SARS-CoV-2 who had never had symptoms indicative of SARS-CoV-2 infection and who had never had contact with an individual with known active SARS-CoV-2 infection.

Enrolled participants were surveyed regarding cardiovascular risk factors (smoking history, hypertension, hyperlipidemia, diabetes mellitus). Enrolled participants with previous infection were surveyed for the date of the positive SARS-CoV-2 infection test result (hereafter referred to as the date of infection) and for the development of critical illness during the course of SARS-CoV-2 infection (e.g., stroke, myocardial infarction, or thromboembolism). Enrolled participants with previous infection were also surveyed for post-COVID neurologic conditions, defined as the onset of new neurologic or psychologic symptoms at the time of or after SARS-CoV-2 infection that persisted for at least 4 weeks after the acute infectious period [16, 17].

MRI Technique

Participants underwent brain MRI for investigational purposes. The same protocol was used in both groups. MRI examinations were performed with a single 3-T system (Discovery, GE Healthcare). Examinations included an anatomic T1-weighted 3D brain volume (BRAVO) sequence and noncontrast perfusion imaging acquired with a pseudocontinuous arterial spin labeling (ASL) technique (TR/TE, 4893/10.68; postlabeling delay, 2025 ms; matrix, 512 × 8; see Cerebral Blood Flow and Cerebrovascular Reactivity Measurements). Examinations also included VWI performed with a 3D high-resolution variable flip angle black-blood sequence (TR/TE, 1200/15.99; echo-train length, 31; slice thickness, 1.00 mm; gap, –0.50 mm; matrix, 512 × 512; parallel imaging [autocalibrating reconstruction for cartesian imaging] acceleration factor, 2), performed after IV administration of 0.2 mL/kg of gadolinium-based contrast medium (MultiHance, Bracco).

Cerebral Blood Flow and Cerebrovascular Reactivity Measurements

Brain perfusion imaging was performed by ASL acquisition before and 10 minutes after stimulus by IV administration of 1 g of acetazolamide over 4 minutes [26]. For both ASL acquisitions, the

mean tagged and untagged images were postprocessed to compute quantitative CBF maps by previously described methods [25]. CVR was defined as the absolute increase in CBF (in milliliters per 100 grams per minute) between the two ASL acquisitions (before and after acetazolamide administration) [26, 27].

The CBF maps generated from the two ASL acquisitions were coregistered to the 3D T1-weighted images based on linear registration by use of the Functional Magnetic Resonance Imaging of the Brain Software Library and then normalized to the Harvard-Oxford Atlas. On the basis of combinations of ROIs within the atlas, CBF values before and after acetazolamide administration were extracted for the entire cerebral cortex and for lobar subregions corresponding to the frontal, occipital, parietal, and temporal cortexes [28].

Evaluation of Arterial Vessel Wall Imaging

Two board-certified neuroradiologists (V.M.T. with 8 and A.L.C. with 2 years of posttraining experience) evaluated VWI of each patient. They were blinded to whether the patient had had or had never had SARS-CoV-2 infection and to ASL perfusion findings. The radiologists in consensus qualitatively classified arterial VWI abnormalities as present or absent in each participant. When present, VWI abnormalities were characterized in terms of features described by prior expert consensus recommendations [24]. These included location, extent (long segment [involving more than one named anatomic vascular segment] vs short segment [limited to less than one vascular segment]), morphology (concentric or eccentric), and categorization of the abnormality as consistent with vasculitis or atherosclerosis.

The evaluated locations included the supraclinoid internal carotid artery; carotid terminus; M1, M2, and M3 segments of the middle cerebral artery (MCA); A1, A2, and A3 segments of the anterior cerebral artery (ACA); P1, P2, and P3 segments of the posterior cerebral artery; and intradural segment (V4) of the vertebral artery. All locations were assessed bilaterally, as was the basilar artery. Care was taken to not mistake normal periarterial venous enhancement at the V4 segment for pathology [22]. The M4 and A4 segments of the MCA and ACA were not routinely evaluated given that their size and perivenular locations typically precluded accurate characterization. A third board-certified neuroradiologist (A.A.T. with 6 years of posttraining experience) independently evaluated the VWI for the same findings the other two readers did. For any discrepancies, the findings of the first two consensus readers were used for further analysis.

