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Myocardial Blood Flow Quantified Using Stress Cardiac Magnetic Resonance After Mild COVID-19 Infection

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Abstract

BACKGROUND—Severe COVID-19 infection is known to alter myocardial perfusion through its effects on the endothelium and microvasculature. However, the majority of patients with COVID-19 infection experience only mild symptoms, and it is unknown if their myocardial perfusion is altered after infection.

OBJECTIVES—The authors aimed to determine if there are abnormalities in myocardial blood flow (MBF), as measured by stress cardiac magnetic resonance (CMR), in individuals after a mild COVID-19 infection.

METHODS—We conducted a prospective, comparative study of individuals who had a prior mild COVID-19 infection (n = 30) and matched controls (n = 26) using stress CMR. Stress and rest myocardial blood flow (sMBF, rMBF) were quantified using the dual sequence technique.

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Myocardial perfusion reserve was calculated as sMBF/rMBF. Unpaired t-tests were used to test differences between the groups.

RESULTS—The median time interval between COVID-19 infection and CMR was 5.6 (IQR: 4-8) months. No patients with the COVID-19 infection required hospitalization. Symptoms including chest pain, shortness of breath, syncope, and palpitations were more commonly present in the group with prior COVID-19 infection than in the control group (57% vs 7%, $P < 0.001$). No significant differences in rMBF (1.08 ± 0.27 mL/g/min vs 0.97 ± 0.29 mL/g/min, $P = 0.16$), sMBF (3.08 ± 0.79 mL/g/min vs 3.06 ± 0.89 mL/g/min, $P = 0.91$), or myocardial perfusion reserve (2.95 ± 0.90 vs 3.39 ± 1.25, $P = 0.13$) were observed between the groups.

CONCLUSIONS—This study suggests that there are no significant abnormalities in rest or stress myocardial perfusion, and thus microvascular function, in individuals after mild COVID-19 infection.

Keywords

mild COVID-19 infection; quantitative myocardial perfusion; stress cardiac magnetic resonance

Myocardial ischemia and coronary microvascular dysfunction (CMD) are known manifestations of SARS-CoV-2 infection, which has been demonstrated to alter myocardial perfusion through its effects on the endothelium and microvasculature.[1-3] However, a significant proportion of the world population suffered from only mild COVID-19 symptoms. Furthermore, patients with persistent symptoms after recovering from the COVID-19 infection have been reported in recent studies.[4,5] Chronic COVID-19, also known as long COVID syndrome, is defined as symptoms extending beyond 12 weeks following acute infection, and postacute sequelae of SARS-CoV-2 infection[6,7] are frequently encountered in outpatient clinic. Because of the known adverse effects of the COVID-19 infection on the cardiovascular system, the pathophysiology of cardiac sequelae of the viral illness has generated great clinical and research interest. The objective of our study is to determine if myocardial perfusion is altered in patients following COVID-19 infection, particularly in outpatients with a history of mild infection.

It has been postulated that microvascular thrombosis and impaired endothelial function are important pathophysiological contributors to the cardiovascular symptomatology of COVID-19 infection.[8] Cardiac magnetic resonance (CMR) is a noninvasive imaging modality that has been used to detect myocardial injury following the COVID-19 infection.[9,10] In addition to changes in T1 myocardial relaxation time and late gadolinium enhancement (LGE), which represent areas of myocardial inflammation, patients with COVID-19 infection have also been demonstrated to have alterations in myocardial perfusion due to direct infection of the vascular endothelium by the virus.[1-3] CMR perfusion imaging uses a dual sequence technique, which consists of a separate pulse sequence with a short saturation pulse used to accurately quantify the arterial input function (AIF) and a traditional perfusion pulse sequence to quantify the tissue function. Motion correction, myocardial segmentation, and Fermi function deconvolution are processed automatically to produce the quantitative myocardial blood flow map.[11-13] In this study, we use the technique developed by Hsu et al.[11] In recent years, with the development of fully quantitative

CMR perfusion sequences, CMR now has the potential to detect CMD in a variety of patient populations.[12,13] A recent study demonstrated that cardiovascular abnormalities are uncommon in health care workers 6 months following mild COVID-19 infection.[10] However, the quantification of myocardial perfusion, and thus CMD, has not been fully studied in this patient population. In this study, we aimed to determine if there are detectable abnormalities in myocardial perfusion as measured by stress CMR in individuals following a mild COVID-19 infection.

METHODS

We conducted a single-center, prospective, cross-sectional comparative study. An individual one-to-one matching strategy was used. For every individual enrolled with a history of mild COVID-19 infection, one matching control was selected with similar age, gender, and cardiovascular risk factors. All participants were enrolled in outpatient clinics from October 2020 to December 2021 at the University of Chicago Hospital in Chicago, Illinois. Subjects were screened until the prespecified number of subjects were enrolled. The exclusion criteria were as follows: patients with myocardial infarction or unstable angina within 30 days, hypertrophic cardiomyopathy, hemodynamically significant ventricular arrhythmia within 30 days, evidence of hemodynamic instability, contraindications to gadolinium-enhancement magnetic resonance examination, advanced renal disease (glomerular filtration rate [GFR] <30 mL/min), severe claustrophobia, current pregnancy, uncontrolled obstructive pulmonary disease, or asthma. All participants provided written informed consent, which was approved by the institutional review board (IRB; Biological Sciences Division IRB Committee A; Ethics Registration Number IRB20-2016).

