JAMA Cardiology | Original Investigation

Combined Cardiac Fluorodeoxyglucose–Positron Emission Tomography/Magnetic Resonance Imaging Assessment of Myocardial Injury in Patients Who Recently Recovered From COVID-19

Kate Hanneman, MD, MPH; Christian Houbois, MD; Alice Schoffel, MPH; Dakota Gustafson, BSc; Robert M. Iwanochko, MD; Bernd J. Wintersperger, MD; Rosanna Chan, BSc; Jason E. Fish, PhD; Kathryn L. Howe, MD, PhD; Paaladinesh Thavendiranathan, MD, SM

IMPORTANCE Although myocardial injury can occur with acute COVID-19, there is limited understanding of changes with myocardial metabolism in recovered patients.

OBJECTIVE To examine myocardial metabolic changes early after recovery from COVID-19 using fluorodeoxyglucose–positron emission tomography (PET) and associate these changes to abnormalities in cardiac magnetic resonance imaging (MRI)–based function and tissue characterization measures and inflammatory blood markers.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study took place at a single-center tertiary referral hospital system. A volunteer sample of adult patients within 3 months of a diagnosis of COVID-19 who responded to a mail invitation were recruited for cardiac PET/MRI and blood biomarker evaluation between November 2020 and June 2021.

EXPOSURES Myocardial inflammation as determined by focal fluorodeoxyglucose (FDG) uptake on PET.

MAIN OUTCOMES AND MEASURES Demographic characteristics, cardiac and inflammatory blood markers, and fasting combined cardiac ^{18}F-FDG PET/MRI imaging were obtained. All patients with focal FDG uptake at baseline returned for repeated PET/MRI and blood marker assessment 2 months later.

RESULTS Of 47 included patients, 24 (51%) were female, and the mean (SD) age was 43 (13) years. The mean (SD) interval between COVID-19 diagnosis and PET/MRI was 67 (16) days. Most patients recovered at home during the acute infection (40 [85%]). Eight patients (17%) had focal FDG uptake on PET consistent with myocardial inflammation. Compared with those without FDG uptake, patients with focal FDG uptake had higher regional T2, T1, and extracellular volume (colocalizing with focal FDG uptake), higher prevalence of late gadolinium enhancement (6 of 8 [75%] vs 9 of 39 [23%], $P = .009$), lower left ventricular ejection fraction (mean [SD], 55% [4%] vs 62% [5%], $P < .001$), worse global longitudinal and circumferential strain (mean [SD], −16% [2%] vs −17% [2%], $P = .02$ and −18% [2%] vs −20% [2%], $P = .047$, respectively), and higher systemic inflammatory blood markers including interleukin 6, interleukin 8, and high-sensitivity C-reactive protein. Among patients with focal FDG uptake, PET/MRI, and inflammatory blood markers resolved or improved at follow-up performed a mean (SD) of 52 (17) days after baseline PET/MRI.

CONCLUSIONS AND RELEVANCE In this study of patients recently recovered from COVID-19, myocardial inflammation was identified on PET in a small proportion of patients, was associated with cardiac MRI abnormalities and elevated inflammatory blood markers at baseline, and improved at follow-up.

JAMA Cardiol. 2022;7(3):298-308. doi:10.1001/jamacardio.2021.5505
Published online January 12, 2022.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Authors: Kate Hanneman, MD, MPH, 1 PMB-298 (kate.hanneman@uhn.ca), and Paaladinesh Thavendiranathan, MD, SM, 4N-490 (dinesh.thavendiranathan@uhn.ca), University of Toronto, Toronto General Hospital, University Health Network, 585 University Ave, Toronto, ON M5G 2N2, Canada.

As of October 2021, COVID-19 caused by SARS-CoV-2 has affected more than 247 million individuals globally with more than 5 million deaths.[1] Among hospitalized patients, early studies suggested that approximately 1 in 4 experience cardiovascular injury, defined by elevation in troponin levels, which was associated with a 5- to 10-fold increase in the risk of death.[2,3] However, because most individuals (>95%) survive the acute illness and do not require hospitalization, there is concern for undetected cardiovascular injury.

Several cardiac magnetic resonance imaging (MRI) studies have examined myocardial disease in patients who had recovered from COVID-19[4-7] and have reported a broad range in prevalence of abnormal myocardial tissue characteristics (7%-73%).[5,6,8] However, there is limited understanding of persistent changes in myocardial metabolism in recovered patients, which is a potential concern given that COVID-19 is associated with systemic inflammation during the acute illness. Combined cardiac ^{18}fluorodeoxyglucose (FDG) positron emission tomography (PET)/MRI can reliably characterize myocardial inflammation and its relationship to myocardial abnormalities on MRI. Furthermore, it may help determine whether persistent cardiac symptoms are related to residual myocardial inflammation; inform the need for cardiac screening and longer-term follow-up; and prognosticate longer-term cardiovascular disease risk.

The purpose of this study was to (1) examine myocardial inflammation using cardiac FDG-PET, (2) compare the presence and absence of inflammation to cardiac MRI-based function and tissue characterization parameters, and (3) assess the association between myocardial inflammation, cardiac symptoms, and blood biomarkers in patients recently recovered from COVID-19.

Key Points

Question Is myocardial inflammation present in patients recently recovered from COVID-19 and is this associated with tissue characterization abnormalities and blood biomarkers?

Findings In this cohort study of 47 participants recently recovered from COVID-19, myocardial inflammation was identified in a small proportion based on focal fluorodeoxyglucose uptake on cardiac positron emission tomography/magnetic resonance imaging. Fluorodeoxyglucose uptake was associated with cardiac magnetic resonance imaging T1, T2, and extracellular volume abnormalities, and systemic inflammatory blood markers at baseline and all findings improved at follow-up.

Meaning Myocardial inflammation is present in a minority of patients after COVID-19 illness, is associated with systemic inflammation, and may improve over short-term follow-up.

Methods

Study Design and Participants

This prospective cohort study was approved by the institutional research ethics board of the University Health Network, Toronto, Canada. Written informed consent was obtained from all participants. Between November 2020 and June 2021, adult patients (≥18 years of age) who had a positive SARS-CoV-2 test (reverse transcriptase–polymerase chain reaction assays of oro/nasopharyngeal throat swabs) at our center were invited for cardiac PET/MRI and blood biomarker evaluation within 3 months after the positive test through mail invitation. Interested patients who voluntarily contacted our study team were recruited. Exclusion criteria were contraindication to PET/MRI, including impaired kidney function and claustrophobia. Clinical data were obtained from patient history at the time of PET/MRI and the electronic patient record. Clinical disease severity during the acute illness with COVID-19 was classified according to the World Health Organization.[9] Data on race and ethnicity were collected by self-report. All patients with focal FDG uptake on the initial study had a follow-up PET/MRI and blood collected 2 months later.

