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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LETTERS TO THE EDITOR

Perimyocardial Injury Specific for SARS-CoV-2-Induced Myocarditis in Comparison With Non-COVID-19 Myocarditis

A Multicenter CMR Study

Coronavirus disease-2019 (COVID-19) is among the greatest medical challenges, provoking pulmonary manifestations and cardiovascular consequences. In this study, we compared cardiac injury between patients with myocarditis and COVID-19 and those with myocarditis without COVID-19.

All consecutive patients (March 2020 to April 2021) who recovered from COVID-19 (confirmed on reverse-transcriptase polymerase chain reaction swab test) referred to 1 of 5 cardiovascular magnetic resonance (CMR) centers because of suspected myocarditis and cardiac symptoms were prospectively enrolled in the study group (n = 300). Afterward, a retrospective non-COVID-19 myocarditis (2018-2019) group was enrolled (n = 150). Patients with histories of myocardial infarction or coronary artery disease, significant valve diseases, congenital heart diseases, cardiomyopathy, or previous cardiac surgery were not included. The CMR images were acquired on 1.5-T systems (Optima MR450w [GE Healthcare], Magnetom Aera [Siemens], or Magnetom Avanto [Siemens]) with a dedicated phased-array cardiac coil or body matrix coil. The cardiac CMR studies were electrocardiographically gated, performed during a breath hold, and based on routine clinical protocols according to guidelines. The scanning protocol included: 1) functional sequences using conventional noncontrast multiplanar cine acquisitions (steady-state free precession); 2) edema imaging: T2-weighted triple inversion recovery (short-tau inversion recovery); and 3) viability imaging: late gadolinium enhancement (LGE) 10 to 15 minutes after contrast injection (0.1 mmol/kg body weight of Gadovist [Bayer]). The study was conducted in accordance with the principles of the Declaration of Helsinki and the local ethics committees (Medical Universities of Silesia and Gdansk).

The COVID-19 study group included 300 patients who had COVID-19 a mean of 10.7 ± 4.8 weeks earlier. All studies were performed within 6 months of COVID-19 onset, and the clinical manifestation of infection was mostly moderate (83 patients required hospitalization). The COVID-19 group included slightly older patients (mean age 45.6 ± 12 years vs 42.8 ± 14 years; $P = 0.03$), with no other clinical differences compared with the non-COVID-19 group. Our study confirmed myocarditis-like LGE in 51% of post-COVID-19 patients, with no relation to primary symptoms or hospitalization during COVID-19. We found dilatation (8%) and moderate (5%) or severe (2%) systolic dysfunction of the left ventricle with mainly segmental (not global) wall motion abnormalities (14%). Most left ventricular (LV) segments (74.5%) showed a minor (<25%) transmural extent of LGE (**Figure 1**). Patients with COVID-19 and myocarditis showed a similar number of injured segments (4.2 ± 4.4 vs 4.3 ± 2.9; $P = 0.82$), smaller total LV LGE (7.2% ± 7.1% vs 9.66% ± 8.1%; $P < 0.01$), lower LV end-diastolic volume (149 ± 41 mL vs 166.8 ± 58 mL; $P < 0.01$), limited functional consequence (ejection fraction 59.5% ± 8.7% vs 55.6% ± 12.7%; $P < 0.01$) and a higher rate of pericarditis (15% vs 7%; $P = 0.03$) compared with non-COVID-19 myocarditis. Only wall motion score index (WMSI) showed weak predictive power for LV LGE (area under the curve [AUC]: 0.589; $P < 0.001$).

In this prospective multicenter study, we evaluated a large group of post-COVID-19 patients and showed prevalent myocardial injury, mostly with preserved LV systolic function. Clinical characteristics were not associated with the presence or severity of LGE or LV dysfunction. COVID-19-induced myocarditis showed a similar number of diseased LV segments but less severe LGE injury, lower rates of LV dysfunction, and more frequent pericarditis compared with the non-COVID-19 group.

A thorough search of published research confirmed that this is the first study to evaluate the differences between COVID-19 and non-COVID-19 myocarditis among patients sampled for clinical practice.