Forty participants with a history of laboratory-confirmed COVID-19 infection and 26 matched controls were enrolled. Two cases were excluded due to having a severe COVID-19 infection requiring hospitalization. One COVID-19-recovered subject with evidence of prior myocardial infarction on LGE images was excluded from the analysis. Four subjects in the group of prior COVID-19 infection were excluded because fully quantitative perfusion was unable to be performed, and 3 subjects after COVID-19 infection were excluded because the AIF, which is necessary to calculate myocardial blood flow (MBF) and myocardial perfusion reserve (MPR), could not be accurately measured due to errors during scan prescription. Following the exclusion of these individuals, 56 total participants were included in the study: 30 had a prior mild COVID-19 infection and 26 risk-factor-matched controls. Laboratory-confirmed polymerase chain reaction (PCR) testing was used to confirm prior SARS-CoV-2 infection. Patients were considered to have had prior COVID-19 infection after at least 1 month had passed following their most recent laboratory-confirmed PCR test. Ninety-seven percent (29/30) of patients after COVID-19 infection and 73% (19/26) of controls underwent laboratory testing on the day of their stress CMR.

All blood testing was completed on-site at the University of Chicago Medical Center.[14] High-sensitivity troponin T ≥17 ng/L, high-sensitivity C-reactive protein ≥5 mg/L, lactate dehydrogenase ≥245 μ/L, D-dimer ≥0.4 μg/mL, ferritin ≥300 ng/mL, and NT-pro-B-type natriuretic peptide ≥125 pg/mL were considered as abnormal values. All participants were asked by the study if they experienced symptoms including chest pain, shortness of breath,

syncope, or palpitations 30 days prior to their outpatient visit. Demographic and clinical history was extracted from the electronic medical record. The definition of myocarditis was based on the 2018 Lake Louise consensus criteria.[15]

IMAGE ACQUISITION.

CMR imaging was performed using a 1.5T scanner (SIGNA Artist, GE Healthcare). A 30-channel anterior array, 40-channel posterior array coil, and electrocardiographic (ECG) gating were used for all scans in the protocol. Patients were asked to refrain from caffeine consumption for 24 hours before the regadenoson-based stress CMR. Before the contrast injection, T1 mapping, T2 mapping, and T2-weighted images were acquired (Figure 1). T2-weighted imaging was performed using a fast spin echo with short tau inversion recovery sequence (T2-STIR). A precontrast T1 map was acquired using a standard MOLLI sequence with 5(3)3 pattern. Multiecho fast spin echo was employed for T2 mapping. First-pass perfusion was performed during infusion of a gadolinium-based contrast agent (0.05-0.10 mmol/kg based on GFR), followed by a saline flush (50 mL) via an antecubital vein. Following resting perfusion imaging, retrospectively gated cine images were acquired using a steady-state free precession technique. Standard long-axis views were obtained including 4-, 2-, and 3-chamber images. In addition, 6 to 10 short-axis slices were obtained from the left ventricular (LV) and right ventricular (RV) bases to the apex (slice thickness 8 mm, 2-mm gap).

For the stress portion of the study, regadenoson 0.4 mg was injected over approximately 10 seconds into a peripheral vein, followed by a 5 mL saline flush. The perfusion sequence was started within 1 to 2 minutes of regadenoson administration and during first pass of the gadolinium-based contrast agent (0.05-0.10 mmol/kg based on GFR). All patients were monitored by a CMR-compatible, 3-lead wireless continuous ECG system and pulse oximetry during the study. Blood pressure and heart rate were monitored at baseline and after regadenoson administration, and a 12-lead ECG was performed prior to the study. Aminophylline 75 mg was administered intravenously for reversal of hyperemia after stress images were acquired. For perfusion imaging, a dual sequence method was used to acquire a low-resolution AIF image, and 3 slices of myocardial images were obtained in standard short-axis views of the left ventricle, with coverage from base to apex, during stress and resting conditions. Imaging parameters were as follows: slice thickness 8 mm, variable interslice gap to accommodate adequate spacing of slices through the left ventricle, flip angle 20°, NEX 0.75, parallel imaging factor 2, field of view 36 to 50 cm × 27 to 37.5 cm, and acquired matrix 192 × 148 pixels. Two proton-density-weighted images were also acquired for correcting surface-coil-related intensity inhomogeneity. After a 5-minute delay, LGE imaging was performed in the same short- and long-axis views as the cine images. A MOLLI sequence with a 4(1)3(1)2 pattern was performed for postcontrast T1 mapping.

CMR IMAGE ANALYSIS.

All analysis was performed in a blinded fashion. The cine CMR, T1 mapping, and T2 mapping images were analyzed using commercially available software (Medis Medical Imaging). Using the short-axis cine images, the LV and RV end-diastolic and end-systolic frames were identified, and the Simpson method of disks was used to calculate LV end-

diastolic mass, LV and RV end-diastolic and end-systolic volumes, and the corresponding ejection fractions. Native and postcontrast myocardial T1 relaxation times and T2 decay times were measured in the septal myocardium of the mid-short axis slice. Extra-cellular volume fraction (ECV) was calculated using the following formula: ECV = (1-Hct) [(1/post-contrast T1 of myocardium – 1/native T1 of myocardium)/(1/postcontrast T1 of blood pool – 1/native T1 of blood pool)]. In this study, subjects with COVID-19 infection with native T1, T2, and ECV values more than 2 SDs from control subject values were classified as abnormal (pre-T1 >1,100 ms, T2 >57 ms, ECV >36%).[16] These abnormal cut-off values were similar to those described in the literature for other 1.5T GE scanners.[17,18] LGE burden was quantified as the LGE mass on short-axis images using the full width half maximum method by SuiteHEART software (version 5.0.4, Neosoft).