PET/MRI Acquisition

Participants were provided with detailed preparation instructions to suppress physiologic myocardial glucose uptake, including a high-fat, high-protein, very low-carbohydrate diet starting 24 hours before PET/MRI and a complete fast other than water for 12 hours prior to PET/MRI.[10,11] PET/MRI was performed 60 to 90 minutes after intravenous administration of ^{18}F-FDG, dosed based on body weight, using a 3-T scanner (Biograph mMR; Siemens Healthineers). The MRI protocol included 2-, 3-, 4-chamber and a stack of short-axis cine balanced steady-state free precession slices (eTable 1 in the Supplement). T2 and T1 mapping were acquired at matching basal, mid, and apical short-axis locations. T2 mapping used a T2-prep fast low-angle shot technique, and T1 mapping used a modified look-locker inversion recovery technique before and 15 minutes after injection of 0.15 mmol/kg of body weight Gadobutrol (Bayer Healthcare). Late gadolinium-enhanced (LGE) images were acquired starting 12 minutes after contrast administration. Listmode PET acquisition occurred simultaneously with the MRI examination in 1 bed position centered over the heart, with electrocardiogram gating and 3-dimensional image reconstruction using ordered subset expectation maximization (3 iterations and 21 subsets). A 2-point Dixon scan was acquired for attenuation correction, and a 4-compartment model attenuation map was calculated including air, fat, water, and tissue.

PET/MRI Analysis

PET/MRI studies were analyzed independently by 3 experienced fellowship trained cardiac imagers (C.H., K.H., and R.M.I.) blinded to clinical symptoms, biomarker information, and the time point of imaging. PET and MRI images were fused by translating and rotating PET images onto the MRI coordinate system. FDG uptake, T1, T2, extracellular volume (ECV), and LGE were evaluated globally and using the American Heart Association 17-segment model.[12] Myocardial FDG uptake was categorized as none, diffuse, focal, or focal on diffuse. Focal or focal-on-diffuse patterns were considered positive and none or diffuse FDG uptake patterns were considered negative.[13] FDG uptake was quantified

using cardiac metabolic volume (CMV) as the volume of myocardium with a standardized uptake value intensity above a threshold ratio of 1.2 of left ventricular blood pool to maximum cardiac standardized uptake value (OsiriX MD version 12.0.1). As a sensitivity analysis, CMV was also calculated using a threshold ratio of 1.5.[14] The predominant pattern of LGE was classified as subendocardial, midwall, subepicardial, or transmural. LGE was quantified using a signal-intensity threshold of 4 SD above normal myocardium. Global T1 and T2 relaxation times were assessed by contouring endocardial and epicardial borders on all short-axis images applying a 15% offset adjustment. Regional T1 and T2 values were measured in the region of visually maximum FDG uptake in participants with focal FDG uptake or at the interventricular septum of the midventricular short-axis slice in participants without focal FDG uptake. In participants who were PET positive, remote T1 and T2 were measured at the interventricular septum on the midventricular slice in an area without FDG uptake. ECV was calculated using pre- and postcontrast myocardial and blood pool T1 values and hematocrit.[15] Regional T1, T2, and ECV were categorized as normal/abnormal based on established sequence-specific cut points of 2 SD above the respective means in local healthy controls (T2 >45 milliseconds; T1 >1286 milliseconds; and ECV >30%). Ventricular volumes, function, and mass were assessed per established standards.[16] For feature tracking strain analysis, global circumferential strain was calculated using the short-axis cine balanced steady-state free precession stack and global longitudinal strain as the mean of 2-, 3- and 4-chamber cines.[17] All MRI analysis was performed using Circle cmr42 (Circle Cardiovascular Imaging).

Blood Biomarkers

Peripheral blood samples were collected on the day of PET/MRI and were drawn from the cubital vein into BD Vacutainer Blood Collection Tubes (BD BioscienceNJ) containing K_2EDTA and processed within 3 hours. Circulating levels of interleukin 6 (IL-6), IL-8, high-sensitivity C-reactive protein, myeloperoxidase, high-sensitivity troponin I (hsTnI), and B-type natriuretic peptide were quantified (eMethods and eTable 2 in the Supplement).

Statistical Analysis

Statistical analysis was performed using Stata version 14.1 (StataCorp). Data were visualized with GraphPad Prism version 9.0.2 (GraphPad Software). A 2-tailed *P* value of less than .05 was considered statistically significant. All continuous data were tested for normal distribution using the Shapiro-Wilk test. Comparisons between groups were made by independent-samples *t* test for continuous variables with normal distribution, Wilcoxon rank sum test for continuous variables with non-normal distribution, and Fisher exact test for categorical variables. Paired *t* test or Wilcoxon signed rank test were used for paired comparisons of continuous variables. κ Statistic was used for assessment of interobserver agreement.

Results

Participant Characteristics

Mail invitations were sent to 1263 patients recently recovered from COVID-19 (eResults in the Supplement). A voluntary cohort of 47 participants was included, of whom 24 (51%) were female, and the mean (SD) age was 43 (13) years. There was no difference in age and sex of invited vs included patients (eTable 3 in the Supplement). Baseline characteristics of included participants are provided in **Table 1**. Most participants (40 [85%]) recovered at home during the acute infection, with 4 (9%) admitted to the ward and 3 (6%) admitted to the intensive care unit. All admitted participants received corticosteroids, 1 admitted to the intensive care unit received an IL-6 antagonist, and 2 received antiviral therapy. Among the admitted participants, hsTnI was elevated in 1 during admission (6877 pg/mL). None of the participants who recovered at home had hsTnI measurements, received immunosuppressive therapy, or had a second intercurrent illness prior to PET/MRI. At the time of PET/MRI, 19 participants (40%) reported at least 1 cardiac symptom, including palpitations in 11 (23%), chest pain in 9 (19%), and shortness of breath in 10 (21%). Prior to PET/MRI, 13 participants had received at least 1 dose of a COVID-19 vaccine (10 had the first dose only and 3 had 2 doses; Pfizer/BioNTech in 8, Moderna in 2, and AstraZeneca in 3). None had new onset of symptoms after vaccination.

PET/MRI Findings

Cardiac imaging findings are summarized in **Table 2**. PET/MRI was performed a mean (SD) of 67 (16) days after the diagnosis of COVID-19 and a mean (SD) of 76 (6) minutes after intravenous administration of 390 (70) MBq of ^{18}F-FDG. FDG uptake on PET was positive in 8 participants (17%), with a focal uptake pattern in all. Examples of FDG-positive and FDG-negative participants are shown in **Figure 1**, while other FDG-positive examples and an example of diffuse FDG uptake are shown in eFigure 1 in the Supplement.

The most common myocardial segments involved were the midinferolateral wall in 7 of 8, basal inferolateral wall in 6 of 8, basal anteroseptum in 4 of 8, midinferoseptum in 2 of 8, and midinferior wall in 2 of 8. Six participants (13%) had diffuse FDG uptake due to inadequate diet preparation. Interobserver agreement was high for presence of FDG uptake (κ = 0.95) and the number of FDG-positive myocardial segments (κ = 0.93). There was no significant difference in the proportion of patients who had received at least 1 COVID-19 vaccine dose prior to PET/MRI between those who were PET positive and negative (2 of 8 [25%] were PET positive vs 11 of 39 [28%] were PET negative; *P* > .99).