Our findings are consistent with the results of previous studies regarding positive CMR findings in COVID-19-related myocarditis, with small differences, which depend on the time and the severity of the disease (1-3). Puntmann et al (2) showed a higher rate of positive findings and myocardial inflammation on CMR (60%), irrespective of the clinical presentation or the time of acute COVID-19. However, a lower rate of post-COVID-19 myocardial injury (30%) was reported in 44 post-COVID-19 patients (3).

Hooper et al (4) reported an interesting large multicenter autopsy series of patients with COVID-19. As expected, patients had multiple pathological

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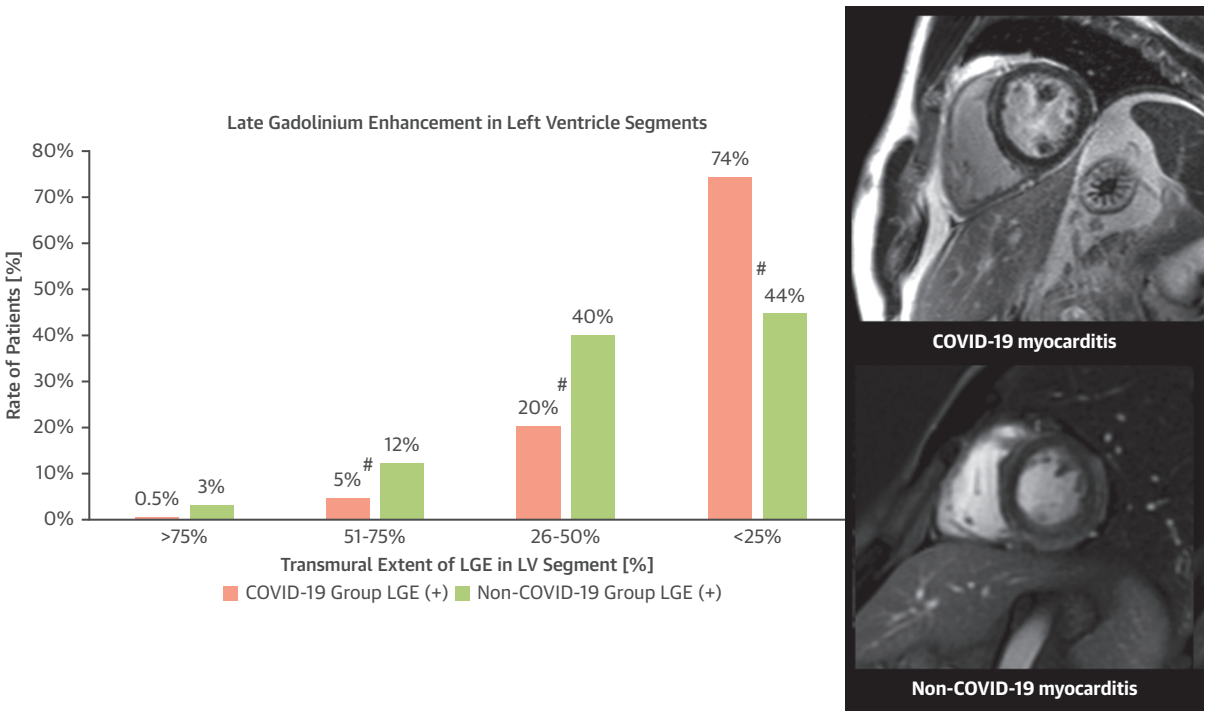
FIGURE 1 LGE in the COVID-19 and Non-COVID-19 Groups



Transmural extent of late gadolinium enhancement (LGE) in left ventricular (LV) segments on cardiovascular magnetic resonance in patients with coronavirus disease-2019 (COVID-19) and non-COVID-19 myocarditis. #$P < 0.05$.

conditions, with acute myocardial dysfunction in 35%. Nevertheless, myocarditis was present in 6% of patients, which was the cause of death in only 4%. Our findings showing a high prevalence of LGE, but mild severity and minor functional consequences, are in line with the autopsy study. We also showed that LV wall motion abnormalities were found in only 16% of the COVID-19 study group. This suggests that echocardiographic screening misses a substantial number of COVID-19-related injuries on the basis of LV dysfunction and wall motion abnormalities, leading to wrong clinical conclusions.

The severity of the COVID-19-induced myocardial injury is smaller, and the rate of systolic dysfunction is lower and not dependent on clinical characteristics compared with non-COVID-19 myocarditis. Given the mean age of study patients, even mild residual myocardial injury plays a role in the progression to cardiomyopathy or heart failure. Regular follow-up of post-COVID-19 patients should verify the impact of residual injury on clinical outcomes.