First-pass images were analyzed using CVI42 (version 2774, Circle Cardiovascular Imaging) (Figure 2). Seventy consecutive frames were identified to analyze quantitative perfusion. The LV and RV endocardial and epicardial boundaries were generated automatically on the 3 short-axis perfusion images and AIF images at rest and stress by the software and then adjusted manually as necessary by an expert user. Once LV and RV segmentation and heart rate were verified, pixel-wise maps and time-signal intensity curves at rest and stress were displayed along with the corresponding bullseye plot of the rest and stress MBF and MPR according to the American Heart Association 16-segment model. The MBF values were derived using Fermi deconvolution. The MPR was defined as the ratio between MBF at stress/MBF at rest. Fermi deconvolution is an empirical mathematical model that predicts the kinetics of the contrast flow through the myocardium during first-pass perfusion.[19] Deconvolution of the AIF and myocardial time-signal intensity curves were calculated automatically by the imaging software to obtain MBF pixel-wise maps. The median pixel values in each segment were calculated automatically to produce the MBF bullseye plot.[11] Quality control of the segmental values was performed, and the following segments were excluded from the analysis: 1) segments with thin myocardium significantly impacted by partial volume effects from the LV cavity signal; 2) segments with significant motion artifact; and 3) segments that included the left ventricular outflow tract. The remaining segments were used to calculate the average rest MBF, stress MBF, and MPR values for each individual. To correct for potential differences in resting heart rate and blood pressure between patients, the rest MBF was normalized to rate pressure product measured during resting conditions using the following formula: corrected rest MBF = rest MBF/rest rate pressure product × 10,000. The corrected MPR was calculated as: corrected MPR = stress MBF/corrected rest MBF.[20]

STATISTICS.

Based on prior literature, stress myocardial blood flow can vary by as much as 15 to 20% in healthy volunteers depending on where in the cardiac cycle a perfusion image is acquired.[21-23] We thus powered our study to detect a 15% difference in MBF between controls and patients after COVID-19 infection. The sample size necessary to detect this difference is 28 subjects in the COVID group based on a sample size calculation with an alpha of 0.05 and a power of 80%. A Shapiro-Wilk test was used for testing normality. Continuous variables were presented as mean ± SD when normally distributed or as median

(IQR) when not normally distributed. Intergroup differences were tested using unpaired t-tests for normal distribution or the Mann-Whitney U tests for non-normal distributions, respectively. Categorical variables were presented as absolute numbers with percentages and tested using the chi-squared test. *P* values and confidence intervals were not adjusted for multiplicity. Analysis was performed using SPSS software (2017 release, IBM SPSS Statistics for Windows, Version 25.0, IBM Corp) and GraphPad Prism (Prism 9 for Windows Version 9.4.1 [681]).

RESULTS

Patient characteristics are shown in Table 1 along with the relevant clinical and imaging findings. At the time of positive PCR test, no patients in the prior COVID-19 infection group were hospitalized, and all were considered as having a mild infection. The median time interval between PCR positivity and CMR was 5.6 months (IQR: 4-8 months). The 2 groups were similar in age, gender, and BSA. Symptoms including chest pain, shortness of breath, syncope, and palpitations were more frequent in the prior COVID-19 infection group than in the matched control group (17/30 (57%) vs 2/26 (7%), $P < 0.001$). Chest pain (9/30 (30%) vs 2/26 (7%), $P = 0.04$) and shortness of breath (8/30 (27%) vs 1/26 (4%), $P = 0.03$) were more commonly present in patients after COVID-19 infection than matched controls. There were no significant differences in laboratory biomarkers, electrocardiographic abnormalities, or comorbidities between the 2 groups.

Rest MBF (1.08 ± 0.27 mL/g/min vs 0.97 ± 0.29 mL/g/min, $P = 0.16$), stress MBF (3.08 ± 0.79 mL/g/min vs 3.06 ± 0.89 mL/g/min, $P = 0.91$), and MPR (2.95 ± 0.90 vs 3.39 ± 1.25, $P = 0.13$) in patients after COVID-19 infection were not statistically different when compared to the matched controls (Figure 3, Table 2). Corrected rest MBF (1.42 ± 0.52 mL/g/min vs 1.27 ± 0.46 mL/g/min, $P = 0.31$) and corrected MPR (2.40 ± 0.89 vs 2.72 ± 1.20, $P = 0.44$) in the prior COVID-19-infected patients showed no significant difference compared to the group of matched controls.

