

Hypothesis on the Pathogenesis of Sub-Epicardial Scar Associated with Myocarditis

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The typical pattern of myocardial injury and subsequent fibrosis in patients with viral myocarditis is subepicardial.¹ However, other patterns of injury and scar, as detected by contrast enhanced magnetic resonance imaging (cMRI), commonly occur, including sub-endocardial injury mimicking the ischemic heart disease pattern, and mid-wall circumferential scar seen more often in patients with advanced disease and dilated cardiomyopathies. In patients with myocarditis, who present malignant arrhythmias in the scenario of a preserved left ventricle (LV) function, it is not uncommon to find the typical subepicardial scar pattern in the presence of normal or mildly abnormal LV systolic function.² However, the pathogenesis of sub-epicardial scars in patients with myocarditis accompanied or not by significant LV dysfunction remains obscure.

In addition to myocarditis, subepicardial myocardial scar is found in association with various disease processes that are not believed to be secondary to a virally induced myocardial injury. The list includes disease processes with disparate etiologies, such as Duchenne and Fabry's disease, Chagas cardiomyopathy, and rheumatic heart disease, among others.³⁻⁵ Therefore, different theories have been proposed to explain this pattern of scar formation in patients with different pathologies. Increase in excessive regional stress and local perfusion alterations have been postulated as contributing mechanisms, but both fall short as main mechanisms.⁶ Calculated wall stress is greater at the level of the subendocardium, and reversible perfusion defects secondary to ischemia are commonly subendocardial. After scar formation, perfusion is diminished in proportion to capillary density reduction (fixed defect), but that does not implicate local ischemia as the pathogenetic mechanism underlying subepicardial scar formation.

The COVID-19 pandemic may, however, provide a working hypothesis to explain the pathogenesis of focal subepicardial myocardial fibrosis in patients with myocarditis. COVID-19 cardiac involvement has been amply documented

by biomarker, electrocardiographic, echocardiographic and pathologic studies conducted during the acute infection.⁷ Myocardial dysfunction leading to clinically manifested heart failure is uncommon, but it can occur during acute SARS-CoV-2 infection. Moreover, cardiac magnetic resonance imaging (MRI) studies performed on COVID-19 convalescing patients with different degrees of systemic and pulmonary involvement during the acute phase have demonstrated different types, extents, anatomical distributions and degrees of severity of cardiac injury.⁷⁻⁸ Frequently, in these studies, both pericardial leaflets appear hyperenhanced 10-20 minutes after gadolinium administration, suggesting pericardial inflammation (Figure 1). In some patients, the subepicardial myocardial layer contains areas of localized delayed enhancement, reflecting fibrosis and/or inflammation. These abnormalities can persist in repeated imaging performed later in the convalescing period (Figure 1) and resemble subepicardial injury commonly seen in patients with myocarditis due to other viral etiologies. These suggest that subepicardial damage may be related to pericardial inflammation in patients with myocarditis, either as an inflammatory process originated in the pericardial space or in association with pericardial inflammation as markers of pancardiac inflammation. The combination of pericardial inflammation and subepicardial injury or scar is also commonly seen in patients with rheumatic heart disease.⁵

Viral infection leading to pericardial inflammation is seen not only in SARS-CoV-2 infection, but also in diverse types of viral cardiac infections, including Coxsackie B viruses, known to cause acute myocarditis that may evolve to dilated cardiomyopathy (9). In addition, clinically manifested acute pericarditis is also attributed to viral infection, sometimes leading to chronic constrictive pericarditis. Importantly, significant acute viral myocarditis can be unassociated with ventricular systolic dysfunction and therefore, the true prevalence of subclinical viral cardiac involvement in the community, as in the case of SARS-CoV-2 infection, remains largely unknown. In COVID-19, while severe cardiac involvement in non-hospitalized patients appears to be uncommon, the true prevalence of cardiac and also pulmonary involvement in the community has not been established. Much of the information obtained in non-hospitalized individuals comes from MRI studies performed in athletes before resuming intense physical activity after COVID-19 infection.¹⁰ Findings from these studies suggest that myo-pericardial as well as pleural and parenchymal pulmonary involvement is common, although their long-term clinical significance remains unknown.