Statistical Analysis

A linear mixed model with a random intercept, adjustment for age and sex, and application of a Bonferroni correction for multiple comparisons was used to evaluate associations between CVR magnitude and SARS-CoV-2 infection status. The inferential model treated CVR as the absolute value difference (in units of CBF) rather than as a ratio because of statistical concerns regarding analyzing ratios of numbers with small sample sizes. Subanalyses were performed to repeat these comparisons when excluding previously infected participants who experienced critical illness during the course of SARS-CoV-2 infection. A *t* test was used to assess for an association between the presence of post-COVID neurologic conditions and CVR in participants with previous infection. A difference of proportions test was used to assess for an association between the frequency of VWI abnormalities and SARS-CoV-2 infection status. A *t* test was used to assess for statistically significant differences in age and mean time from diagnosis between participants with previous infection with and without VWI abnormalities. Whole-brain and lobar CVR was compared within participants with VWI abnormalities to assess for an interaction between VWI abnormalities and CVR impairment. Values of $p < .05$ were considered statistically significant. Analysis was performed with R software (version 4.1.2).

Results

Study Participants

A total of 29 individuals (17 with previous infection, 12 with previous infection) underwent screening for enrollment. All 17 individuals with previous infection were deemed eligible. Two of these individuals declined to participate without providing a specific reason for their decision. Thus, a total of 15 individuals with previous infection were enrolled. Of these participants, five had independently contacted the study coordinator to volunteer to participate, and 10 had their involvement proposed by a health care practitioner. Two of the 12 individuals without previous infection were deemed ineligible because of a sulfa allergy. Thus, a total of 10 individuals who had never had SARS-CoV-2 infection were enrolled. Of these participants, nine had independently contacted the study coordinator to volunteer to participate, and one had their involvement proposed by a health care practitioner. No individual was excluded after consenting to participate. Figure 1 summarizes the flow of participant selection.

Table 1 shows information regarding participant demographic characteristics, cerebrovascular risk factors, and prior SARS-

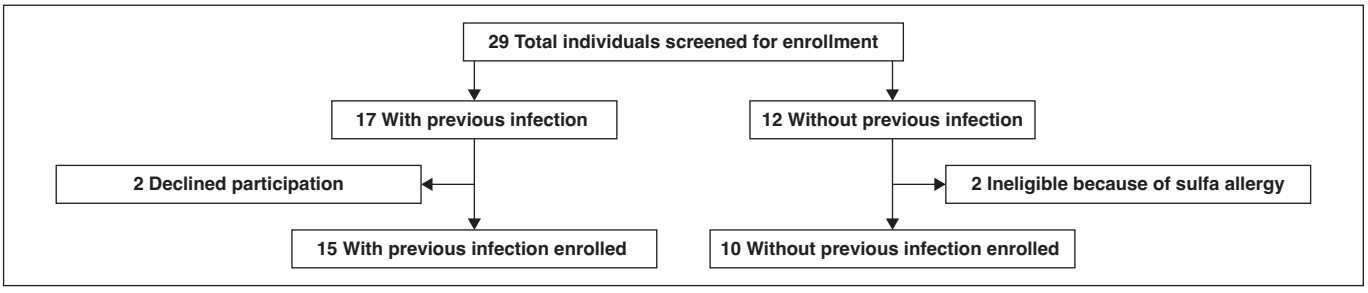

Fig. 1—Flowchart shows steps in participant enrollment.