CMR findings are shown in Table 2. Compared with matched controls, there was no statistical difference in LV and RV functional parameters. With regards to myocardial tissue characterization, native T1, T2, and ECV showed no significant differences between the 2 groups. One patient in the prior COVID-19 infection group had elevated signal on T2 STIR images, increased T2 time, and native T1 myocardial relaxation time related to active inflammation, along with a borderline increase in hs-TnT (12 months post-COVID-19 infection); however, left ventricular ejection fraction was normal and no evidence of LGE. In a prior COVID-19-infected cohort, thirty percent of patients (9/30) had at least 1 myocardial abnormality (T1, T2, ECV) on CMR or demonstrated an ischemic or nonischemic LGE pattern. No significant differences were observed in prevalence of LGE and LGE patterns between the 2 groups.

DISCUSSION

Absolute quantification of myocardial perfusion has been applied in the evaluation of myocardial ischemia in both epicardial coronary artery disease and CMD.[24,25] In our study,

we used a fully quantitative stress perfusion CMR-based approach to measure myocardial blood flow and MPR while also comprehensively assessing cardiac function and myocardial tissue characteristics. Our results show that after mild COVID-19 infection, patients do not appear to have significant CMD when compared to risk-factor-matched controls. Despite persistent symptoms in 57% of patients after COVID-19 infection, no CMD was identified suggesting that this may not be the mechanism of long COVID-19 symptoms (see Central Illustration).

FULLY QUANTITATIVE PERFUSION AND CORONARY MICROCIRCULATION.

Fully quantitative perfusion by stress positron emission tomography or stress CMR has been recommended for the evaluation of CMD.[26] Automated myocardial perfusion quantification by stress CMR has recently become more widely available.[11] Kotecha et al[13] were able to differentiate CMD from multivessel disease using an in-line myocardial perfusion mapping technique in patients who also underwent invasive fractional flow reserve and index of microcirculatory resistance as the reference standard. Stress MBF >2.25 mL/g/min was able to correctly identify normal patients from a group of obstructive CAD and multivessel disease with 95% sensitivity and 88% specificity. Stress MBF and MPR were 2.10 ± 0.35 mL/g/min and 2.41 ± 0.79, respectively, when index of microcirculatory resistance ≥25 and fractional flow reserve >80%.[27] The stress MBF values seen in both groups in our study were much greater than those seen for CMD patients in previous CMR and PET-based studies. We found that CMD was not present in patients after mild COVID-19 infection. In our study, both MBF and MPR values were normal in COVID-19-recovered patients as well as control patients.

LONG COVID-19 AND CORONARY MICROVASCULAR DYSFUNCTION.

Prior studies have implicated CMD in the long COVID-19 syndrome. Bruno et al[28] proposed that viral particles maintain a persistent ability to invade the vascular tissue resulting in endothelial inflammation and microvascular thrombosis. A study of patients with moderate to severe COVID-19 infection discharged from the hospital showed that 64% of patients presented with persistent symptoms including shortness of breath and fatigue 2 to 3 months following COVID-19 infection, and that 26% had cardiac abnormalities identified by magnetic resonance imaging.[29] Puntmann et al[30] demonstrated that during the 3 months following mild COVID-19 infection, abnormalities in native T1 and T2 occurred at a significantly higher frequency than expected in the general population. Most previous studies have followed COVID-19-infected patients for 1 to 3 months.[31] Logue et al[32] followed COVID-19 patients for up to 9 months and found that 30% reported persistent symptoms. A few prior studies have shown reduced myocardial blood flow and MPR using stress CMR in patients recovered from COVID-19 infection. Ahmed et al[33] published a retrospective study that showed that the prevalence of myocardial flow reserve (MFR) <2.0 was higher in patients with prior COVID-19 infection than in those without prior COVID-19 infection. However, this study only compared the percentage of patients with low MPR in the 2 groups using PET imaging, and details about the actual MPR and associated rest and stress MBF values were not described. Another small study of 22 patients after COVID-19 infection with persistent symptoms after 1 to 6 months utilized velocity-encoded phase-contrast imaging of the coronary sinus flow to suggest a role of

CMD in long COVD-19 symptoms.[34] Doeblin et al enrolled 33 patients recovered from hospitalized COVID-19 infection, 57% of them with long COVID-19 symptoms, and used stress CMR to determine that normalized stress MBF was significantly lower compared to 17 non-age-matched controls for T1 and T2 relaxation times taken from previously unpublished data,[35] rather than clinically matched control subjects as were used in our study. The IQR of follow-up in our study was 4 to 8 months, which was longer than most studies described above. In contrast to the studies described above, which included many patients who had a more severe COVID infection, our study focused on patients after a mild COVID-19 infection and found that myocardial blood flow and MPR were preserved. This suggests that cardiac symptoms in subjects who had a prior mild COVID-19 infection are unlikely to be due to CMD.

UTILITY OF MULTIPARAMETRIC CMR IN PATIENTS WITH COVID-19 INFECTION.