Participants with focal FDG uptake had higher prevalence of hypertension compared with those without (4 of 8 [50%] vs 5 of 39 [13%]; *P* = .03). Cardiac symptoms were more common among participants with focal FDG uptake vs those without (5 of 8 [63%] vs 14 of 39 [36%]), although this was not statistically significant (*P* = .24).

On cardiac MRI, participants with focal FDG uptake had significantly higher prevalence of LGE, higher regional T2, T1,

Table 1. Baseline Clinical Parameters

Characteristic	No. (%)			
	All patients (N = 47)	PET negative (n = 39)	PET positive (n = 8)	*P* value[a]
Age, mean (SD), y	43 (13)	42 (13)	51 (10)	.09
Women	24 (51)	20 (51)	4 (50)	.99
Men	23 (49)	19 (49)	4 (50)	.99
Weight, mean (SD), kg	79 (19)	77 (19)	88 (14)	.16
Height, mean (SD), cm	170 (11)	169 (11)	178 (9)	.047
Body surface area, mean (SD), m^2	1.9 (0.3)	1.9 (0.3)	2.1 (0.2)	.08
Race and ethnicity				
Black or African American	4 (9)	3 (8)	1 (13)	.54
Central/West Asian	3 (6)	3 (8)	0	.99
East/Southeast Asian	5 (11)	5 (13)	0	.57
Hispanic or Latino	3 (6)	3 (8)	0	.99
South Asian	4 (9)	4 (11)	0	.99
White or European American	28 (60)	21 (54)	7 (88)	.12
Comorbidities				
Diabetes	3 (6)	3 (8)	0	.99
Hypertension	9 (19)	5 (13)	4 (50)	.03
Dyslipidemia	8 (17)	5 (13)	3 (38)	.12
Coronary artery disease	0	0	0	.99
Myocardial infarction	0	0	0	.99
Heart failure	0	0	0	.99
Valvular heart disease	1 (2)	0	1 (13)	.17
Arrythmia	0	0	0	.99
Prior cardiac procedure or surgery	0	0	0	.99
Peripheral vascular disease	0	0	0	.99
History of venous thromboembolism	1 (2)	1 (3)	0	.99
Obesity	8 (17)	6 (15)	2 (25)	.61
Family history of cardiac disease	23 (49)	17 (44)	6 (75)	.14
COPD	1 (2)	1 (3)	0	.99
History of malignant neoplasm	2 (4)	1 (3)	1 (13)	.32
Smoking history				
Never	29 (62)	26 (67)	3 (38)	.23
Previously	10 (21)	7 (18)	3 (38)	.34
Current	5 (11)	3 (8)	2 (25)	.20
Alcohol intake				
None	17 (36)	15 (38)	2 (25)	.69
Casual	27 (57)	22 (56)	5 (63)	.99
Chronic	3 (6)	2 (5)	1 (13)	.44
Cardiac medications				
None	36 (77)	31 (79)	5 (63)	.37
β-Blocker	1 (2)	1 (3)	0	.99
ACE inhibitor	2 (4)	2 (5)	0	.99
ARB	3 (6)	1 (3)	2 (25)	.07
Statin	6 (13)	4 (10)	2 (25)	.27
Calcium channel blocker	1 (2)	1 (3)	0	.99
Anticoagulant	3 (6)	2 (5)	1 (13)	.44
Interval between COVID-19 diagnosis and PET/MRI, mean (SD), d	67 (16)	68 (17)	64 (14)	.64
Hospital admission				
Recovered at home	40 (85)	34 (87)	6 (75)	.59
Admitted to ward	4 (9)	2 (5)	2 (25)	.13
Admitted to ICU	3 (6)	3 (8)	0	.99

(continued)

Table 1. Baseline Clinical Parameters (continued)

Characteristic	No. (%) All patients (N = 47)	PET negative (n = 39)	PET positive (n = 8)	*P* value[a]
Symptoms				
Palpitations	11 (23)	8 (21)	3 (38)	.37
Chest pain	9 (19)	7 (18)	2 (25)	.64
Shortness of breath	10 (21)	7 (18)	3 (38)	.34
Any symptom	19 (40)	14 (36)	5 (63)	.24
NYHA functional classification				
1	36 (77)	29 (74)	7 (88)	.66
2	8 (17)	8 (21)	0	.32
3	3 (6)	2 (5)	1 (13)	.44
CCS angina score				
0	43 (91)	36 (92)	7 (88)	.54
1	2 (4)	2 (5)	0	.99
2	2 (5)	1 (3)	1 (14)	.32

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; MRI, magnetic resonance imaging; NYHA, New York Heart Association; PET, positron emission tomography.

[a] *P* values are for the comparison between patients with focal fluorodeoxyglucose uptake (PET positive) and those without (PET negative).

and ECV, lower left ventricular ejection fraction (LVEF), and worse global longitudinal strain and global circumferential strain compared with participants without focal FDG uptake (**Figure 2** and Table 2). None of the participants had subendocardial LGE or pericardial enhancement. Focal FDG uptake colocalized with LGE in 4 of 8 participants, high T2 in 3 of 8, high T1 in 3 of 8, and high ECV in 2 of 8 (eTable 4 in the Supplement). Two participants with focal FDG uptake had no abnormal MRI findings. Among participants who were PET-positive, regional T2, T1, and ECV values in areas of FDG uptake were significantly higher compared with remote myocardial values (mean [SD], 44 [2] milliseconds vs 41 [2] milliseconds, $P < .001$; 1271 [22] milliseconds vs 1245 [15] milliseconds, $P = .02$; and 28% [3%] vs 25% [2%], $P < .001$, respectively). Notably, the 6 participants with diffuse FDG uptake due to inadequate diet preparation all had normal T2, T1, and ECV values, normal LVEF, and no LGE and T2, T1, and ECV values and LVEF in these patients were not different from patients without FDG uptake (eTable 5 in the Supplement). Three participants met updated Lake Louise Criteria for myocarditis, and all had focal FDG uptake, LGE, high regional T2, and high regional T1.[15]

Blood Biomarkers

Blood biomarker findings are summarized in Table 2. On the day of PET/MRI, hsTnI was detectable in 5 participants (ie, >2 pg/mL) but was not significantly elevated in any (ie, >26 pg/mL). Markers of systemic inflammation, including high-sensitivity C-reactive protein, IL-6, and IL-8, were higher in participants with focal FDG uptake compared with those without (Figure 2). In patients with diffuse FDG uptake, these markers were not different from patients without FDG uptake (eTable 5 in the Supplement).

Sensitivity Analysis

Conclusions of our primary analyses were unchanged with analysis of CMV using a threshold ratio of 1.5 (eTable 4 in the Supplement) or on removing the 6 participants with diffuse FDG uptake or the 7 participants who required hospital admissions (eTables 6 and 7 in the Supplement).

