Viewpoint

Post-COVID-19 Cardiomyopathy in Children and Adults: Fact or Fiction?

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Since the emergence of the novel coronavirus 2019 disease (COVID-19), cardiovascular impairment and alterations in cardiology laboratory tests suggestive of myocardial injury, even in patients without cardiovascular symptoms, have been observed in hospitalized children and adults.[1-4]

Epidemiological data from China have suggested that cardiac injury may occur in 19% to 28% of hospitalized patients with COVID-19.[5] Several factors seem to contribute to myocardial damage, and potential mechanisms of injury include: hypoxic injury, stress cardiomyopathy, ischemic lesion caused by cardiac microvascular dysfunction, small vessel cardiac vasculitis, endotheliitis, epicardial coronary artery disease, right heart distention (acute cor pulmonale with pulmonary embolism), myocarditis, systemic inflammatory response syndrome (cytokine storm), and others [3,4] (Figure 1).

Cases of myocarditis after infection with the SARS-CoV-2 virus have been reported in the literature, including cases of fulminant myocarditis, and their true incidence is still difficult to establish. The main theories indicate direct action of the virus or hyperimmune response. The first endomyocardial biopsy-proven case that satisfied the Dallas criteria for myocarditis was consistent with virus-negative lymphocytic myocarditis, suggestive of immune-mediated pathogenesis. On the other hand, the first report of myocarditis due to COVID-19 corroborated by histological evidence of direct infection of the cardiomyocyte by SARS-CoV-2 was associated with limited myocyte necrosis, supporting the hypothesis of a hyperinflammatory response involving the myocardium, rather than direct loss of cardiomyocytes due to viral infection.[5-7]

Although it is considered a separate entity from post-COVID-19 myocarditis, it is important to note the occurrence of myopericarditis following COVID-19 messenger RNA (mRNA) vaccination. Cases are rare, occurring more frequently in male adolescents and young adults within 7 days after receiving the second dose of the vaccine.[8] Most patients evolve favorably, with signs of clinical and laboratory improvement, with or without treatment. A meta-analysis published in 2022 showed that the risk of myocarditis is 7 times greater in people infected with SARS-CoV-2 than in those who have received the vaccine, demonstrating that it is recommendable to use mRNA vaccines in people who are eligible, according to current recommendations.[9]

Adults, children, and adolescents can also develop a late form of multisystem inflammatory disease temporally related to prior exposure to SARS-CoV-2, which can lead to severe cardiac impairment, including fulminant myocarditis. This situation, known as multisystem inflammatory syndrome in children (MIS-C) or multisystem inflammatory syndrome in adults (MIS-A), occurs days to weeks after a patient becomes ill with COVID-19.[7,10-13]

MIS-C is considered a rare, albeit severe post-inflammatory complication that can cause acute myocardial dysfunction, arrhythmias, conduction abnormalities, and coronary artery dilation. The outcome of MIS-C is generally very favorable, with resolution of inflammation and cardiovascular abnormalities within 1 to 4 weeks of diagnosis. Mortality is also rare, with an estimated occurrence in 1.4% to 1.9% of cases. However, some series have reported the progression of coronary artery aneurysms after discharge and the potential for long-term complications.[12]

MIS-A is less common than MIS-C and more difficult to distinguish from acute COVID-19. However, as in MIS-C, adults with MIS-A seem to recover quickly from severe cardiac complications.[13]

The long-term cardiovascular effects of patients affected by COVID-19 are still not very well defined, and studies in this regard have appeared in the literature. Some patients infected with SARS-CoV-2 experience cardiac symptoms such as chest pain, dyspnea, fatigue, and palpitations that persist for months after the onset of the illness.[14,15]

Two studies were published in 2022 with large cohorts of adult patients who had acute COVID-19, with a follow-up of up to 1 year after the illness. Both studies included patients who were hospitalized, patients with outpatient follow-up only, and control groups.[16,17]

The first study, by Yan Xie et al.,[16] used national healthcare databases from the United States Department of Veterans Affairs and demonstrated that the risk and increase in cases of cardiovascular disease at 1 year are high in hospitalized and non-hospitalized patients who survived COVID-19. The cardiovascular diseases found in the study encompass several categories, such as ischemic and non-ischemic heart disease, cardiac arrhythmias, and others. Probable mechanisms of cardiovascular sequelae

