Radiology

Myocardial Scar in COVID-19: Innocent Marker versus Harbinger of Clinical Disease

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SARS-CoV-2 infection and its accompanying immune response are characterized by intense inflammation in the acute phase of infection. The cardiopulmonary system is involved either directly and indirectly through a systemic inflammatory response (ie, cytokine release and prothrombotic state) (1). Up to 60% of patients hospitalized due to COVID-19 have been reported to have evidence of myocardial injury (2). Following hospital discharge, investigators estimate that approximately 10% of patients report palpitations and 5% have ongoing chest pain months later (3). Prolonged symptoms due to COVID-19 (frequently referred to as "long-haul COVID") portend the potential for chronic cardiac sequelae, as of yet, unknown duration and severity. These concerns have led to detailed investigation using powerful phenotyping tools such as cardiac MRI.

In this issue of *Radiology*, Kravchenko et al (4) studied 41 participants with chronic symptoms including fatigue and exertional dyspnea 3 months after COVID-19 infection. Patients were compared with 42 volunteer study participants matched by sex and age who had no history of previous exposure to SARS-CoV-2. Importantly, none of the study patients had been hospitalized for COVID-19. Patients had no evidence of acute myocardial inflammation at T2 mapping or interstitial fibrosis at MRI. However, three of 41 patients (7%) had unequivocal late gadolinium enhancement (LGE) at MRI and two of them (5%) had subepicardial LGE compatible with subacute or chronic replacement fibrosis. The third patient had a focal midmyocardial LGE abnormality commonly seen in a patient with right ventricular overload due to pulmonary hypertension, pulmonary disease, or in asymptomatic individuals. As incidental findings at cardiac MRI, the authors also report that one patient (2%) had a pericardial effusion, another patient (2%) presented with signs of right ventricular overload, and four patients (10%) had pulmonary findings including persistent opacities (one patient) and pleural effusions (two patients).

The findings of Kravchenko et al (4) are important for several reasons. First, these results underscore early reports of convalescing patients with COVID-19 who also showed replacement myocardial fibrosis. Second, the patients evaluated by Kravchenko et al were neither hospitalized nor were they individuals who required evaluation before returning to sports activities. Instead, these patients enrolled in the study because of chronic symptoms and physical limitations many weeks after recovery from acute infection. Interestingly, active myocardial inflammation was not present at the 3-month cardiac MRI after COVID-19. Previous studies in previously hospitalized and nonhospitalized patients after COVID-19 with and without persisting symptoms have reported active cardiac inflammation (demonstrated with T2-weighted imaging or T2 mapping). Finally, despite subepicardial myocardial scar, chronic interstitial fibrosis was not found, also in contrast to other studies. The work by Kravchenko et al highlights the dissociation between diffuse interstitial and focal replacement fibrosis as sequelae from SARS-CoV-2–induced myocarditis.

Subepicardial myocardial scars are the hallmark of myocardial damage commonly seen in conditions classified as nonischemic cardiomyopathies. Subepicardial LGE is also common in patients with acute viral myocarditis not caused by SARS-CoV2. The same MRI pattern may persist into the subacute and chronic phases of the disease, representing a harbinger of potential progression to myocardial dysfunction or arrhythmia. In patients with acute or subacute myocarditis, as well as in those with other conditions (such as autoimmune rheumatic processes, Duchenne cardiomyopathy, and Fabry

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

See also the article by Kravchenko et al in this issue.

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disease), the precise pathogenetic pathways leading to subepicardial inflammation and/or scar remain unknown.

In contrast to nonischemic injury, myocardial damage due to coronary artery disease is more common in the subendocardial (inner) layer of the myocardium. Subendocardial injury results from severely reduced myocardial perfusion or unusually elevated levels of wall stress. The subendocardial layer of the myocardium is perfused by perforating transmural arterioles that supply blood from epicardial coronary arteries to these innermost myocardial layers. The myocardial blood supply traverses the ventricular wall in perpendicular orientation and is compressed during myocardial contraction. Such structural-functional characteristics place subendocardial myocytes at greater risk of damage in conditions associated with ischemia and overload.

In certain nonischemic cardiomyopathies, subepicardial myocytes may be exposed to greater risk than those in other myocardial layers in conditions associated with pericardial inflammation. These conditions include infectious pathogens, autoimmune diseases, and invasive processes originating in the lungs or other organs in contiguity or close proximity to the heart. Viral pericardial involvement has been well documented not only in isolated pericarditis, but also in association with viral myocarditis and systemic disease. Similarly, autoimmune rheumatic diseases, particularly lupus erythematosus and scleroderma, are well known to preferentially involve the pericardium and subepicardium in many patients, supporting the idea of subepicardial inflammation, necrosis, and replacement fibrosis in association with pericardial inflammatory involvement. However, a multitude of other cardiomyopathic processes are also associated with subepicardial and midmyocardial scar formation without prominent pericardial involvement. In addition, the concept of contiguity between the pericardium and subepicardium does not entirely explain why such diseases may demonstrate involvement of the entire thickness of the myocardium, rather than preferential subepicardial myocardial damage. In this regard, further investigation into the pathogenesis of nonischemic myocardial MRI LGE patterns is needed.

What is the clinical importance of SARS-CoV-2–associated myocardial scar? How common are myocardial scars in considering the entire population of individuals who have had COVID-19? Will the extent of cardiac scarring become a broader public health problem, given that sooner or later an ever-growing number of individuals across the world are being exposed to SARS-CoV2? In the best case, COVID-19–associated myocardial scar is a mere marker of having had acute COVID-19 infection. Unfortunately, early reports suggest that at least in some individuals, myocardial scar from COVID-19 is associated with lower myocardial function.

In middle-aged and older adults in the United States, approximately 4% of individuals have MRI-depictable nonischemic myocardial scar without direct clinical consequence. However, MRI-depicted scar tends to be associated with risk factors for cardiovascular disease, myocardial interstitial fibrosis, and left ventricular hypertrophy. Among patients with myocarditis accompanied by chest pain and troponin elevation, myocardial scars may be associated with ventricular arrhythmias and sudden cardiac arrest, even in the setting of normal or near-normal left ventricular function. The work by Kravchenko et al suggests that myocardial scar may be uncommon (or even rare) among patients who did not have moderate to severe acute COVID-19 infection. However, the true prevalence of persistent myocardial injury among individuals who had COVID-19 with or without prolonged long-haul COVID-19 symptoms remains unknown at the present time.

The work by Kravchenko et al invites further epidemiologic investigation regarding the prevalence of myocardial involvement in individuals who have been infected by SARS-CoV-2. Ideally, we need to examine individuals who have had different degrees of systemic, pulmonary, or upper respiratory involvement, as well as different levels and types of comorbidities and cardiovascular risk factor profiles. Their work suggests the need for detailed cardiovascular phenotyping of patients with long COVID symptoms in relationship to inflammation, healing, or adverse patterns of hypertrophy, fibrosis, and myocardial injury. In this regard, an ongoing initiative to carefully demarcate the cardiopulmonary and cerebral consequences of COVID-19 by the National Heart Lung and Blood Institute, together with other related units composing the National Institutes of Health, is extremely important.

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References

1. 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.
2. Giustino G, Croft LB, Stefanini GG, et al. Characterization of Myocardial Injury in Patients With COVID-19. J Am Coll Cardiol 2020;76(18):2043–2055.
3. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021;397(10270):220–232.
4. Kravchenko D, Isaak A, Zimmer S, et al. Cardiac MRI in patients with prolonged cardiorespiratory symptoms after mild to moderate COVID-19. Radiology 2021;301(3):E419–E425.