TABLE 1: Descriptive Statistics of Study Participants With and Without Previous SARS-CoV-2 Infection

Covariate	With Previous Infection (n = 15)	Without Previous Infection (n = 10)	p
Age (y)	43 ± 12	44 ± 15	.97
Sex			> .99
Female	11 (73)	8 (80)	
Male	4 (27)	2 (20)	
Tobacco use (pack-years)	4.5 ± 7.5	0.6 ± 1.7	.07
Hypertension	1 (7)	3 (30)	.54
Hyperlipidemia	2 (13)	3 (30)	.36
Diabetes mellitus	2 (13)	0 (0)	.50
Time from infection to research MRI (d)	238 ± 154	—	—
Acute ischemic stroke and hospitalization after infection	3 (20)	—	—
Post-COVID neurologic conditions	7 (47)	—	—

Note—Between-group differences were tested by two-sample *t* test for continuous variables (age, tobacco use) and Fisher exact test for dichotomous variables (sex, hypertension, hyperlipidemia, diabetes mellitus). Data are mean ± SD or number of participants with percentage in parentheses. Dash (—) indicates not applicable.

CoV-2 infection if applicable. Participant age ranged from 22 to 72 years. The ages of participants in the two groups were similar. Among those with previous infection (11 women, four men), the mean age was 43 ± 12 [SD] years; range, 22–65 years; median, 42 years (IQR, 36–49 years). Among those without previous infection (eight women, two men), the mean age was 44 ± 15 years; range, 26–72 years; median, 38 years (IQR, 33.25–54.5 years). The prevalence of cerebrovascular risk factors was not significantly different between the two groups (all $p > .05$). In participants with previous infection, the research MRI examinations were performed a mean of 238 ± 154 days (range, 21–498 days) after SARS-CoV-2 infection. Three of the 15 participants with previous infection experienced critical illness during the course of infection (acute ischemic stroke requiring hospitalization for all three). The other 12 experienced mild illness (no acute neurovascular event, hospitalization, or other critical illness). Seven of 15 participants with previous infection reported persistent post-COVID neurologic conditions at least 1 month after infection (five participants, headache; five participants, memory impairment; three participants, insomnia; three participants, depression; two participants, disequilibrium; and one participant each, fatigue, neuropathy, personality change, phantosmia, dysgeusia, and tinnitus. One participant had seven symptoms; two, five symptoms; one, three symptoms; one, two symptoms; and two, one symptom.

Cerebral Blood Flow and Cerebrovascular Reactivity Measurements

Mean whole-cortex CBF before acetazolamide administration was not significantly different between participants without previous infection (46.0 ± 10.4 mL/100 g/min) and those with previous infection (41.4 ± 11.9 mL/100 g/min) ($p = .32$). Mean whole-cortex CBF after acetazolamide administration was greater in participants without previous infection (73.8 ± 13.2 mL/100 g/min) than in participants with previous infection (60.5 ± 15.8 mL/100 g/min) ($p = .04$). Mean CVR was greater in participants without previous infection (27.8 ± 5.3 mL/100 g/min) than in participants with previous infection (19.1 ± 6.4 mL/100 g/min) ($p < .001$). After adjustment for age and sex, prior infection was associated with an 8.9-mL/100 g/min (95% CI, 4.6–13.3 mL/100 g/min) decrease in whole brain CVR ($p < .001$). The distribution of CVR in participants with and those without previous infection is presented in Figure 2.

After exclusion of the three participants with previous infection who experienced acute ischemic stroke and hospitalization