Follow-up

Follow-up PET/MRI and blood biomarker analysis was performed in all participants with focal FDG uptake on baseline PET/MRI at a mean (SD) of 52 (17) days after the initial study. None of the participants received any intercurrent cardiac or immunosuppressive therapy. One participant had a nondiagnostic follow-up PET study due to inadequate diet preparation, 2 had partial resolution of FDG uptake with decrease in CMV (participant 1: 167 cm^3 to 62 cm^3; participant 2: 51 cm^3 to 45 cm^3), and 5 had complete resolution (eFigure 2 in the Supplement). All had interval improvement in LVEF (mean [SD], 55% [4%] vs 60% [4%], $P = .02$), regional T2 (44 [2] milliseconds vs 40 [2] milliseconds, $P = .001$), regional T1 (1271 [22] milliseconds vs 1240 [12] milliseconds, $P = .012$), ECV (28% [2%] vs 25% [2%], $P = .02$), and inflammatory blood markers IL-6 (6.0 [3.1] vs 1.9 [0.8] pg/mL, $P = .012$), IL-8 (5.7 [2.4] vs 2.6 [1.4] pg/mL, $P = .001$), high-sensitivity C-reactive protein (5.7 [3.5] pg/mL vs 1.0 [0.7] pg/mL, $P = .011$), and myeloperoxidase (242 [90] ng/mL vs 196 [77] ng/mL, $P = .008$) (**Figure 3**).

Discussion

Although myocardial injury can occur with acute COVID-19 illness, there is limited understanding of changes to myocardial metabolism in recovered patients. This is a prospective report on a cohort of participants recently recovered from COVID-19 who voluntarily underwent evaluation for myocardial inflammation with combined cardiac PET/MRI and blood biomarkers. Myocardial inflammation based on focal FDG uptake was identified in a small proportion of participants imaged approximately 2 months after COVID-19 diagnosis. Focal FDG uptake on PET was associated with higher cardiac MRI regional native T1, T2, and ECV values, worse measures of myocardial systolic function, and elevated inflammatory

Table 2. PET/MRI and Blood Biomarker Findings

Variable	No. (%)			*P* value[a]
	All patients (N = 47)	PET negative (n = 39)	PET positive (n = 8)	
FDG-PET, median (range)				
Focal pattern FDG uptake, No. (%)	8 (17)	0	8 (100)	NA
Focal FDG extent, No. of segments	NA	NA	5 (1-7)	NA
SUVmax, g/mL	NA	NA	3 (2.4-7.5)	NA
CMV (1.2), cm^3	NA	NA	44 (7-167)	NA
CMV (1.5), cm^3	NA	NA	6 (0.1-120)	NA
Cardiac MRI				
LV, mean (SD)				
LVEDVi, mL/m^2	69 (15)	69 (15)	72 (13)	.52
LVESVi, mL/m^2	27 (8)	26 (2)	32 (2)	.04
LVSVi, mL/m^2	42 (2)	42 (2)	40 (8)	.56
LVEF, %	61 (2)	62 (2)	55 (4)	<.001
Abnormal low LVEF	6 (13)	2 (5)	4 (50)	.005
LVMi, g/m^2	53 (8)	52 (8)	57 (7)	.17
GLS, %	−17 (2)	−17 (2)	−16 (2)	.02
GCS, %	−19 (2)	−20 (2)	−18 (2)	.047
RV, mean (SD)				
RVEDVi, mL/m^2	75 (14)	74 (15)	79 (8)	.43
RVESVi, mL/m^2	34 (8)	33 (2)	34 (2)	.75
RVSVi, mL/m^2	41 (8)	41 (9)	44 (4)	.30
RVEF, %	55 (6)	55 (6)	56 (2)	.63
Atrial area, mean (SD), cm^2				
Left	20 (4)	20 (4)	22 (4)	.17
Right	17 (4)	17 (4)	19 (3)	.13
Tissue characterization				
LGE				
Presence	15 (32)	9 (23)	6 (75)	.009
Subendocardial	0 (0)	0 (0)	0 (0)	.99
Midwall	13 (28)	8 (21)	5 (63)	.03
Subepicardial	2 (4)	1 (3)	1 (13)	.32
Transmural	0 (0)	0 (0)	0 (0)	.99
LGE extent				
Median (range), %	2 (0 to 9)	2 (0 to 9)	2 (0 to 7)	.93
Median (range), g	1 (0 to 4)	1 (0 to 4)	1 (1 to 4)	.24
Pericardial enhancement	0 (0)	0 (0)	0 (0)	.99
Native T2, mean (SD), ms				
Global	40 (2)	40 (2)	41 (2)	.054
Regional	40 (3)	40 (3)	44 (2)	<.001
Abnormal high T2				
Regional	3 (6)	0 (0)	3 (38)	.003
Global	0 (0)	0 (0)	0 (0)	.99
Native T1, mean (SD), ms				
Global	1222 (24)	1218 (23)	1238 (26)	.04
Regional	1243 (28)	1238 (26)	1271 (22)	.001
Abnormal high native T1				
Regional	3 (6)	0 (0)	3 (38)	.003
Global	0 (0)	0 (0)	0 (0)	.99
ECV, mean (SD), %[b]				
Global	25 (3)	24 (3)	26 (3)	.16
Regional	25 (3)	24 (3)	28 (3)	.004
Abnormal high ECV[b]				
Regional	4 (9)	2 (6)	2 (25)	.13
Global	3 (7)	2 (5)	1 (13)	.44
Any abnormality on MRI[c]	17 (36)	11 (28)	6 (75)	.02
Any abnormality on PET/MRI[c]	19 (40)	11 (28)	8 (100)	<.001

(continued)

Table 2. PET/MRI and Blood Biomarker Findings (continued)

Variable	No. (%) All patients (N = 47)	PET negative (n = 39)	PET positive (n = 8)	*P* value[a]
Blood biomarkers				
High-sensitivity troponin I, median (IQR), pg/mL	2 (2-2)	2 (2-2)	2 (2-3)	.14
B-type naturietic peptide, median (IQR), pg/mL	7.7 (5.4-13.2)	6.5 (5.4-13.4)	8.1 (5.4-8.4)	.92
IL-6, mean (SD), pg/mL	2.7 (2.2)	2.0 (1.0)	6.0 (3.1)	<.001
IL-8, mean (SD), pg/mL	3.6 (1.5)	3.2 (0.8)	5.7 (2.4)	<.001
High-sensitivity CRP, mean (SD), pg/mL	3.2 (2.8)	2.7 (2.4)	5.7 (3.5)	.005
MPO, mean (SD), ng/mL	195 (77)	185 (71)	242 (77)	.056