CMR can detect myocardial abnormalities despite normal serum biomarkers.[36] Throughout the COVID-19 pandemic, CMR has been used to provide guidance to athletes recovering from mild or asymptomatic COVID-19 infection on when to safely return to competition.[37] Although coronary microvascular function was normal in the cohort with prior mild COVID-19 infection in our study, a few subjects had CMR evidence of myocardial pathology. Of 30 patients, 9 (30%) had at least 1 myocardial abnormality. However, there was no clear difference noted between the absolute values of any of these parameters in 2 groups. While it is unclear if a singular myocardial tissue characteristic abnormality is clinically significant, on a cohort basis, our myocardial tissue characteristic findings are consistent with those reported by Joy et al,[10] who showed no statistically significant differences in CMR findings between patients recovered from mild SARS-CoV-2 infection and control patients at 6 months, suggesting that myocardial abnormalities may resolve over time. Similarly, Kotecha et al showed that chronic inflammation and diffuse fibrosis were not dominant features in surviving COVID-19 patients based on no significant differences observed in native T1 and T2 myocardial relaxation times in patients recovered from COVID-19 infection compared to matched controls,[38] which is consistent with the results of our study.

Our findings are consistent with other studies. Gorecka et al[39] demonstrated no significant differences in cardiac function, T1 time, MBF, MPR, and LGE between 20 patients with a clinical diagnosis of long COVD-19 syndrome and healthy matched controls. Similarly, Thornton et al[1] showed no significant difference in the stress MBF in patients following severe COVID-19 infection compared to risk-matched controls, with no definitive evidence of persistent CMD in this cohort. In our study, we excluded patients with severe COVID-19 infection and instead focused on patients with mild COVID-19 infection, given that this represents the majority of patients with prior COVID-19 infection worldwide. Thus, ongoing research is needed to determine whether patients who have recovered from a moderate-to-severe COVID-19 infection have residual CMD.

STUDY LIMITATIONS.

This is a single-center study performed on a relatively small number of patients. Selection bias associated with patient recruitment cannot be completely excluded, despite clear

inclusion and exclusion criteria as detailed in the Methods section. Given the presence of intervendor differences in CMR metrics, caution should be exercised when comparing our results to other studies. Our study findings are limited to patients after mild COVID-19 infection and cannot be extrapolated to patients with more severe COVID-19 infection. Additionally, our study was powered to detect a 15% decrease in stress MBF. While significant differences in MBF and MPR may exist below the 15% threshold, these differences would require larger datasets to fully assess. However, the ability to detect smaller changes in MBF is likely beyond the capability of stress perfusion CMR at the current time.

CONCLUSIONS

In this prospective study, we used fully quantitative stress CMR-based imaging to evaluate myocardial blood flow in individuals following mild SARS-CoV-2 infection. We found no significant abnormalities in myocardial perfusion in individuals after mild COVD-19 infection compared to matched controls. Despite persistent symptoms in 57% of the prior COVID-19-infected group, no CMD was identified suggesting that CMD may not be the cause of long COVID-19 syndrome.

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ABBREVIATIONS AND ACRONYMS

AIF	artery input function
CMD	myocardial microvascular dysfunction
CMR	cardiac magnetic resonance
IRB	Institutional Review Board
MBF	myocardial blood flow
MPR	myocardial perfusion reserve
rMBF	rest myocardial blood flow
SARS-CoV-2	severe acute respiratory syndrome-coronavirus-2
sMBF	stress myocardial blood flow

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Based on stress CMR, individuals with prior mild COVID-19 infection do not have significant differences in MPR and absolute myocardial blood flow during resting and stress conditions when compared to control subjects. It remains to be determined if patients who have recovered from a moderate or severe COVID-19 infection have long-term abnormalities in coronary microvascular function.

TRANSLATIONAL OUTLOOK:

Stress CMR with absolute quantitative myocardial blood flow analysis has the potential to provide a comprehensive evaluation of the impact of mild SARS-CoV-2 infection on the heart. Myocardial perfusion reserve using stress CMR is a tool for non-invasively determining the presence coronary microvascular dysfunction. This cardiac imaging technique is well suited to not only improve our understanding of the cardiac manifestation of prior mild COVID-19 infection but to also facilitate translation of any potential diagnostic pathways into clinical practice.

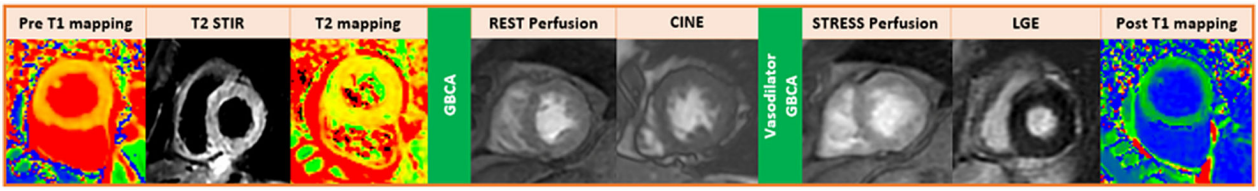
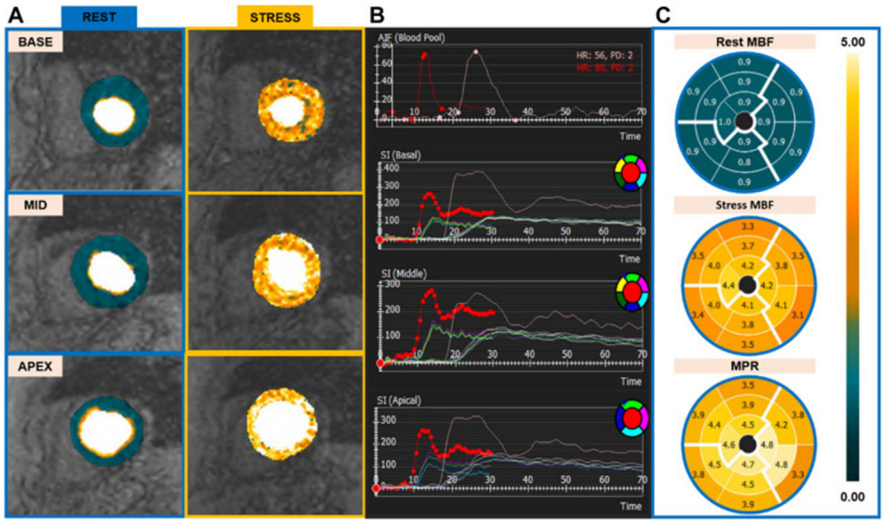