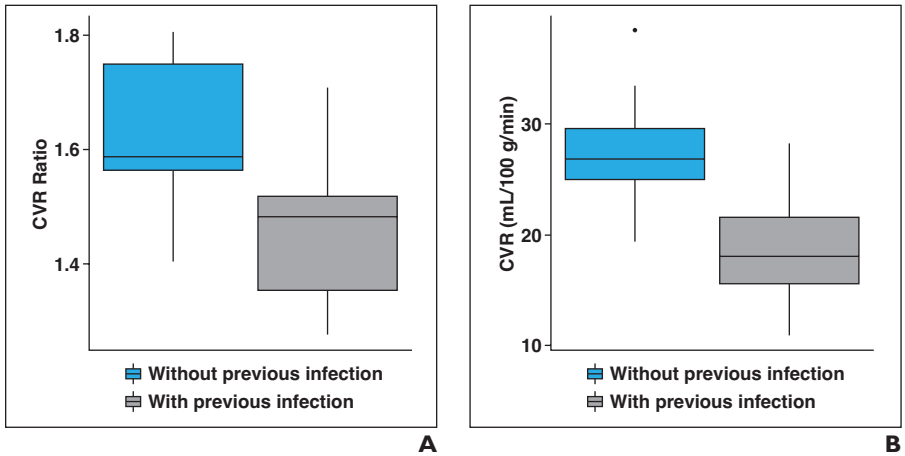

Fig. 2—Charts show distribution of cerebrovascular reactivity (CVR) stratified by prior SARS-CoV-2 infection status. Infection is associated with lower CVR. After adjustment for age and sex, prior infection is associated with 8.9-mL/100 g/min (95% CI, 4.6–13.3 mL/100 g/min) decrease in CVR ($p < .001$). Horizontal lines represent medians; edges of boxes represent IQRs; length of whiskers represents 1.5 times quartile ranges; point beyond whiskers represents outlier.
A, Distribution expressed as ratio.
B, Distribution expressed as absolute value.

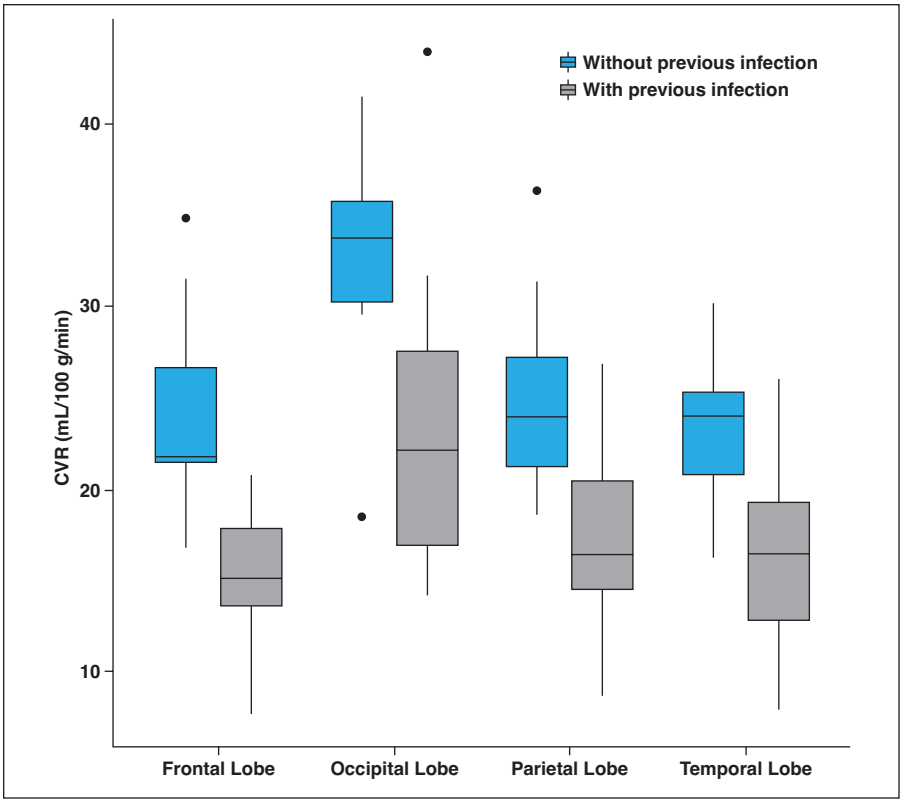

Fig. 3—Chart shows distribution of cerebrovascular reactivity (CVR) difference grouped by lobe and stratified by prior SARS-CoV-2 infection status. Plot suggests that prior infection is associated with smaller CVR in all four analyzed lobes. In linear mixed model adjusted for age and sex with Bonferroni correction for multiple comparisons, significant decrease in CVR was observed in all analyzed lobes (frontal, occipital, parietal, and temporal). Horizontal lines indicate medians; edges of boxes, IQRs; ends of whiskers, interdecile ranges; points beyond whiskers, outliers.