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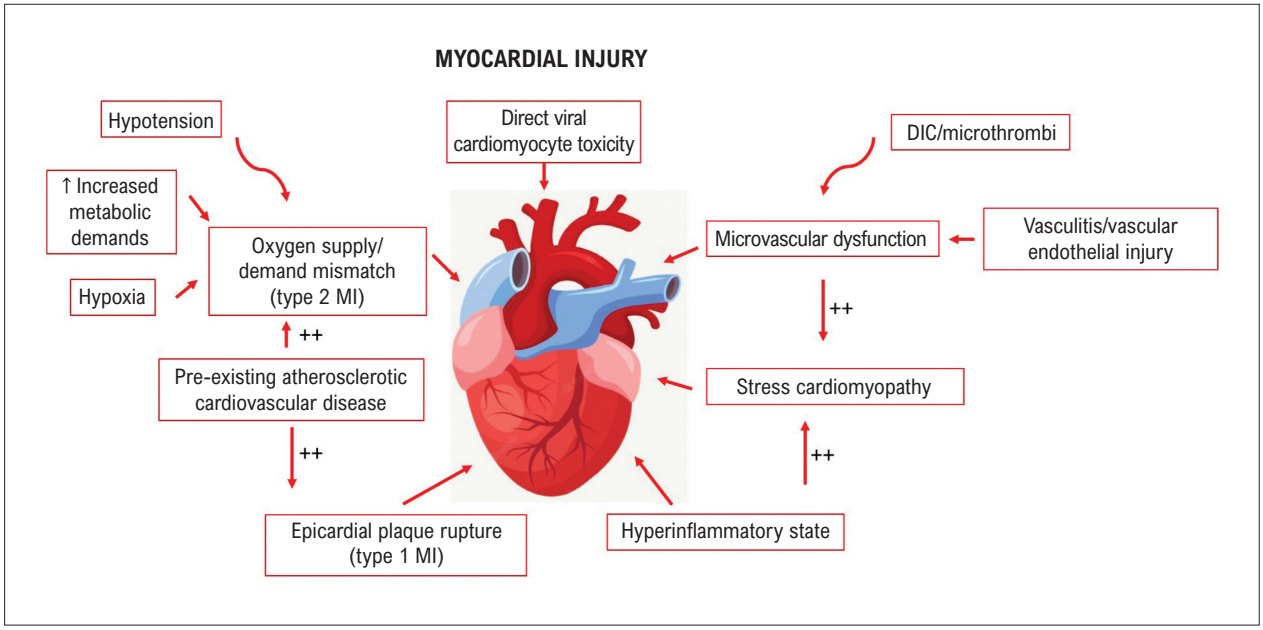

Figure 1 – *Potential mechanisms of myocardial injury in COVID-19. DIC: disseminated intravascular coagulation; MI: myocardial infarction. Source: Figure adapted from Atri D, Siddiqi HK, Lang J et al. COVID-19 for the Cardiologist: Basic Virology, Epidemiology, Cardiac Manifestations, and Potential Therapeutic Strategies. JACC Basic Transl Sci. 2020;5(5):518–536. https://doi:10.1016/j.jacbts.2020.04.002.*

include direct viral invasion of cardiomyocytes, endothelial cell infection and endotheliitis, transcriptional alteration of multiple cell types in cardiac tissue, complement activation, complement-mediated coagulopathy and microangiopathy, dysregulation of the renin-angiotensin-aldosterone system, persistent hyperactive immune response, autoimmunity, or persistence of the virus in immune-privileged sites, among others. The study provides robust evidence, but it is worth emphasizing that the majority of the study population was composed of White men.

A subsequent publication, by Weijie Wang et al.[17] used data from 48 health care institutions in the United States contained in the TriNetX platform (a global platform for collaborative clinical research in health, which collects electronic medical data in real time from several health organizations worldwide). TriNetX currently holds the largest global COVID-19 dataset. The institutions involved in the study were hospitals, primary health care units, or specialists. COVID-19 survivors had a higher risk of cardiovascular complications (cerebrovascular complications, arrhythmias, inflammatory or ischemic heart disease, and thromboembolic disorders) than those in the control group. The risks of two composite endpoints, major adverse cardiac events and any cardiovascular complication, were also higher in COVID-19 survivors. The risks of cardiovascular complications were evident in both the male and the female sex. These findings could be justified by irreversible damage previously caused to the cardiovascular or cerebrovascular system during SARS-CoV-2 infection; damage to the respiratory system with impaired lung function and systemic hypoxia, causing ischemic heart disease, acute coronary syndrome, and ischemic stroke; hyper-coagulopathy status caused by COVID-19 persisting after recovery from COVID-19, increasing the risks of thromboembolic events and embolism; cytokine storm with damage to various organs, among others. Finally, some drugs eventually used by some individuals with COVID-19, such as hydroxychloroquine and azithromycin, have adverse effects on the cardiovascular system. The authors conclude that the risk of 1-year burden of cardiovascular disease is substantially higher in COVID-19 survivors than in controls and that patients with a history of COVID-19 should be mindful of their long-term cardiovascular health.

In the absence of robust data from clinical trials, with the intention of providing practical guidance related to the evaluation and management of patients whose cardiac symptoms persist after the acute phase of COVID-19, in May 2022, the American College of Cardiology published an Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults.[18] The publication aims to serve as a resource for doctors who care for this group of patients, mainly in the outpatient setting, also addressing the return of athletes to physical activities and the management of patients with myopericarditis following COVID-19 mRNA vaccination. As the recommendations reflect current knowledge up to early 2022, the authors recognize that the guidance provided will change over time as understanding of COVID-19 evolves.

