Viewpoint

Post-COVID Cardiomyopathy

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The COVID-19 pandemic caused by the SARS-CoV-2 virus has had an indelible impact on contemporary human society. In addition to the severe morbidity and mortality during the first weeks after infection, up to 70% of COVID-19 survivors may experience long-term medical complications.[1] In a publication at the beginning of the pandemic, Clyde and Gregg[2] already expressed concern about the future consequences of cardiac damage, regardless of the acute clinical manifestation caused by COVID-19.

The association of previous heart disease, with increased lethality rate and need for mechanical ventilation, initially led to the expectation of identifying direct myopathic damage, by inferring the increased concentration of angiotensin-converting enzyme 2 (ACE2) receptors in the myocyte. Heart histology of patients who died revealed a peculiar condition. Clinical presentations similar to myocarditis have been described in only a few patients, suggesting that fulminant myocarditis is a rare condition. On the other hand, in cases with clinical suspicion of myocarditis, SARS-CoV-2 infection has been associated with the presence of cardiac inflammation.[3] Other evidence has indicated that there is pronounced cardiac expression of ACE2 in pericytes that line the microvasculature, as well as in muscle cells and fibroblasts. Another aspect is the presence of proteases encoded by TMPRSS2 and CTSL, which facilitate the cellular uptake of SARS-CoV-2, suggesting other possible mechanisms of cardiac aggression.[4]

In an original study, Mezache et al.[5] provided us with an advanced interpretation of myocardial damage. Studying necropsies of 11 patients with COVID-19 and 11 controls (deceased before 2016), the authors analyzed histological characteristics, viral particles, and molecular findings in cardiac tissue. A marked binding of the SARS-CoV-2 spike protein was especially observed in ACE2 of macrophages and interstitial pericytes, with little presence of nucleocapsids. This study consistently suggests that direct myocardial infection by SARS-CoV-2 is not the pathophysiological mechanism of cardiac dysfunction. Although it cannot be ruled out that systemic complications in severe forms of COVID-19 may directly affect the heart,[6] substantial expression of *in situ* cytokines and local complement activation, secondary to endocytosis of the circulating spike protein, has been demonstrated in both macrophages and interstitial pericytes. These are the alterations that would be involved in the development of myocarditis.

These arguments lead us to consider that the myocardial tissue should not be understood in a simplistic manner as a syncytium of myocytes. It is important to consider the complexity of the myocardial tissue when studying the heart and understanding its peculiarity. With this vision in mind, Tadokoro et al.[7] reported a case of acute myocarditis in a previously healthy patient, without cardiovascular comorbidities, but with HLA-C 12:02:02 and HLA-B 52:01:01 alleles, which have been associated with worse evolution in the Japanese population. From the right ventricular myocardial biopsy, during the course of presentation with severe ventricular dysfunction, the main physiopathogenic element was identified as microthrombosis with hypercoagulation, associated with endothelial injury and complement and macrophage activation.[7]

Myocardial inflammation, COVID-19, and HFpEF

Myocardial inflammation is widely considered to be one of the main factors in the development of heart failure (HF).[8] It is believed that persistent myocardial inflammation plays a central role in the development of adverse left ventricular remodeling after myocardial infarction, as well as in the pathogenesis of dilated cardiomyopathy and heart failure with preserved ejection fraction (HFpEF).[8-10]

In May 2020, Tavazzi et al.[11] reported the first case of acute cardiac injury with the finding of SARS-CoV-2 particles and low-grade inflammation in the myocardium, not accompanied by cardiomyocyte necrosis. An important discussion is whether the myocardial changes are caused by direct viral damage to the heart or vasculature or by a cytokine storm related to the infection.[12] It is mainly known that cardiac inflammatory changes induced by viruses are capable of triggering HFpEF and heart failure with reduced ejection fraction.[13] There is currently a growing interest in identifying patients with COVID-19 at risk of developing virus-related HF and cardiovascular problems.[14]

A recent study,[15] which used the HFA-PEFF score[16] for diagnosis of HFpEF, showed that a substantial proportion of patients with COVID-19 were at an increased risk of HFpEF. Patients with biochemical evidence of myocardial injury had higher HFA-PEFF scores in addition to left ventricular diastolic dysfunction and reduced global longitudinal strain.[15]

Myocardial injury defined as increased troponin values has been observed in approximately 20% of patients with COVID-19. It has also been shown that higher concentrations

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of NT-proBNP correlate with the severity of viral infection. Non-specific increase of cardiac enzymes in patients with COVID-19 may reveal not only these patients' predisposition to cardiac lesions, but also the presence of other cardiac dysfunctions.[15]

A paradigm proposed by Paulus et al.[9] to explain the pathophysiology of HFpEF could help clarify the mechanism by which the inflammation associated with COVID-19 causes HFpEF. Comorbidities, including SARS-CoV-2 infection, lead to remodeling and myocardial dysfunction beginning with a sequence of events that consists of inducing a pro-inflammatory state. This pro-inflammatory state causes coronary microvascular endothelial cells to produce reactive oxygen species, which limit the bioavailability of nitric oxide to adjacent cardiomyocytes. This low bioavailability of nitric oxide decreases protein kinase G activity in cardiomyocytes, and low protein kinase G activity removes the brake on cardiomyocyte hypertrophy, thus inducing concentric left ventricular remodeling, stiffening the cardiomyocyte due to hypophosphorylation of the giant cytoskeletal protein titin. Both stiff cardiomyocytes and increased collagen deposition by myofibroblasts cause diastolic left ventricular dysfunction, which is the main cardiac functional deficit in HFpEF.

The evaluation of cardiac tissue by means of nuclear magnetic resonance indicated different tissue expressions of damage. Possible mechanisms would include sites of myocarditis without functional consequence, type I and II myocardial infarction, and induced myocardial ischemia.[17] Myocarditis presented in the multisegmental form, without alteration of the ejection fraction or alterations in regional motility. Inference of the non-COVID myocarditis pattern may predict good long-term evolution.

Some studies have suggested that myocarditis due to COVID-19 in children may be more common than previously thought. However, the exact prevalence is still unknown, and more research is needed to better understand the incidence, risk factors, and long-term effects of myocarditis in children with COVID-19. The clinical presentation of children with myocarditis can range from asymptomatic to severe progression. Children are at an increased risk of developing myocarditis secondary to COVID-19 compared to the mRNA COVID-19 vaccine.[18]

With the intention of observing cardiac clinical and laboratory manifestations in the post-infectious segment in the long term, we are engaged in a project titled "Integrating forces for understanding and handling post-COVID-19 syndrome: Institutional multidisciplinary study of the Fluminense Federal University (UFF)," a prospective cohort study, with projected follow-up of this population for 24 months, which is funded and supported by the Rio de Janeiro State Research Foundation (FAPERJ, acronym in Portuguese) (E-26/210.828/2021).

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Conception and design of the research e Acquisition of data: Carvalho MRM; Writing of the manuscript: Carvalho MRM, Jorge AJL; Critical revision of the manuscript for important intellectual content: Carvalho MRM, Lugon JR, Jorge AJL.

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

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