after SARS-CoV-2 infection, mean whole-cortex CBF after acetazolamide administration remained significantly greater in participants without previous infection (27.8 ± 5.3 mL/100 g/min) than in participants with previous infection (18.9 ± 5.2 mL/100 g/min) ($p < .001$). After exclusion of these three participants and adjustment for age and sex, prior infection was associated with an 8.5-mL/100 g/min (95% CI, 4.6–20.0 mL/100 g/min) decrease in whole-brain CVR ($p < .001$).

The distribution of CVR by brain lobe stratified by prior infection status is shown in Figure 3. In a linear mixed model adjusted for age, sex, and time between infection and MRI to which Bonferroni correction was applied for multiple comparisons, prior infection was associated with a decrease in CVR in all lobes: frontal lobe 95% CI of difference, –13.7 to –2.1 mL/100 g/min ($p = .008$); temporal lobe 95% CI of difference, –12.5 to –1.7 mL/100 g/min ($p = .01$); parietal lobe 95% CI of difference, –13.6 to –1.3 mL/100 g/min ($p = .021$); occipital lobe 95% CI of difference, –18.3 to –0.72 mL/100 g/min ($p = .04$). Representative CBF maps before and after acetazolamide administration to a participant with and a participant without previous infection are shown in Figure 4.

Among participants with previous infection, CVR was lower in those with (16.9 mL/100 g/min) than those without (21.0 mL/100 g/min) post-COVID neurologic conditions, but the difference was not significant (95% CI of difference, –10.9 to 2.7 mL/100 g/min; $p = .22$) (Fig. 5).

Vessel Wall Imaging

All VWI abnormalities detected in both study groups either by the two consensus readers or by the third independent reader were short segment and eccentric and deemed consistent with atherosclerosis (Fig. 6). No VWI abnormalities were deemed consistent with vasculitis. The third independent reader did not identify VWI abnormalities in any studies that the two consensus readers characterized as normal (i.e., as showing no VWI abnormalities) or characterize any studies as normal that the two consensus readers identified as abnormal (i.e., as showing at least one VWI abnormality). The third independent reader identified one additional short-segment eccentric VWI abnormality deemed consistent with atherosclerosis in three patients in whom at least one other VWI abnormality had been detected by the two consensus readers.

Six of 15 participants with previous infection, including the three participants with acute stroke and hospitalization, had at least one VWI abnormality. One of 10 participants without previous infection had at least one VWI abnormality. This frequency of having at least one VMI abnormality was not significantly different between the two groups (40% vs 10%; $p = .18$). Of the six participants with previous infection and VWI abnormalities, three had one vessel segment involved, two had two vessel segments involved, and one had three vessel segments involved. The single participant without previous infection who had a VWI abnormality had one segment involved. These distributions of the number of involved segments were not significantly different between the two groups ($p = .55$). These findings are summarized in Table 2.

Among participants with previous infection, those with and those without VWI abnormalities were not significantly different in terms of mean age (51 vs 38 years; $p = .16$) or time from infection to MRI (190 vs 270 days, $p = .11$).