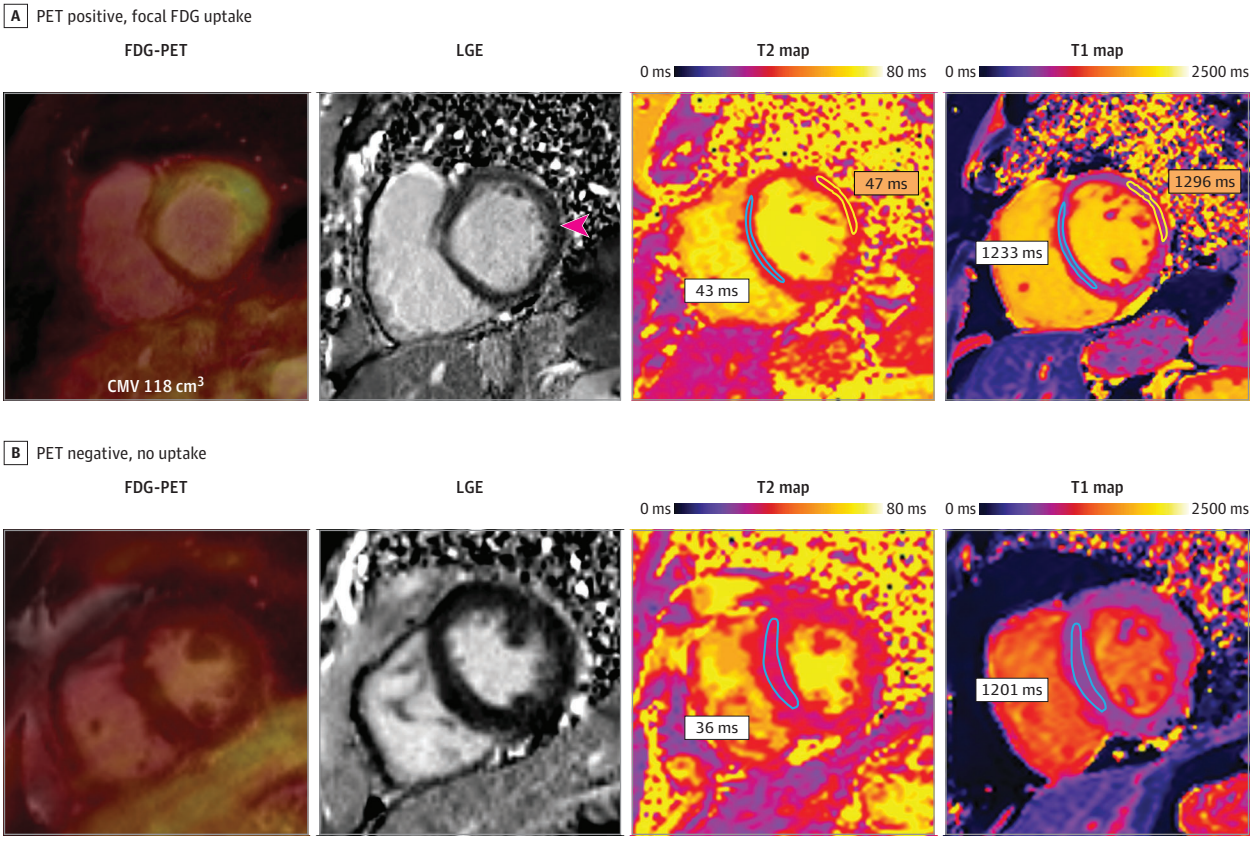
Abbreviations: CMV, cardiac metabolic volume; CRP, C-reactive protein; ECV, extracellular volume; FDG, fluorodeoxyglucose; GCS, global circumferential strain; GLS, global longitudinal strain; IL, interleukin; LGE, late gadolinium enhancement; LV, left ventricle; LVEDVi, indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESVi, indexed left ventricular end-systolic volume; LVMi, indexed left ventricular mass; LVSVi, indexed left ventricular stroke volume; MPO, myeloperoxidase; MRI, magnetic resonance imaging; NA, not applicable; PET, position emission tomography; RV, right ventricle; RVEDVi, indexed right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESVi, indexed right ventricular end-systolic volume; RVSVi, indexed right ventricular stroke volume; SUVmax, maximum standardized uptake value.

[a] *P* values are for the comparison between patients with focal FDG uptake (PET positive) and those without (PET negative).

[b] One patient did not complete blood work on the day of PET/MRI and therefore no contemporary hematocrit is available to calculate ECV.

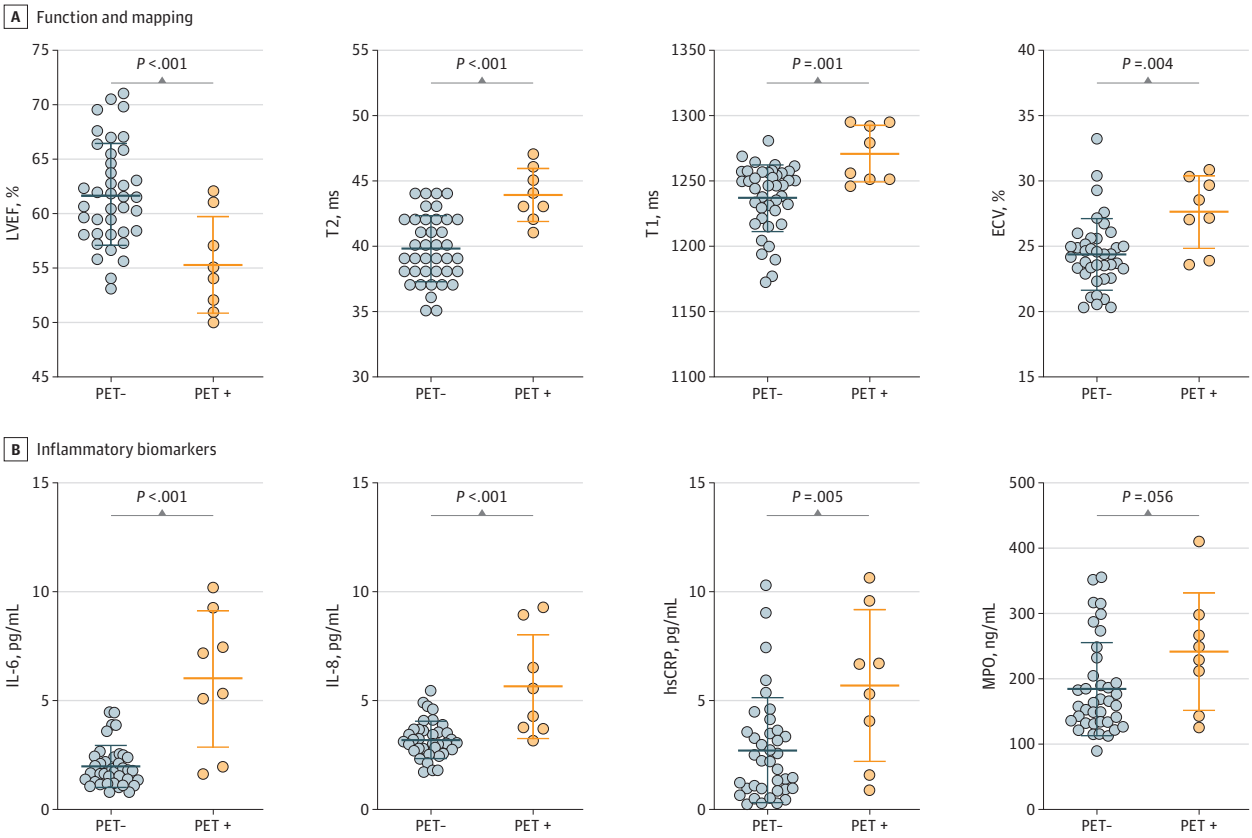
[c] Any abnormality on MRI defined as low LVEF, LGE presence, high regional T2, high regional T1, and/or high ECV. Any abnormality on PET/MRI defined as focal FDG uptake, low LVEF, LGE presence, high regional T2, high regional T1, and/or high ECV.

