Cardiac Involvement in COVID-19: A Matter Close to the Heart, Beyond the Acute Illness

Gláucia Maria Moraes de Oliveira,[1] Fausto J. Pinto[2]

Universidade Federal do Rio de Janeiro (UFRJ),[1] Rio de Janeiro, RJ – Brazil
Centro Hospitalar Universitário Lisboa Norte,[2] CAML, CCUL, Faculdade de Medicina, Universidade de Lisboa – Portugal
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Human infection with the SARS-CoV-2 virus and COVID-19 have been ravaging the entire world since December 2019. As of February 17, 2023, records from the World Health Organization point to more than 756 million confirmed cases and approximately 6,845,000 deaths. In Brazil, until this date, approximately 36,961,000 cases have been reported, with about 698,000 deaths.[1] Among the deaths, the main comorbidities reported are heart disease (40%), diabetes (28%), obesity (10%), neurological diseases (5%), kidney diseases (5%), and pneumopathies (5%). Furthermore, 70% of patients who died were 60 years old or older, and males were prevalent in 60% of the cases.[2]

The impact on mortality is well documented in the acute phase of this disease.[3] Moraes et al., in this systematic review of literature, consolidate the findings described as myocarditis, ventricular dysfunction, cardiogenic shock, takotsubo cardiomyopathy, and sudden cardiac death due to association with ventricular arrhythmias.[4] However, other outcomes linked to more significant morbidity are still not completely understood. In other words, what can and what should we expect from recovered cases?

The incidence of acute myocardial injury, defined as a variation in the serum level of cardiac troponin, is considered high in individuals hospitalized for COVID-19. A Brazilian study showed myocardial injury prevalence of up to 36%, and, regardless of the cause of elevation of this biomarker, these patients had higher in-hospital mortality.[5] However, little is known about the long-term impact of myocardial injury observed during SARS-CoV-2 infection.

The elevation of this cardiac biomarker is probably due to the coexistence of inflammatory and thrombotic processes, without necessarily representing a direct injury by the virus.[6] The advent of imaging in cardiology provided by cardiac magnetic resonance (CMR) contributed to a better understanding of this event. CMR is important in the etiological investigation of cases of new ventricular dysfunction observed in patients with COVID-19. Thus, patients with positive troponins, myocardial dysfunction, and severe arrhythmia/electrocardiographic alterations not explained by other methods may be candidates for CMR.[4,7]

Another crucial point is the concept of long COVID characterized by the persistence of COVID-19 symptoms beyond 3 months, not explained by any other illness. Cardiopulmonary symptoms such as chest pain, shortness of breath, fatigue, autonomic manifestation as postural orthostatic tachycardia syndrome, and palpitations are frequently observed. Other common symptoms include post-exertional malaise, brain fog, headaches, nausea, vomiting, anxiety, depression, skin rash, and joint pain.[8] The estimated prevalence across studies varies from less than 10% to 77% due to different study populations, hospitalized or community patients, the burden of co-morbidities, and the timing of assessment, given that symptom frequency can diminish over time from infection.[9-11] Risk factors for long COVID are female sex, older age, obesity, asthma, poor general health, poor pre-pandemic mental health, and unfavorable sociodemographic factors.[9,10,12] These clinical cardiovascular presentations occurred due to myocardial inflammation, myocardial infarction, right

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Mailing address: Gláucia Maria Moraes de Oliveira
Universidade Federal do Rio de Janeiro. R. Prof. Rodolpho P. Rocco, 255, 8°. Andar, Sala 6. Postal code: 21941-913, Cidade Universitária, RJ – Brazil
E-mail: glauciam@cardiol.br, glauciamoraesoliveira@gmail.com;

ventricular dysfunction, and arrhythmias. Moreover, persistent endothelial dysfunction, microvascular dysfunction, and prothrombotic tendencies may contribute to multiorgan dysfunction involving the lungs heart, liver, kidneys, and brain, as observed in long COVID.[11]

The American College of Cardiology has developed Expert Consensus Decision Pathways to approach myocarditis, post-acute sequelae of SARS-CoV-2 infection, and sports cardiology. This document recommends, in suspected myocardial involvement after 4 weeks, the use of CMR if the patient is hemodynamically stable, because CMR is the most sensitive method to exclude ischemia and preexisting cardiomyopathies and confirm cardiac changes due to SARS-CoV-2 infection, including myocardial inflammation, nonischemic epicardial scar, and pericardial effusion. They also describe an algorithm to manage these patients according to clinical presentation. This paper emphasizes that myocarditis following COVID-19 mRNA vaccination is an entity separate from, but related to myocarditis following SARS-CoV-2 infection.[13]

Myocarditis and pericarditis have recently been linked to the COVID-19 vaccine. An analysis of adverse event reports from the Vaccine Adverse Event Reporting System (VAERS) with systems biology methods indicated that post-vaccine myocarditis and pericarditis were most frequently associated with mRNA COVID-19 vaccines. In addition, 77% and 65% of myocarditis and pericarditis adverse events occurred in male subjects, compared to 22% and 34% in females, respectively. Also, post-COVID-19 vaccine myocarditis and pericarditis adverse events were more prevalent in young males 18 to 29 years

old.[14] Elevated troponin was seen in almost all patients with vaccine-induced myocarditis. Systems biology results suggested a central role of interferon-gamma in the biological processes leading to cardiac adverse events by impacting MAPK and JAK-STAT signaling pathways. Despite these findings, it is important to underline that, in a report by the United States Centers for Disease Control and Prevention, the Advisory Committee on Immunization Practices (ACIP) clearly reported that the benefits of COVID-19 vaccines significantly outweigh the risk of myocarditis in all populations. The most significant benefits were noted in patients > 30 years old in both sexes. The risk of vaccine-induced myocarditis was highest in males 12 to 29 years old, with 39 to 47 cases per million vaccines administered; however, in the same population, vaccination prevented an estimated 11,000 COVID-19 cases, 560 hospitalizations, 139 intensive care unit admissions, and 6 deaths.[15]

Given the enormous challenges related to cardiac involvement in COVID-19 beyond the acute illness, further studies will need to address the high burden of cardiopulmonary symptoms, considering the optimal balance between cost-effective investigations and benefit to the patients, minimizing the inequalities in healthcare provision and maximizing social and mental support, because cardiac involvement in COVID-19 continues to be a significant public health issue. In addition, all our efforts still need to be focused on topics related to the sequelae caused by this disease, improving the understanding of the mechanisms underlying these conditions to find better management strategies in the middle and long term. Therefore, we must ensure this matter remains close to the heart.[3]

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