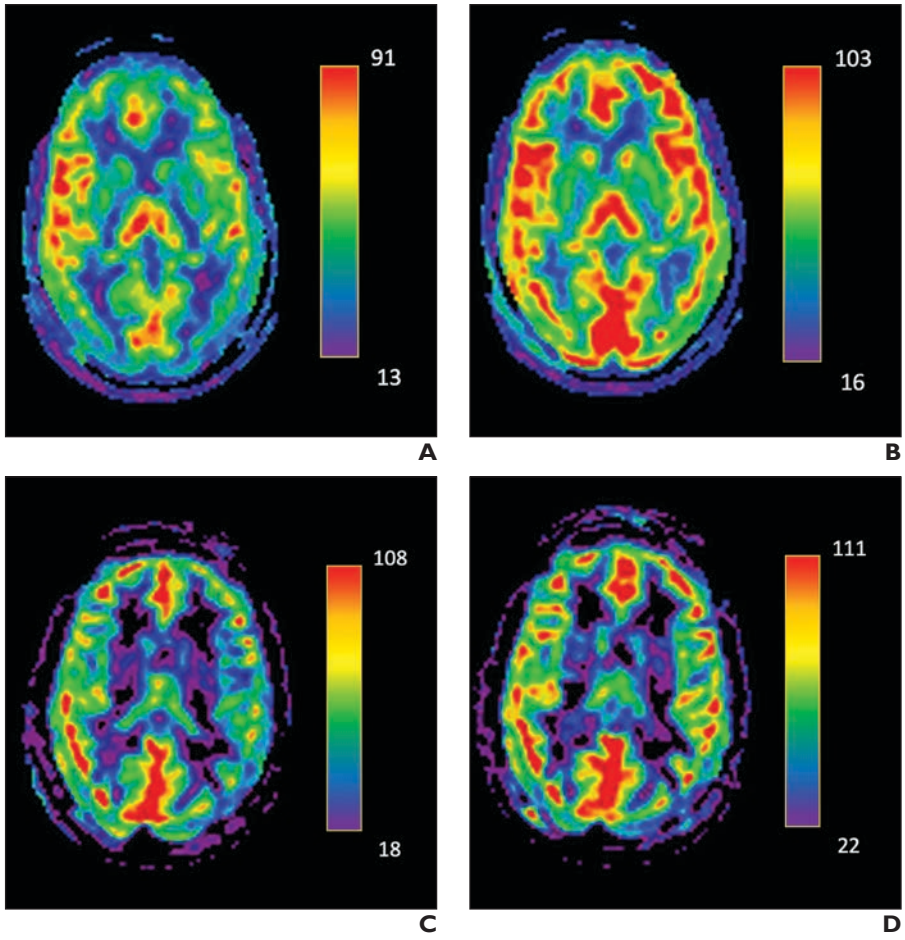

Fig. 4—Color-coded cerebral blood flow maps generated from arterial spin labeling acquisitions before and after acetazolamide administration to two participants.
A and **B,** 34-year-old participant without previous SARS-CoV-2 infection before (**A**) and after (**B**) acetazolamide administration. Map shows whole-brain cortical cerebrovascular reactivity is 38.51 mL/100 g/min.
C and **D,** 39-year-old participant with previous SARS-CoV-2 infection before (**C**) and after (**D**) acetazolamide administration. Map shows whole-brain cortical cerebrovascular reactivity is 18.21 mL/100 g/min.

Potential Interactions Between Cerebral Cerebrovascular Reactivity and Vessel Wall Imaging Abnormalities

Whole-brain CVR was not significantly different between individuals with and those without VWI abnormalities (18.07 vs 16.20 mL/100 g/min; $p = .27$). Participants with previous infection who had VWI abnormalities did not have qualitative decreases in lobar CVR corresponding to the lobes perfused by the affected vessels. For example, frontal and temporal CVR were 16.9 and 17.1 mL/100 g/min in the four participants with previous infection with anterior circulation VWI abnormalities, compared with 16.2 and 14.6 mL/100 g/min in the nine participants with previous infection who did not have VWI abnormalities. Occipital CVR was 23.0 mL/100 g/min in the two participants with previous infection who had posterior circulation VWI abnormalities, compared with 23.7 mL/100 g/min in the nine participants with previous infection who did not have VWI abnormalities.

