Radiology

REVIEWS AND COMMENTARY • EDITORIAL

Cardiac Abnormalities Depicted with MRI in COVID-19: Ongoing Concern for Myocardial Injury

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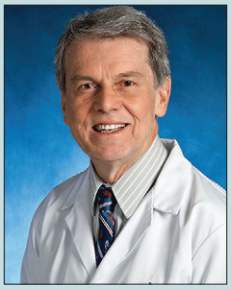

Dr Lima is professor of medicine and radiology at the Johns Hopkins University School of Medicine in the division of cardiology. He is an internationally known pioneer in the development of MRI methods to measure infarct size and the quantification of atherosclerosis by using MRI and CT, and he has developed MRI and CT imaging methods to measure carotid and coronary atherosclerosis. Due to his lifelong contributions to the field with more than 700 publications, Dr Lima received the Gold Medal from the Society of Cardiovascular Magnetic Resonance in 2016.

Dr Bluemke is professor of radiology at the University of Wisconsin School of Medicine and Public Health, as well as Editor of *Radiology*. Over the last 25 years, he has published more than 700 original research articles on the use of CT and MRI focusing on detection and quantification of cardiovascular disease. Dr Bluemke was a principal investigator in the MESA study, as well as for multicenter studies of hypertrophic cardiomyopathy and arrhythmogenic right ventricular dysplasia. Previously, Dr Bluemke was director of radiology and imaging sciences at the NIH Clinical Center in Bethesda, Maryland.

COVID-19 is a systemic disease induced by the SARS-CoV-2 virus affecting the endothelium of different vascular beds throughout the entire human body (1,2). The magnitude of pulmonary parenchymal and vascular involvement in large part defines overall prognosis and the probability of severe outcomes in COVID-19, including death (3). By extension, it also determines the need for hospitalization in the majority of patients admitted for standard and critical care. Yet, the extent of involvement of other organ systems in patients without potentially significant pulmonary disease remains largely unknown. Prior studies suggest that myocardial involvement is associated with unfavorable prognosis in patients with COVID-19 (4,5), but clinically significant myocardial injury is currently believed to occur in a subgroup of patients with symptoms requiring hospitalization (6). However, recent MRI studies suggest the presence of cardiac sequelae not only in hospitalized patients with COVID-19 but also in outpatients (7), including elite athletes (8). Thus, the clinical significance of myocardial alterations identified in convalescing patients with COVID-19 remains incompletely understood (9).

In the May 2021 issue of *Radiology*, Li et al (10) demonstrated myocardial extracellular volume expansion and reduced myocardial strain in a group of convalescing patients with COVID-19 hospitalized with severe or moderate pulmonary disease, compared with age- and sex-matched healthy control participants. In this prospective observational cohort study, the median extracellular volume was 31.4%, 29.7%, and 25.0% ($P < .001$) for comparisons of both patients with severe and moderate COVID-19 versus control participants. The corresponding mean global longitudinal strain values were less negative (representing reduced cardiac function) in both participants with severe and moderate COVID-19 compared with control participants (severe and moderate COVID-19 [both −12.5%] vs healthy control participants [−15.4%]; [$P = .002$ and $P = .001$, respectively]).

Other cardiac MRI parameters showed little difference between groups. The authors did not find evidence of a difference in native T1 values among the three groups, and only one participant with COVID-19 showed replacement fibrosis demonstrated by late gadolinium enhancement. Moreover, despite the myocardial strain alterations, the authors did not find evidence of differences in MRI-derived global indexes of left ventricular (LV) and right ventricular performance among the three groups, such as ejection fraction, end-diastolic and end-systolic volumes, stroke volume, and output. Finally, LV remodeling parameters such as LV mass and calculated LV cell volume were also similar among the three groups. Remarkably, despite severe COVID-19 disease requiring hospitalization for 4–6 months (in the Chinese health system), none of the reported patients had any elevation of cardiac-specific enzymes or clinical evidence of cardiac compromise while in the hospital.

While a dose-response trend was observed for extracellular volume and calculated extracellular matrix volume among the three groups (participants with severe and moderate COVID-19 vs control participants), several comparisons of functional and remodeling indexes suggest greater differences (of borderline statistical significance) between the groups with moderate pulmonary involvement versus control participants than between those in the severe pneumonia group versus control participants. Such inconsistencies likely reflect small sample sizes and the case-control design, which tends to magnify differences and inconsistencies by comparing patients with overt disease against matched control participants without clinically detectable abnormalities. However, they may also reflect heterogeneity of cardiac versus pulmonary involvement in

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Conflicts of interest are listed at the end of this article.