It is a fact that COVID-19 is related to myocardial impairment, both in the acute phase and in later periods of the disease, in adults and children. More long-term studies are needed, however. Up to this moment, it seems to be important to include cardiovascular health in the line of care for patients with acute COVID-19 or patients who have survived this condition.

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References

1. Jiehao C, Jin X, Daojiong L, Zhi Y, Lei X, Zhenghai Q, et al. A Case Series of Children with 2019 Novel Coronavirus Infection: Clinical and Epidemiological Features. Clin Infect Dis. 2020;71(6):1547-51. doi: 10.1093/cid/ciaa198.
2. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children. N Engl J Med. 2020;382(17):1663-65. doi: 10.1056/NEJMc2005073.
3. Ranard LS, Fried JA, Abdalla M, Anstey DE, Givens RC, Kumaraiah D, et al. Approach to Acute Cardiovascular Complications in COVID-19 Infection. Circ Heart Fail. 2020;13(7):e007220. doi: 10.1161/CIRCHEARTFAILURE.120.007220.
4. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and Cardiovascular Disease: From Basic Mechanisms to Clinical Perspectives. Nat Rev Cardiol. 2020;17(9):543-58. doi: 10.1038/s41569-020-0413-9.
5. Castiello T, Georgiopoulos G, Finocchiaro G, Claudia M, Gianatti A, Delialis D, et al. COVID-19 and Myocarditis: A Systematic Review and Overview of Current Challenges. Heart Fail Rev. 2022;27(1):251-61. doi: 10.1007/s10741-021-10087-9.
6. Montera MW, Marcondes-Braga FG, Simões MV, Moura LAZ, Fernandes F, Mangine S, et al. Brazilian Society of Cardiology Guideline on Myocarditis - 2022. Arq Bras Cardiol. 2022;119(1):143-211. doi: 10.36660/abc.20220412.
7. Barhoum P, Chambrun MP, Dorgham K, Kerneis M, Burrel S, Quentric P, et al. Phenotypic Heterogeneity of Fulminant COVID-19--Related Myocarditis in Adults. J Am Coll Cardiol. 2022;80(4):299-312. doi: 10.1016/j.jacc.2022.04.056.
8. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA Vaccines. Circulation. 2021;144(6):471-84. doi: 10.1161/CIRCULATIONAHA.121.056135.
9. Voleti N, Reddy SP, Ssentongo P. Myocarditis in SARS-CoV-2 Infection vs. COVID-19 Vaccination: A Systematic Review and Meta-Analysis. Front Cardiovasc Med. 2022;9:951314. doi: 10.3389/fcvm.2022.951314.
10. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. Circulation. 2020;142(5):429-36. doi: 10.1161/CIRCULATIONAHA.120.048360.
11. Alsaied T, Tremoulet AH, Burns JC, Saidi A, Dionne A, Lang SM, et al. Review of Cardiac Involvement in Multisystem Inflammatory Syndrome in Children. Circulation. 2021;143(1):78-88. doi: 10.1161/CIRCULATIONAHA.120.049836.
12. Jone PN, John A, Oster ME, Allen K, Tremoulet AH, Saarel EV, et al. SARS-CoV-2 Infection and Associated Cardiovascular Manifestations and Complications in Children and Young Adults: A Scientific Statement From the American Heart Association. Circulation. 2022;145(19):e1037-e1052. doi: 10.1161/CIR.0000000000001064.
13. Centers for Disease Control and Prevention. Multisystem Inflammatory Syndrome in Adults (MIS-A) Case Definition Information for Healthcare Providers [Internet]. Atlanta: CDC; 2023 [cited 2023 Jun 6]. Available from: https://www.cdc.gov/mis/mis-a/hcp.html.
14. Caforio ALP. COVID-19: Cardiac Manifestations in Adults [Internet]. Waltham: UpToDate; 2022 [cited 2023 Mar 23]. Available from: https://www.uptodate.com/contents/covid-19-cardiac-manifestations-in-adults.
15. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-Month Consequences of COVID-19 in Patients Discharged from Hospital: A Cohort Study. Lancet. 2021;397(10270):220-32. doi: 10.1016/S0140-6736(20)32656-8.
16. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-Term Cardiovascular Outcomes of COVID-19. Nat Med. 2022;28(3):583-90. doi: 10.1038/s41591-022-01689-3.
17. Wang W, Wang CY, Wang SI, Wei JC. Long-Term Cardiovascular Outcomes in COVID-19 Survivors Among Non-Vaccinated Population: A Retrospective Cohort Study from the TriNetX US Collaborative Networks. EClinicalMedicine. 2022;53:101619. doi: 10.1016/j.eclinm.2022.101619.
18. Gluckman TJ, Bhave NM, Allen LA, Chung EH, Spatz ES, Ammirati E, et al. 2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults: Myocarditis and Other Myocardial Involvement, Post-Acute Sequelae of SARS-CoV-2 Infection, and Return to Play: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2022;79(17):1717-56. doi: 10.1016/j.jacc.2022.02.003.