This hypothesis brought forth here, like hypotheses in general, leads us to additional questions. Why would subepicardial damage, if extending inwards from the pericardial leafs by contiguity, or as a marker of myocardial inflammation, be so often

Keywords

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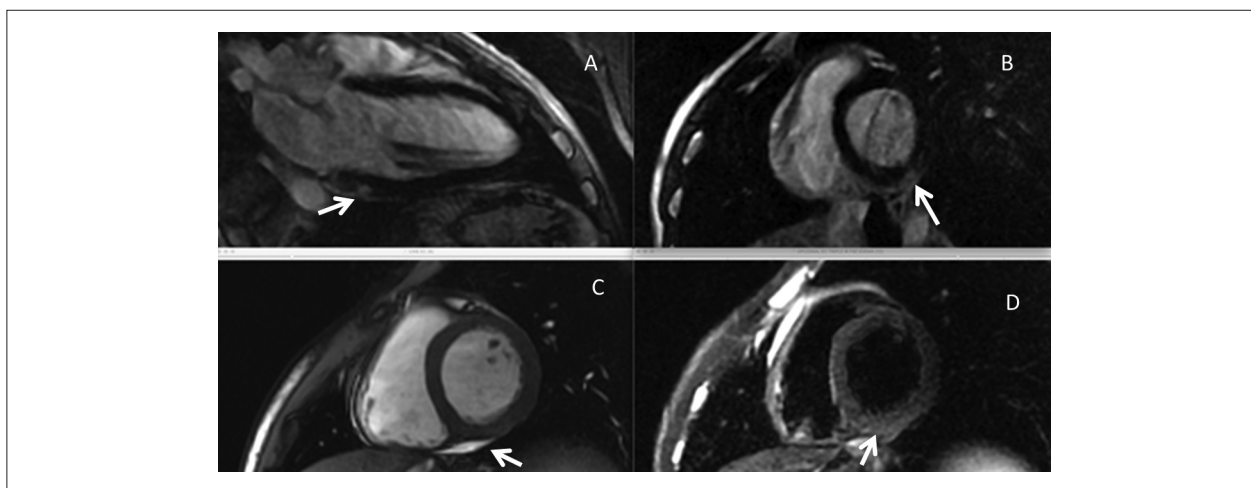


Figure 1 – Example of patient with a post- COVID myocarditis- late gadolinium enhancement and evidence of active inflammation. Late gadolinium enhancement imaging (A and B) shows patchy areas of subepicardial enhancement in the basal inferior wall (white arrows). Short axis steady state free precession image (C) shows small pericardial effusion, and the T2-weighted image shows a small myocardial edema in the same region.

limited to the subepicardium? Much attention has been given to the subepicardium for several reasons, including its proposed distinct embryologic origin.¹¹ Its pivotal role in preserving left ventricular geometry in the face of non-transmural ischemic injury or infarction is well recognized. If by contiguity, the preferential subepicardial localization of myocarditis associated injury can be explained by immediate adjacency to the pericardial space and leaflets. However, this contiguity hypothesis does not explain the other patterns, which not infrequently associate with viral myocardial disease. In addition, it does not take into full consideration the extent of infection and inflammation across the entire myocardium, frequently documented in processes associated with most pathogens, including SARS-CoV-2. Other pathways would have to be invoked to address those questions. In this regard, animal models of viral myocarditis do not reproduce the entire spectrum of disease typically seen in patients, highlighting the importance of clinical phenotypic COVID-19 studies during acute infection and convalescence. In the past, important pathophysiologic insights from endemic myocardial diseases, like Chagas heart disease, provided important insight into the pathogenesis of cardiac disease caused by diverse.¹² Initial observations from patients with COVID-19 or convalescing from SARS-CoV-2 infection suggest that the magnitude of pericardial involvement accompanied or not by subepicardial myocardial injury deserves further study.⁷

In conclusion, our hypothesis places emphasis on the pericardial inflammation as a possible answer to subepicardial injury in myocarditis, based on the findings in post-COVID patients. By analogy, pericardial and subepicardial involvement

from myocardial diseases caused by other viruses and infectious pathogens should also be further investigated.

Author Contributions

Conception and design of the research: Lima JAC, Bluemke DA, Hare J, Wu K, Rochitte CE; acquisition of data: Lima JAC, Bluemke DA, Rochitte CE; analysis and interpretation of the data: Lima JAC, Bluemke DA, Hare J, Sara L, Rochitte CE; writing of the manuscript: Lima JAC, Sara L, Rochitte CE; critical revision of the manuscript for intellectual content: Lima JAC, Bluemke DA, Hare J, Wu K, Sara L, Rochitte CE.

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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