FIGURE 1. Regadenoson Stress Perfusion Cardiac Magnetic Resonance Protocol

Precontrast T1 mapping, T2 STIR, and T2 mapping are obtained prior to contrast administration to obtain myocardial tissue characteristics. Resting perfusion images are acquired following gadolinium-based contrast injection using a first-pass perfusion technique, followed by all cine images. Next, stress perfusion images are obtained following regadenoson and contrast administration. Finally, LGE and postcontrast T1 mapping sequences are performed. LGE = late gadolinium enhancement.



FUGURE 2. Example of Fully Quantitative Myocardial Perfusion Shown for a Control Subject

(A) Quantitative myocardial blood flow pixel-wise maps from base (bottom) to apex (top) at rest (green color) and stress (orange color). (B) Time-signal intensity curves for AIF (top) and myocardium in 3 slices (basal, mid, and apex). Sixteen myocardial segments are shown in different colors. (C) Bullseye diagram for resting myocardial blood flow (rMBF) in units of mL/g/min (top), stress myocardial blood flow (sMBF) in units of mL/g/min (middle), and myocardial perfusion reserve (MPR) (bottom) using the standard American Heart Association 16-segment model. AIF = artery input function.

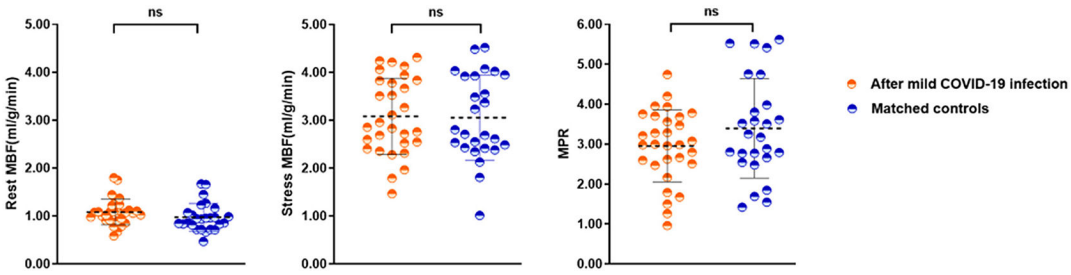
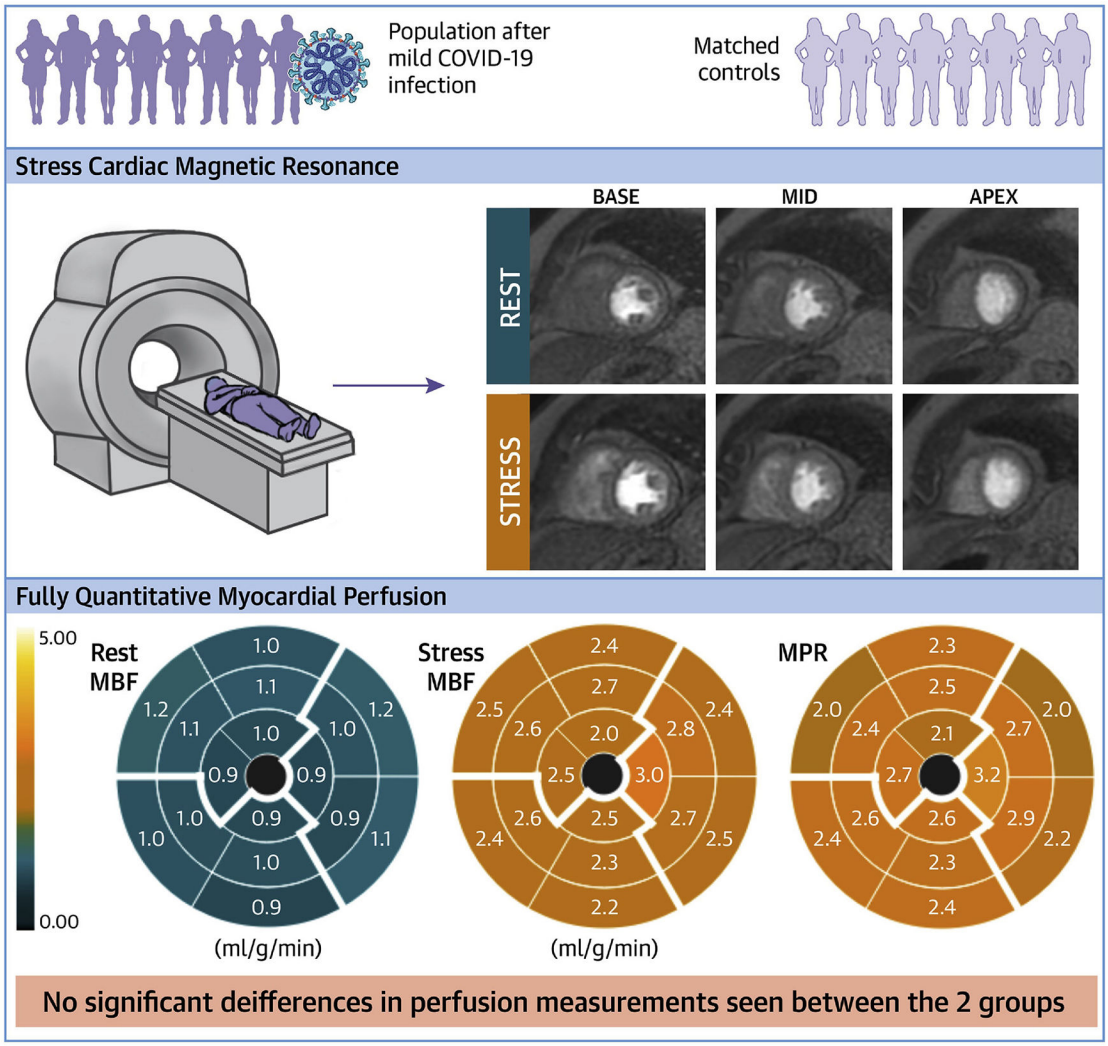