Discussion

This small case-control study showed a potential association between prior SARS-CoV-2 infection and impaired whole-brain and lobar CVR, providing insight beyond the acute infectious period. Mean baseline whole-cortex CBF was not significantly different between participants with and those without previous infection, indicating normalization of resting cerebral perfusion after the acute period. However, a reduction in CVR compared with CVR in individuals without previous infection was observed weeks to months after SARS-CoV-2 infection. This difference in CVR between the two groups remained statistically significant after exclusion of the three participants with previous infection who experienced acute ischemic stroke and hospitalization after infection. The mechanistic basis of this apparent chronic neurovascular endothelial dysfunction remains unknown.

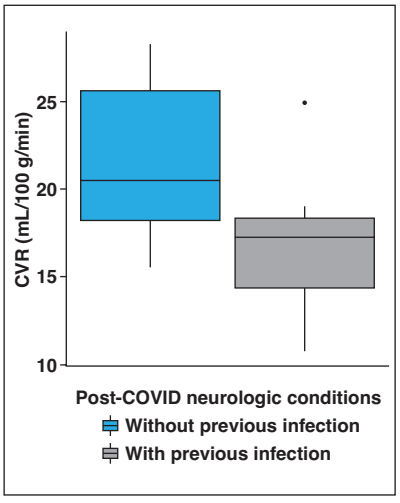

Fig. 5—Chart shows distribution of cerebrovascular reactivity (CVR) in participants with previous SARS-CoV-2 infection stratified by absence versus presence of post-COVID neurologic conditions lasting more than 1 month after infection. Lower CVR in participants with (16.9 mL/100 g/min) than those without (21.0 mL/100 g/min) post-COVID neurologic conditions was not statistically significant ($p = .22$). Horizontal lines indicate medians; edges of boxes, IQRs; ends of whiskers, interdecile ranges; point beyond whiskers, outlier.

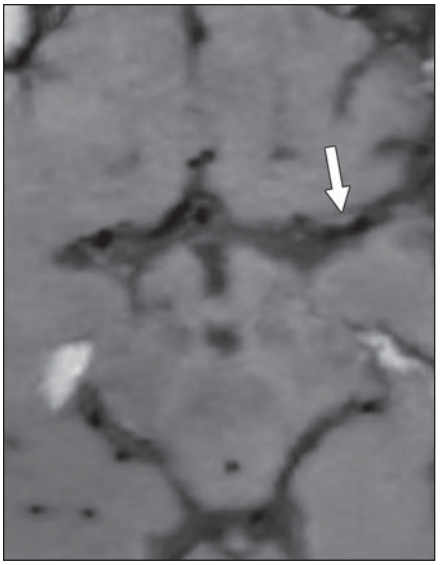

Fig. 6—65-year-old participant with previous SARS-CoV-2 infection. Vessel wall MR image shows short-segment eccentric focus of enhancement (*arrow*) along anterior wall of M1 segment of left middle cerebral artery due to mild focal luminal narrowing. Abnormality was deemed consistent with atherosclerosis.

Further studies are required to delineate the relation between chronic CVR impairment and the chronic clinical neuropsychologic sequelae of SARS-CoV-2 infection. Although mean CVR was lower in participants with previous infection without such symptoms, this difference was not significant. This lack of a difference likewise may relate to either limited statistical power or lack of a mechanistic connection. Studies in which FDG PET was used to evaluate patients experiencing cognitive and neuropsychiatric impairment after SARS-CoV-2 infection have had varied results. One study identified no change in regional cerebral glucose metabolism [29], whereas another showed regional hypometabolism in the inferior frontal lobes and midline structures [30]. Prior studies have also shown correlations between the chronic neuropsychiatric symptoms of post-COVID neurologic conditions and persistent systemic or peripheral endothelial dysfunction, and the authors postulated mechanistic linkage [18, 19]. To date, few studies have examined intracranial endothelial function in individuals with prior SARS-CoV-2 infection. Results of one study suggested that CVR may be impaired in patients with nonspecific neurologic symptoms in the acute to subacute period (30–60 days) after mild SARS-CoV-2 infection [31]. The current study shows that impaired CVR is observed beyond that period, although the clinical sequelae of this impairment require further examination.