Figure 1. Cardiac PET/Magnetic Resonance Imaging Finding in Patients Recently Recovered From COVID-19



A representative patient with focal fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) is shown in panel A (PET positive) and a representative patient without FDG uptake on PET is shown in panel B (PET negative). Magnetic resonance imaging findings are shown in short-axis, including late gadolinium enhancement (LGE; pink arrowhead), T2, and native T1. In the PET-positive patient, T1 and T2 values were higher in the region of focal FDG uptake (yellow contours, values shown in orange boxes) compared with remote myocardium at the interventricular septum on the midventricular slice (blue contours, values shown in white boxes). In the patient who was PET negative, T2 and T1 values at the interventricular septum were normal (blue contours, values shown in white boxes). CMV indicates cardiac metabolic volume.

Figure 2. Comparison of Cardiac Magnetic Resonance Imaging Tissue Characterization and Functional Measures and Blood Biomarkers Between Patients With Focal Fluorodeoxyglucose Uptake (PET+) and Those Without (PET−)



Graphs for magnetic resonance imaging parameters depict individual patient data points with error bars displayed as mean (SD). Graphs for blood biomarkers depict mean values and individual patient data points containing 3 technical replicates with error bars displayed as mean (SD). ECV indicates extracellular volume; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; LVEF, left ventricular ejection fraction; MPO, myeloperoxidase; PET, positron emission tomography.

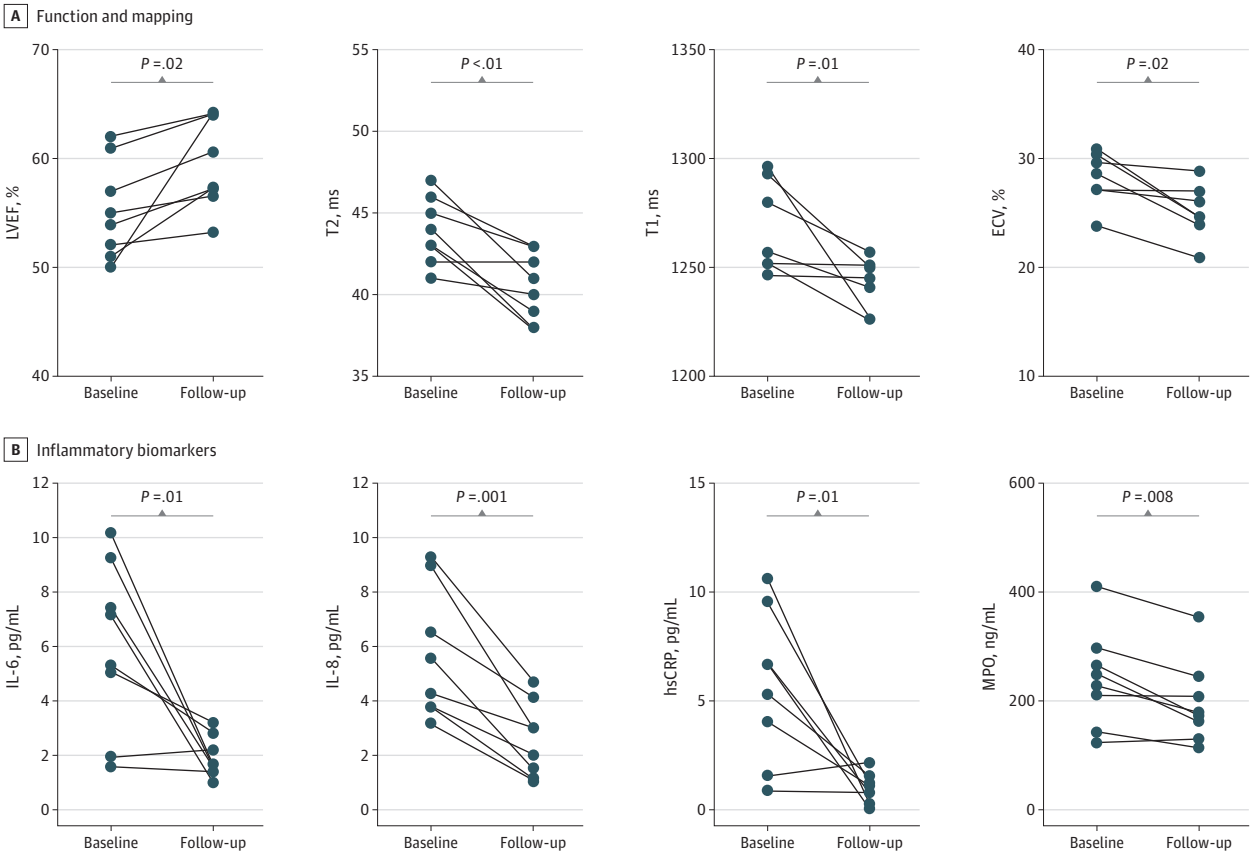
blood markers. In all PET-positive participants, FDG uptake, LVEF, and inflammatory blood markers resolved or improved at follow-up, suggesting that these abnormalities were not related to preexisting cardiovascular disease.

Potential mechanisms for myocardial injury and inflammation in patients recovered from COVID-19 include cell-mediated autoimmune damage triggered by the viral infection, direct injury due to viral infection of the myocardium, and less commonly, ischemic injury.[18] In our cohort, focal FDG uptake was identified in a minority of participants, likely reflecting metabolically active immune cells with increased glucose uptake related to myocardial inflammation. This is consistent with findings of a macrophage-dominated inflammatory pattern on endomyocardial biopsy in patients with COVID-19.[19] FDG-PET may be particularly suited for investigation of COVID-19–related myocardial inflammation given that increased FDG uptake has previously been demonstrated in macrophage-dense regions in cardiac sarcoidosis.[20]

The only cardiac risk factor that was more common in participants with focal FDG uptake was hypertension. This is consistent with prior literature that has shown a greater association between cardiovascular risk factors and myocardial injury in patients with COVID-19.[21,22] Furthermore, although cardiac symptoms were nearly 2 times more common in participants with focal FDG uptake, this difference was not statistically significant. Given the growing number of survivors with similar symptoms, these interesting findings warrant further investigation.