FIGURE 3. Comparison of Myocardial Blood Flow Between Patients After Mild COVID-19 Infection and Matched Controls

Rest MBF (left), stress MBF (middle), and MPR (right) between the 2 groups from left to right. Scatter plots in red represent the prior COVID-19 infected cohort and the scatter plots in blue represent matched controls. Black dashed horizontal lines and whiskers in panels represent means and standard deviations, respectively. MBF = myocardial blood flow; MPR = myocardial perfusion reserve.



CENTRAL ILLUSTRATION. Stress Cardiac Magnetic Resonance Myocardial Blood Flow After Mild COVID-19 Infection

Patients after mild COVID-19 infection and matched controls underwent stress cardiac magnetic resonance (CMR) with a vasodilator (regadenoson). First-pass perfusion images were obtained at rest and stress followed by fully quantitative perfusion analysis by Fermi deconvolution. The rest MBF, stress MBF, and MPR were obtained for each patient, shown here in a bullseye configuration representing the apical, mid, and basal levels. The example of fully quantitative myocardial perfusion depicted here is for an individual after mild COVID-19 infection. MBF = myocardial blood flow; MPR = myocardial perfusion reserve.

TABLE 1

Baseline Characteristics

Empty Cell	Overall (N = 56)	COVID-19 (n = 30)	Control (n = 26)	*P* Value
Age, y	48 (32-62)	41 (32-63)	57 (33-63)	0.32
Male	30 (54%)	13 (43%)	17 (65%)	0.11
BMI, kg/m^2	25.7 (24-30)	28 (24-31)	25 (23-28)	0.07
BSA, m^2	1.90 (1.73-2.10)	1.92 (1.73-2.25)	1.86 (1.69-1.99)	0.15
Symptoms	19 (34%)	17 (57%)	2 (7%)	**<0.001**
Chest pain	11 (20%)	9 (30%)	2 (7%)	**0.04**
Shortness of breath	9 (16%)	8 (27%)	1 (4%)	**0.03**
Syncope	1 (2%)	1 (3%)	0	1.00
Palpitations	4 (7%)	4 (13%)	0	0.12
Comorbidities				
Smoking	4 (7%)	3 (10%)	1 (4%)	0.62
Coronary artery disease	9 (16%)	4 (13%)	5 (19%)	0.72
Hypertension	23 (41%)	14 (47%)	9 (35%)	0.42
Hyperlipidemia	20 (36%)	9 (30%)	11 (42%)	0.41
Diabetes	8 (14%)	5 (17%)	3 (12%)	0.71
Outpatient	56 (100%)	30 (100%)	26 (100%)	1.00
Electrocardiogram				
Normal sinus rhythm	55 (98%)	29 (97%)	26 (100%)	1.00
Atrial fibrillation	1 (2%)	1 (3%)	0	1.00
Abnormal Q wave	3 (5%)	2 (7%)	1 (4%)	0.56
LBBB/RBBB	5 (9%)	2 (7%)	3 (12%)	0.66
Laboratory Testing				
Hs-TnT (ng/L)	5.0 (5.0-10.8)	5.0 (5.0-11.5)	7.0 (5.0-11.0)	0.76
Hs-CRP (mg/L)	1.05 (0.50-2.93)	1.30 (0.70-3.00)	0.85 (0.50-3.3)	0.22
NT-pro-BNP (pg/mL)	36.5 (19.0-93)	41 (19.0-97.0)	28 (19.0-39.0)	0.28
D-Dimer (μg/mL)	0.30 (0.20-0.43)	0.20 (0.20-0.40)	0.34 (0.20-0.45)	0.48
LDH (μ/L)	191.0 (173.0-209.0)	191.0 (170.0-208.0)	190.0 (173.0-212.0)	0.79
Ferritin (ng/mL)	100.0 (60.0-185.5)	111.0 (75.0-215.0)	67.0 (21.0-117.8)	0.19

Values are median (IQR) or n (%). **Bold** values indicate statistical significance.