The endothelial tropism of SARS-CoV-2 is linked to widespread vascular inflammation and vascular dysfunction across multiple organ systems, including the CNS [8, 9]. Several studies have shown cerebrovascular pathology in patients with acute SARS-CoV-2 infection, particularly patients with severe disease requiring hospitalization and ICU care. Scullen et al. [32] described imaging findings of vasculopathy in 19% of patients with acute SARS-CoV-2 infection and neurologic symptoms. Another study, a single-center evaluation of 1683 patients hospitalized with SARS-CoV-2 infection during a 50-day period, showed evidence of cerebrovascular disease in 23 patients [33]. Dixon et al. [23] described abnormal VWI in a patient with SARS-CoV-2 infection who had concomitant intracranial vasculitis. In a case series, Henry-Feugeas et al. [34] evaluated 20 patients with SARS-CoV-2–associated encephalopathy and found all but one to have abnormal resting cerebral perfusion on MRI.

No statistically significant association was observed between prior infection and the presence of VWI abnormalities. This observation may be due to the small sample size and corresponding limited statistical power or may reflect the true absence of a biologic mechanistic connection. All detected VWI abnormalities were morphologically consistent with atherosclerosis rather than vasculitis. In addition, age and time from infection were not significantly associated with the presence of VWI abnormalities among participants with previous infection, and all three participants with previous infection who experienced acute ischemic stroke and hospitalization had VWI abnormalities. Whether the difference in frequency of VWI abnormalities between participants with and those without previous infection reflected age-related atherosclerosis independent of SARS-CoV-2 infection or accelerated atherosclerosis secondary to inflammatory endothelial injury during the acute infectious period remains unknown. Further studies are required to better evaluate putative associations between SARS-CoV-2 viral endothelial tropism, vasculitis, atherosclerotic disease, chronic neurovascular endothelial dysfunction, and acute and chronic ischemic stroke risks.

This study had limitations. A primary limitation was the small number of participants in both groups. Although CVR was significantly different between groups, larger studies are warrant-

TABLE 2: Vessel Wall Imaging Abnormalities Stratified by SARS-CoV-2 Infection Status

Measure	With Previous Infection (*n* = 15)	Without Previous Infection (*n* = 10)	Overall (*n* = 25)
Vessel wall imaging abnormality			
Present	9 (60)	9 (90)	18 (72)
Absent	6 (40)	1 (10)	7 (28)
No. of segments involved			
0	9 (60)	9 (90)	18 (72)
1	3 (20)	1 (10)	4 (16)
2	2 (13)	0 (0)	2 (8)
3	1 (7)	0 (0)	1 (4)

Note—Data are number of participants with percentage in parentheses.

ed. Also, participants varied widely in terms of age and time since SARS-CoV-2 infection. Furthermore, participants with persistent post-COVID neurologic conditions had heterogeneous symptoms, and SARS-CoV-2 infection was not proven to have caused these symptoms. Additionally, the MRI protocol did not include T2-weighted, FLAIR, or susceptibility-weighted sequences; imaging performed with such sequences may have shown differences in the extent of white matter hyperintensities or microbleeds. Future research should include these sequences to potentially identify additional features of small-vessel disease in individuals with previous infection. Finally, the explanations of observed associations and lack of associations are unknown from the current study.

Conclusion

SARS-CoV-2 infection is associated with chronic CVR impairment, and never having had SARS-CoV-2 infection is not. Future studies are needed to determine the clinical implications arising from SARS-CoV-2–associated CVR impairment.

Acknowledgment

We thank Daniel Litwiller for assistance in protocol optimization and image curation.

Provenance and review: Not solicited; externally peer reviewed.

Peer reviewers: Colin Poon, Providence St. Peter Hospital; Abdulnasser Alhajeri, University of Kentucky; additional individuals who chose not to disclose their identity.

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