Participants with focal FDG uptake had higher regional T1, T2, and ECV compared with those without. However, 2 participants had focal FDG uptake without any cardiac MRI abnormalities. This suggests that inflammation may be the only manifestation in a small proportion of patients and highlights the incremental value of combined FDG-PET/MRI compared with MRI alone. Isolated FDG uptake on PET without abnormal MRI findings has been described in patients with cardiac sarcoidosis and other causes of myocarditis.[23,24] However, there remains a possibility that FDG uptake at the lateral wall identified in participants in our study without corresponding MRI abnormalities could be nonspecific, due to inadequate myocardial glucose suppression or challenges related to repeatability of qualitative interpretation of FDG uptake. This is particularly relevant in our study given the single-center nature and the absence of an age-, sex-, and comorbidity-matched control group. However, in all participants in our study with focal FDG uptake, T1, T2, and ECV val-

Figure 3. Change Between Baseline and Follow-up in Magnetic Resonance Imaging and Blood Biomarker Parameters



All patients with focal fluorodeoxyglucose (FDG) uptake on baseline evaluation returned for follow-up 2 months later with interval improvement in positron emission tomography/magnetic resonance imaging and blood inflammatory marker parameters. ECV indicates extracellular volume; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; LVEF, left ventricular ejection fraction; MPO, myeloperoxidase.

ues were higher in regions of FDG uptake compared with remote myocardium, including the patients without colocalizing MRI abnormalities. Furthermore, the 2 participants with focal FDG uptake without MRI abnormalities also had elevated inflammatory biomarkers (eTable 4 in the Supplement). Six of the 8 participants had FDG uptake in myocardial segments other than the lateral wall (septum and inferior wall). Furthermore, although discordance in qualitative assessment of FDG uptake has been reported, the repeatability of quantitative FDG measurements is excellent.[25]

Only 3 of 8 participants with evidence of myocardial inflammation on PET had elevated T2 values on MRI (based on local normal reference ranges). T2 is prolonged in the setting of increased tissue water content, while focal FDG uptake reflects metabolically active immune cells. The discordance between PET and T2 findings in 5 participants raises the possibility that myocardial edema resolves earlier after SARS-CoV-2 infection with local immune cell activation persisting longer.[26] This is supported by the fact that T2 values in areas of FDG uptake were still higher than remote segments. The presence of inflammatory cell infiltrates without focal myocyte necrosis may explain the minimal LGE and absence of troponin elevations at the time of PET/MRI.

Short-term follow-up of participants with focal FDG uptake demonstrated improvement in cardiac function and inflammation, T1, T2, and ECV and a decrease in inflammatory blood markers. This suggests that myocardial inflammation after COVID-19 might resolve without treatment. Overall, the study findings suggest an imaging phenotype that is expected to have good prognosis. However, longer-term follow-up studies are required to understand the need for ongoing cardiac surveillance, relationship to cardiac symptoms, guidance for safe return to exercise and sports participation, and long-term cardiovascular disease risk.[27]

There are limited data regarding blood biomarkers in patients who have recovered from COVID-19 and their association to myocardial abnormalities. One prior study described elevations in hsTnI at the time of imaging[6] while others have not.[4,5] In our cohort, no participants had elevated hsTnI at the time of PET/MRI, and values did not differ between PET groups. This suggests that there was no ongoing myocyte necrosis at the time of imaging and that troponin is a poor screening test for ongoing inflammation. However, we did identify elevations in systemic inflammatory biomarkers in participants with focal FDG uptake. This supports the biological plausibility of our findings especially given their concordant improvement

along with FDG uptake at follow-up. It is possible that a more intense systemic inflammatory process may be contributing to cardiac inflammation and the consequential alteration to regional and global myocardial function in PET-positive participants.

Limitations

Our study has limitations including a modest sample size and susceptibility to survivor bias similar to prior studies.[4-7] There is also a potential for selection bias given that participants volunteered for the study based on invitation letters and therefore may not reflect the entire population of patients recovered from COVID-19. Participants with concerns about their health or symptoms may have been more motivated to participate. However, the proportion of participants with cardiac symptoms in our study was similar to prior studies.[6] We compared patients with and without FDG uptake but did not have a control group given concerns with respect to radiation exposure in healthy controls. Although it is possible that some of the focal FDG uptake we observed was due to incomplete suppression of physiologic myocardial uptake, this is unlikely given that physiologic myocardial uptake is typically diffuse or in a basal ringlike pattern, which was not observed in our PET-positive group.[28] Low false-positive rates of FDG uptake have been reported after low-carbohydrate diet preparation and prolonged fasting as in our protocol.[29,30] Most importantly, we show biological plausibility with elevations in inflammatory blood markers and lower myocardial function in those who had focal FDG uptake and recovery of these abnormalities with improvement in FDG uptake. It is possible that some of the cardiac MRI abnormalities detected were preexisting; however, the colocalization with focal FDG uptake and improvement at follow-up indicates that at least some of these abnormalities are associated with myocardial inflammation. Finally, given the single-center nature of our study and a predominantly outpatient cohort, the generalizability of the study findings is unknown. These findings should be confirmed in future multicenter studies, ideally with comparison with age-, sex-, and comorbidity-matched controls.

Conclusions

In conclusion, our study demonstrates that localized myocardial inflammation is present in a small proportion of patients who have recovered from COVID-19, is associated with MRI abnormalities and elevated systemic inflammatory blood biomarkers, and improves at follow-up. Overall, imaging findings are generally consistent with an imaging phenotype with good prognosis; however, it does emphasize the importance of studies examining the longer-term effects of COVID-19 on the heart.

ARTICLE INFORMATION

Accepted for Publication: November 12, 2021.

Published Online: January 12, 2022. doi:10.1001/jamacardio.2021.5505

Author Affiliations: Department of Medical Imaging, Toronto General Hospital, Peter Munk Cardiac Center, University Health Network (UHN), University of Toronto, Toronto, Ontario, Canada (Hanneman, Houbois, Wintersperger, Chan, Thavendiranathan); Department of Diagnostic and Interventional Radiology, University of Cologne, Cologne, Germany (Houbois); Division of Cardiology, Peter Munk Cardiac Centre, Toronto General Hospital, University Health Network (UHN), University of Toronto, Toronto, Ontario, Canada (Schoffel, Iwanochko, Thavendiranathan); Toronto General Hospital Research Institute, University Health Network (UHN), Department of Laboratory Medicine & Pathobiology, University of Toronto, Toronto, Ontario, Canada (Gustafson, Fish); Department of Vascular Surgery, Toronto General Hospital, University Health Network (UHN), University of Toronto, Toronto, Ontario, Canada (Howe).

Author Contributions: Drs Hanneman and Thavendiranathan had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Hanneman, Gustafson, Fish, Howe, Thavendiranathan.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Hanneman, Schoffel, Thavendiranathan.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Hanneman, Schoffel, Gustafson.
Obtained funding: Hanneman, Howe, Thavendiranathan.
Administrative, technical, or material support: Houbois, Schoffel, Gustafson, Iwanochko, Wintersperger, Howe, Thavendiranathan.
Supervision: Hanneman, Fish, Thavendiranathan.

Conflict of Interest Disclosures: Dr Hanneman reported personal fees from Sanofi Genzyme, Amicus, and Medscape outside the submitted work. Dr Wintersperger reported personal fees from Siemens Healthineers, nonfinancial research support from Siemens Healthineers, and personal fees from Bayer AG outside the submitted work; had a patent for IG fitting method for T1 mapping (US10314548B2) issued (owned by the University Health Network); and University Health Network has a master research agreement with Siemens Healthineers. No other disclosures were reported.

Funding/Support: This study was funded by operating grants from the Joint Department of Medical Imaging Academic Incentive Fund, Peter Munk Cardiac Center Innovation Committee, and Ted Rogers Center for Heart Research. Dr Houbois receives research support from the German Research Foundation (#419344766). Dr Thavendiranathan is supported by a Canada Research Chair in Cardiooncology. Mr Gustafson receives support from the Canadian Institutes of Health Research Frederick Banting & Charles Best Canada Graduate Scholarships-Doctoral Award, Ted Rogers Education Fund Award, and an Ontario Graduate Scholarship.