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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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Noninvasive Identification of Carditis in Acute Rheumatic Fever

Diagnostic difficulties have been reported in one third of suspected cases of acute rheumatic fever (ARF) (1). Myocardial tissue characterization by cardiac magnetic resonance (CMR) through the highly reproducible technique of myocardial T1 mapping can identify interstitial changes, including myocardial edema, necrosis, and fibrosis (2). Therefore by using CMR to assess for prolongation of native T1 time, we sought to characterize carditis, the fundamental pathology in ARF and rheumatic heart disease (RHD), and to establish a noninvasive measure of myocardial involvement to enhance diagnostic certainty of ARF.

Given the high rates of ARF in central Australia, we prospectively recruited patients from Alice Springs Hospital. Aboriginal and Torres Strait Islander peoples make up 40% of this population. In Australia, Aboriginal and Torres Strait Islander peoples experience profound social and health disparities. To investigate RHD, we used patients at a major city tertiary referral hospital (The Alfred Hospital, Melbourne). This study was approved by the Central Australia Human Research Ethics Committee, the Alfred Ethics Committee, and the Baker Heart and Diabetes Institute Research Governance Unit.

Consecutive patients older than 9 years presenting acutely to Alice Springs Hospital with symptoms and signs fulfilling the Australian modified Jones criteria for the diagnosis of ARF (3) were invited to participate. Inpatients at Alice Springs Hospital with other acute inflammatory conditions, but without other features of ARF, were matched for age, sex, and Aboriginal or Torres Strait Islander status and formed one control group. A second group of matched healthy control subjects was recruited with no significant current or past medical history.

To investigate RHD, eligible patients with classic rheumatic morphological features of the mitral valve were recruited with matched control subjects. CMR was performed on all patients using clinical 1.5-T scanners. Native T1 mapping was performed using a modified Look-Locker inversion recovery sequence (Alice Springs) or a single-shot acquisition (Smart T1) sequence (Melbourne).

Forty one patients (16 with ARF, 15 with acute noncardiac inflammatory conditions, and 10 healthy control subjects) were included. Continuous data are reported as median (IQR). The Kruskal-Wallis H test was used to compare patients with ARF with the 2 control groups. The Mann-Whitney U test was used to compare patients with ARF with inflammatory control subjects and patients with ARF with healthy control subjects. The Mann-Whitney U test was used to compare patients with stable RHD with control subjects. Categorical variables are presented as frequency (percentage) and were compared using the chi-square test or Fisher exact test as appropriate. P values < 0.05 were considered to indicate statistical significance.

There were no baseline differences between patients with ARF and either control group with respect to age (patients with ARF vs inflammatory control subjects vs healthy control subjects: 20.5 years [IQR: 12.3-31.0 years] vs 22.0 years [IQR: 15.0-34.0 years] vs 24.5 years [IQR: 14.8-35.5 years]; $P = 0.75$,) female sex (10 [63%] vs 8 [53%] vs 6 [60%]; $P = 0.58$), Aboriginal Australian status (15 [94%] vs 14 [93%] vs 9 [90%]; $P = 0.93$), presence of diabetes (2 [13%] vs 3 [20%] vs 1 [10%]; $P = 0.75$), or body mass index (26.0 kg/m^2 [IQR: 20.0-35.8 kg/m^2] vs 28.0 kg/m^2 [IQR: 25.0-33.0 kg/m^2] vs 31.0 kg/m^2 [IQR: 27.0-37.3 kg/m^2]; $P = 0.52$). There was a statistically significant difference in ejection fraction between the ARF group and healthy control subjects, (57.0% [IQR: 56.0%-60.0%] vs 64.3% [IQR: 59.1%-67.0%]; $P = 0.004$), but both median ejection fractions were within the normal range. Other baseline CMR parameters, specifically left ventricular end-diastolic volume indexed to body surface area, left ventricular mass indexed to body surface area, and left atrial volume index, were not different between the groups.

Patients with ARF had markedly elevated median native myocardial T1 times. The median native myocardial T1 time in patients with ARF was 945 ms (IQR: 864-1,072 ms), compared with 848 ms (IQR: 803-897 ms) in those with noncardiac inflammatory