Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Coronary Microvascular Health in Patients With Prior COVID-19 Infection

Cardiovascular injury has been observed in SARS-CoV-2 infection.[1] However, whether endothelial inflammation persists chronically and if this would have any clinical implications is unknown. We aimed to study the potential impact of prior COVID-19 infection on the myocardial flow reserve (MFR) and consequent vascular health using positron emission tomography (PET) myocardial perfusion imaging.

The study population was identified from within an institutional prospective registry of patients who had clinically indicated PET imaging from August 20, 2019, to December 1, 2021, and were followed through April 2, 2022. The registry and its analysis were approved by the Houston Methodist Hospital Institutional Review Board.

Cases consisted of patients with previous COVID-19 infection and were matched on clinical (age and sex) and cardiovascular risk factors (hypertension, diabetes, dyslipidemia, known coronary artery disease and heart failure) with control subjects having no documented prior COVID-19 infection. COVID-19 status was prospectively confirmed by patient report and supplemented by a search of medical records.

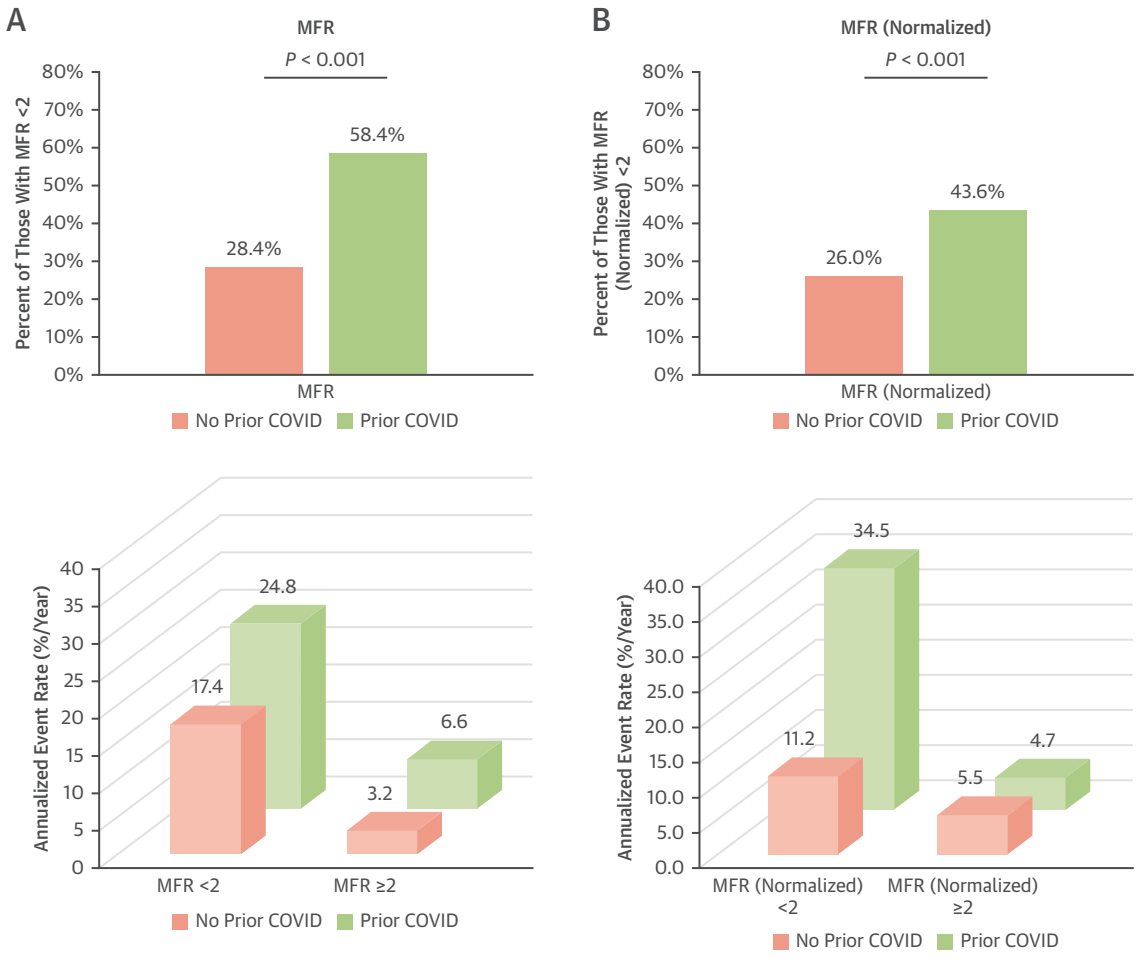
Myocardial perfusion imaging was performed according to societal guidelines.[2] Myocardial blood flow in mL/g/min was obtained from dynamic images at rest and peak hyperemia. The global MFR was calculated as the ratio of left ventricular stress to rest myocardial blood flow. Patients were followed after PET imaging for occurrence of major adverse cardiovascular events, including all-cause death, myocardial infarction, heart failure admission, and unplanned revascularization—percutaneous coronary intervention or coronary artery bypass grafting occurring >90 days after PET imaging.

Annualized event rates (% per year) were determined stratifying by COVID-19 status and MFR. Logistic regression was used to assess the association of MFR <2 between cases and control subjects. Sensitivity analysis was done in subgroups of patients with diabetes, in those with no prior coronary artery disease with a normal perfusion study (sum difference score <3, sum rest score <3) and stratified by time from COVID-19 to PET imaging (#6 months vs >6 months).