Role of the Funder/Sponsor: The Joint Department of Medical Imaging, Peter Munk Cardiac Centre, and Ted Rogers Centre for Heart Research had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. 2020;20(5):533-534. doi:10.1016/S1473-3099(20)30120-1

2. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(7):811-818. doi:10.1001/jamacardio.2020.1017

3. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5(7):802-810. doi:10.1001/jamacardio.2020.0950

4. Huang L, Zhao P, Tang D, et al. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. *JACC Cardiovasc Imaging*. 2020;13(11):2330-2339. doi:10.1016/j.jcmg.2020.05.004

5. Kotecha T, Knight DS, Razvi Y, et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. *Eur Heart J*. 2021;42(19):1866-1878. doi:10.1093/eurheartj/ehab075

6. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(11):1265-1273. doi:10.1001/jamacardio.2020.3557

7. Li X, Wang H, Zhao R, et al. Elevated extracellular volume fraction and reduced global longitudinal

strains in participants recovered from COVID-19 without clinical cardiac findings. *Radiology*. 2021; 299(2):E230-E240. doi:10.1148/radiol.2021203998

8. Kravchenko D, Isaak A, Zimmer S, et al. Cardiac MRI in patients with prolonged cardiorespiratory symptoms after mild to moderate COVID-19 infection. *Radiology*. 2021;211162(August):211162. doi:10.1148/radiol.2021211162

9. World Health Organization. Living guidance for clinical management of COVID-19. Updated January 25, 2021. Accessed August 15, 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1

10. Williams G, Kolodny GM. Suppression of myocardial 18F-FDG uptake by preparing patients with a high-fat, low-carbohydrate diet. *AJR Am J Roentgenol*. 2008;190(2):W151-6. doi:10.2214/AJR.07.2409

11. Okumura W, Iwasaki T, Toyama T, et al. Usefulness of fasting 18F-FDG PET in identification of cardiac sarcoidosis. *J Nucl Med*. 2004;45(12): 1989-1998.

12. Cerqueira MD, Weissman NJ, Dilsizian V, et al; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105 (4):539-542. doi:10.1161/hc0402.102975

13. Ohira H, Tsujino I, Yoshinaga K. ^{18}F-Fluoro-2-deoxyglucose positron emission tomography in cardiac sarcoidosis. *Eur J Nucl Med Mol Imaging*. 2011;38(9):1773-1783. doi:10.1007/s00259-011-1832-y

14. Ahmadian A, Brogan A, Berman J, et al. Quantitative interpretation of FDG PET/CT with myocardial perfusion imaging increases diagnostic information in the evaluation of cardiac sarcoidosis. *J Nucl Cardiol*. 2014;21(5):925-939. doi:10.1007/s12350-014-9901-9

15. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol*. 2018;72(24): 3158-3176. doi:10.1016/j.jacc.2018.09.072

16. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance–2020 update: Society for Cardiovascular Magnetic Resonance (SCMR): Board of Trustees Task Force on Standardized Post-Processing. *J Cardiovasc Magn Reson*. 2020;22(1):19. doi:10.1186/s12968-020-00610-6

17. Mathur S, Dreisbach JG, Karur GR, et al. Loss of base-to-apex circumferential strain gradient assessed by cardiovascular magnetic resonance in Fabry disease: relationship to T1 mapping, late gadolinium enhancement and hypertrophy. *J Cardiovasc Magn Reson*. 2019;21(1):45. doi:10.1186/s12968-019-0557-0

18. Bearse M, Hung YP, Krauson AJ, et al. Factors associated with myocardial SARS-CoV-2 infection, myocarditis, and cardiac inflammation in patients with COVID-19. *Mod Pathol*. 2021;34(7):1345-1357. doi:10.1038/s41379-021-00790-1

19. Weckbach LT, Curta A, Bieber S, et al. Myocardial inflammation and dysfunction in COVID-19-associated myocardial injury. *Circ Cardiovasc Imaging*. 2021;14(1):e012220. doi:10.1161/CIRCIMAGING.120.011713

20. Li X, Rosenkrans ZT, Wang J, Cai W. PET imaging of macrophages in cardiovascular diseases. *Am J Transl Res*. 2020;12(5):1491-1514.

21. O'Hearn M, Liu J, Cudhea F, Micha R, Mozaffarian D. Coronavirus disease 2019 hospitalizations attributable to cardiometabolic conditions in the United States: a comparative risk assessment analysis. *J Am Heart Assoc*. 2021;10(5): e019259. doi:10.1161/JAHA.120.019259

22. Richardson S, Hirsch JS, Narasimhan M, et al; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020; 323(20):2052-2059. doi:10.1001/jama.2020.6775

23. Coulden RA, Sonnex EP, Abele JT, Crean AM. Utility of FDG PET and cardiac MRI in diagnosis and monitoring of immunosuppressive treatment in cardiac sarcoidosis. *Radiol Cardiothorac Imaging*. 2020;2(4):e190140. doi:10.1148/ryct.2020190140

24. Nensa F, Kloth J, Tezgah E, et al. Feasibility of FDG-PET in myocarditis: comparison to CMR using integrated PET/MRI. *J Nucl Cardiol*. 2018;25(3): 785-794. doi:10.1007/s12350-016-0616-y

25. Alvi RM, Young BD, Shahab Z, et al. Repeatability and optimization of FDG positron emission tomography for evaluation of cardiac sarcoidosis. *JACC Cardiovasc Imaging*. 2019;12 (7 pt 1):1284-1287. doi:10.1016/j.jcmg.2019.01.011

26. Luetkens JA, Homsi R, Dabir D, et al. Comprehensive cardiac magnetic resonance for short-term follow-up in acute myocarditis. *J Am Heart Assoc*. 2016;5(7):e003603. doi:10.1161/JAHA.116.003603

27. Sanchez Tijmes F, Thavendiranathan P, Udell JA, et al. Cardiac MRI assessment of nonischemic myocardial inflammation: state of the art review and update on myocarditis associated with COVID-19 vaccination. *Radiology Cardiothoracic Imaging*. Published online November 18, 2021. doi:10.1148/ryct.210252

28. Morooka M, Moroi M, Uno K, et al. Long fasting is effective in inhibiting physiological myocardial 18F-FDG uptake and for evaluating active lesions of cardiac sarcoidosis. *EJNMMI Res*. 2014;4(1):1. doi:10.1186/2191-219X-4-1

29. Coulden R, Chung P, Sonnex E, Ibrahim Q, Maguire C, Abele J. Suppression of myocardial 18F-FDG uptake with a preparatory "Atkins-style" low-carbohydrate diet. *Eur Radiol*. 2012;22(10): 2221-2228. doi:10.1007/s00330-012-2478-2

30. Demeure F, Hanin F-X, Bol A, et al. A randomized trial on the optimization of 18F-FDG myocardial uptake suppression: implications for vulnerable coronary plaque imaging. *J Nucl Med*. 2014;55(10):1629-1635. doi:10.2967/jnumed.114.138594