See also the article by Li et al in the May 2021 issue.

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COVID-19 groups conventionally stratified by pulmonary involvement. Heterogeneity in different organ system involvement among individuals with COVID-19 who require hospitalization and those not requiring hospitalization may also account for perceived inconsistencies in the literature (7–9). Cardiac MRI is undoubtedly the most robust phenotyping tool for the purposes of this study. The authors used state-of-the-art methodology, but they did not use techniques that probe the presence of active inflammation such as T2 mapping, which the authors mention as a study limitation. The authors assert that inflammation was unlikely at the time of the MRI examinations, which were performed at least 90 days from hospital discharge.

Clinically manifested acute myocarditis is characterized by myocardial inflammation that can be mapped with topographic T1 mapping and with contrast-enhanced MRI using late gadolinium enhancement. The LV ejection fraction can be severely compromised in patients admitted with acute myocarditis but can also be entirely preserved. Therefore, the absence of clinically detected dysfunction in the acute phase of infection by SARS-CoV-2 does not imply the absence of clinically significant myocardial involvement. Among infected individuals who do not seek medical attention or who are not hospitalized, the incidence of acute myocarditis due to SARS-CoV-2 remains entirely unknown. Chronic myocardial functional deterioration and increased susceptibility are well-established potential sequelae from acute viral myocarditis in general. But chronic dilated cardiomyopathy and clinically significant LV dysfunction have not been reported as specific COVID-19 sequelae, as originally speculated.

Myocardial fibrosis, characterized by extracellular space expansion and excessive collagen accumulation in the extracellular matrix, is commonly a response to repeated or unresolved injury and stress. The extracellular matrix has a crucial role in cardiac physiology as the structural frame supporting all other cell types required for normal cardiac function. However, excessive fibrosis affects not only structural myocardial integrity and chamber mechanical performance but also myocardial electrical properties, potentially leading to heart failure, decreased cardiac output, and arrhythmias. Focal areas of replacement fibrosis, often referred to as myocardial scars, generally occur as a result of myocyte loss caused by acute myocardial infarction, infection, inflammation, genetic disease, or myocardial overload. However, in chronic ischemic and nonischemic conditions, inflammation secondary to recurring injury leads to tissue damage and repair through activation of innate immunity responses with consequent diffuse interstitial fibrosis. The inflammatory process underlying interstitial fibrosis is often associated with cellular apoptosis, perpetuating a cycle of progressive collagen accumulation and extracellular volume enlargement leading to pathologic myocardial remodeling. As a main component of pathologic cardiac remodeling, interstitial fibrosis is commonly caused by inflammation secondary to ischemia, smoking, diabetes, or prolonged myocardial overload. However, innate immune responses are often activated by viral infections that may be latent but also lead to or accelerate fibrogenesis and structural remodeling. Chronic HIV infection, for example, has been associated with myocardial fibrosis and cardiac hypertrophy assessed with cardiac MRI with T1 mapping. Other viral diseases and chronic parasitic infections are also well known for causing progressive replacement and interstitial myocardial fibrosis.

COVID-19–associated interstitial myocardial fibrosis, as documented by Li and colleagues (10), will hopefully represent the resolved consequence of acute SARS-CoV-2, with minimal alterations of myocardial compliance that will remain subclinical and unimportant to life expectancy and quality of life for those exposed to the acute infectious process. Conversely, it could contribute to cardiac remodeling associated with exposure to hypertension and other cardiovascular risk factors promoting unfavorable clinical outcomes, particularly if developed early in the human life span. COVID-19–induced myocardial fibrosis may involve not only the LV but also the right ventricle, and may be aggravated by pulmonary hypertension secondary to concomitant COVID-19–related pulmonary fibrosis.

In summary, the COVID-19 pandemic is already catastrophic and unprecedented. The pathophysiology of acute SARS-CoV-2 disease has rapidly unfolded but remains incompletely understood. Midterm chronic sequelae have been well documented and, in many instances, clinically debilitating. The medical toll of COVID-19 to humans in the 21st century may be compounded by chronic cardiac sequelae, particularly if enhanced myocardial interstitial fibrosis induced by SARS-CoV-2 proves to be an important pathogenetic mechanism of adverse cardiac remodeling leading to heart failure with preserved ejection fraction, atrial fibrillation, and other cardiovascular diseases.

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