The study population consisted of 101 cases with prior COVID-19 infection matched to 292 control subjects (mean age 65 ± 11 years, 51% men). Cardiovascular risk factors were prevalent (hypertension [61%], diabetes [43%], dyslipidemia [49%], obesity [55%]) and comparable in cases vs control subjects ($P > 0.10$).

The median number of days between the COVID-19 diagnosis and PET imaging was 190 (IQR: 84-266) days. The most common indication for imaging was chest pain (66% vs 54%; $P = 0.032$ in cases vs control subjects), followed by dyspnea (41% vs 37%; $P = 0.52$ in cases vs control subjects). The rates of reversible and fixed perfusion defects were comparable in cases versus control subjects.

FIGURE 1 **Comparison of Global MFR and Annualized Event Rates in Cases vs Control Subjects**



(A) Global myocardial flow reserve (MFR) <2 and annualized rates of the composite outcome (including all-cause death, myocardial infarction, heart failure admission, and unplanned revascularization—percutaneous coronary intervention or bypass surgery occurring >90 days after positron emission tomography imaging) were higher in cases versus control subjects. **(B)** Results were similar with global MFR normalized to patients' rate systolic blood pressure product.

A higher proportion of cases had a reduced global MFR (58% vs 28%; $P < 0.001$) and global MFR normalized to patients' rate systolic blood pressure product (44% vs 26%; $P < 0.001$) when compared with control subjects (Figure 1). After adjusting for matching variables, patients with prior COVID-19 had a statistically significant higher odds of having an MFR <2 (OR: 4.0 [95% CI: 2.4-6.6]; $P < 0.001$) and a normalized MFR <2 (OR: 2.4 [95% CI: 1.4-3.9]; $P = 0.001$). Results were similar on sensitivity analysis of patients with no prior coronary artery disease with normal perfusion study (OR: 2.9 [95% CI: 1.6-5.6]; $P = 0.001$), of patients with diabetes, and when stratified by time from COVID-19 to PET imaging. After a median follow-up of 323 (IQR: 199-465) days, 34 patients experienced major adverse cardiovascular events. Annualized event rates were higher in cases versus control subjects and in those with an MFR <2 (Figure 1).

Our analysis suggests that patients with prior COVID-19 infection have higher rates of reduced MFR (likely related to new onset endothelial injury or exacerbation of pre-existing endothelial dysfunction—particularly considering the high prevalence of obesity) and that reduced MFR is a marker of a poor prognosis. Our study is limited by single-center design, use of chart review for follow-up, and high prevalence of cardiovascular risk factors, including obesity. Our findings are particularly relevant to long-haul COVID-19, as persistence of the acute

endotheliopathy and inflammation can hypothetically lead to endothelial dysfunction and potentially explain long-haul COVID-19 cardiopulmonary symptoms. Further studies are needed to investigate our findings.

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TO THE EDITOR

Further Insights Into the Prognostic Value of Left Atrial Strain in Dilated Cardiomyopathy?

We read with great interest the paper by Raafs et al[1] about the incremental prognostic value of left atrial (LA) conduit strain in nonischemic dilated cardiomyopathy (DCM). Atrial function could indeed have a role in the context of multiparametric risk stratification in DCM.

The authors observed that the addition of LA conduit strain significantly improved the predictive ability of a model including only New York Heart Association functional class >II and late gadolinium enhancement (LGE); this is arguably a rather poor model, deprived of any parameter of left ventricular function or LA size, which are currently used for risk-stratification. We believe that, to truly estimate the additional prognostic value of LA conduit strain, the authors should compare the best model with LA conduit strain (New York Heart Association functional class >II, LGE, and LA strain <12%) to the best model without LA strain. To obtain the best model without LA strain, the authors could perform the same statistical procedure (backward stepwise regression) including all variables with significant association with outcome at univariate analysis except LA strain; such a model might include some of the variables with a significant univariate association, such as age, left ventricular ejection fraction, left ventricular strain, or LA volume. By doing this, the authors will be able to evaluate the additional prognostic value of LA strain compared with a standard-of-care risk stratification model.

LA conduit strain was not associated with ventricular arrhythmias. This finding is in line with the absence of a clear and direct pathophysiological link between atrial function and ventricular arrhythmias. However, LA conduit strain was significantly associated with the combined endpoint of "sudden or cardiac death." Could the author specify how many sudden deaths occurred and elaborate on the causes of the remaining cardiac deaths? It would be highly informative if the authors could separately report the association (also multivariate if statistically significant at univariate analysis) between LA conduit strain and the following: 1) a combined arrhythmic endpoint of sudden death and ventricular arrhythmias; and 2) a combined heart failure endpoint of nonsudden cardiac death and heart failure hospitalizations. Considering that the selection of patients for primary prevention implantable cardioverter-defibrillator (ICD) is one of the major unresolved issues in DCM, and because heart failure events (especially non-sudden death) are competing episodes that may limit the benefit of ICD, we believe that it is of utmost importance to separately analyze the arrhythmic and heart failure outcomes. Finding specific predictors for each outcome category may help with improving patient selection for primary prevention ICD.

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