BMI = body mass index; BSA = body surface area; Hs CRP = high-sensitivity-C-reactive protein; Hs-TnT = high-sensitivity troponin T; LBBB = left bundle branch block; LDH = lactate dehydrogenase; NT-pro-BNP = NT-pro-B-type natriuretic peptide; RBBB = right bundle branch block.

TABLE 2

Cardiac Magnetic Resonance Imaging Parameters

Empty Cell	Overall (N = 56)	COVID-19 (n = 30)	Control (n = 26)	*P* Value
CMR parameters				
LV EDV, mL	158 ± 36	166 ± 37	148 ± 32	0.06
LV EDVi, mL/m^2	81 ± 14	83 ± 13	78 ± 15	0.17
LV ESV, mL	63 (49-75)	64 (53-78)	58 (43-69)	0.13
LV ESVi, mL/m^2	33 ± 9	34 ± 7	31 ± 10	0.21
LV SV, mL	95 ± 20	100 (83-112)	86 (77-98)	0.08
LV EF, %	60 (57-64)	59 (57-63)	60 (57-68)	0.29
LV Mass, g	86 (75-106)	85 (74-119)	86 (75-100)	0.89
LV Massi, g/m^2	47 (40-54)	45 (39-55)	48 (41-52)	0.44
RV EDV, mL	164 ± 46	173 ± 43	156 ± 49	0.18
RV EDVi, mL/m^2	84 ± 18	86 ± 15	82 ± 21	0.35
RV ESV, mL	75 ± 26	81 ± 26	69 ± 24	0.08
RV ESVi, mL/m^2	38 ± 10	40 ± 10	36 ± 10	0.12
RV SV, mL	90 ± 23	92 ± 19	87 ± 27	0.45
RV EF, %	55 ± 6	54 ± 5	56 ± 5	0.11
RV EFi	29 ± 6	28 ± 6	30 ± 5	0.05
T1 time pre (myocardial) (ms)	1,018 ± 58	1,028 ± 66	1,007 ± 46	0.17
T1 time post (myocardial) (ms)	520 (377-553)	522 (383-558)	517 (370-552)	0.62
T1 time pre (blood pool) (ms)	1,510 ± 86	1,500 ± 75	1,521 ± 798	0.40
T1 time post (blood pool) (ms)	430 (245-467)	413 (240-467)	420 (251-467)	0.81
ECV, %	30 ± 4	30 ± 4	30 ± 3	0.84
T2 time (ms)	52 (50-55)	53 ± 5	52 ± 3	0.22
T2 STIR (regional increase in SI)	1 (2%)	1 (3%)	0 (0)	1.00
Abnormal pre T1 (%) (n > 2SD from control)	4 (7%)	4 (13%)	0 (0)	0.08
Abnormal T2 (%) (n > 2SD from control)	2 (4%)	2 (7%)	0 (0)	0.30
Abnormal ECV (%) (n > 2SD from control)	2 (4%)	2 (7%)	0 (0)	0.30
LGE	6 (11%)	3 (10%)	3 (12%)	1.00
ischemia	1 (3%)	1 (4%)	0	0.53
Insertion point	2 (3.4%)	0	2 (7%)	0.21
Other nonischemia	3 (6%)	2 (7%)	1 (4%)	0.56
LGE burden (g)	1.6 (1.0-2.1)	1.58 (1.22-1.64)	2.0 (1.5-2.1)	0.40
Perfusion defect	3 (5%)	2 (7%)	1 (4%)	0.56
Pericardial perfusion	2 (3%)	2 (6%)	0 (0)	0.50
Hemodynamic parameters				
Rest heart rate (beats/min)	65 ± 11	65 ± 10	65 ± 13	0.78
Rest systolic blood pressure (mm Hg)	124 ± 15	124 ± 16	124 ± 15	0.95
Rest diastolic blood pressure (mm Hg)	71 ± 11	70 ± 11	73 ± 11	0.34
Stress heart rate (beats/min)	102 (85-115)	104 (93-116)	97 (83-115)	0.14

Empty Cell	Overall (N = 56)	COVID-19 (n = 30)	Control (n = 26)	*P* Value
Stress systolic blood pressure (mm Hg)	119 (109-132)	121 (113-135)	113 (107-129)	0.32
Stress diastolic blood pressure (mm Hg)	67 ± 11	67 ± 11	67 ± 12	0.89
Myocardial quantitative perfusion parameters				
Rest MBF (mL/g/min)	1.03 ± 0.28	1.08 ± 0.27	0.97 ± 0.29	0.16
Stress MBF (mL/g/min)	3.07 ± 0.82	3.08 ± 0.79	3.06 ± 0.89	0.91
MPR	3.16 ± 1.09	2.95 ± 0.90	3.39 ± 1.25	0.13

Values are mean ± SD, median (IQR), or n (%).

ECV = extracellular volume; EDV = end-diastolic volume; EDVi = end-diastolic volume index; EF = ejection fraction; ESV = end-systolic volume; ESVi = end-systolic volume index; LGE = late gadolinium enhancement; LV = left ventricular; RV = right ventricular; SI = signal intensity; STIR = short tau inversion recovery; SV = stroke volume.