

Post-Vaccine Myocarditis: A Risk Worth the Reward?

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See also the article by Fronza et al.

The benefits of mass-vaccine roll out are undeniable. Millions of deaths, hospitalisations, and intensive care admissions have been averted across all ages owing to the success of national vaccine programs. The link between cases and fatal outcomes may finally be severed in some countries. Economic growth is expected to reach pre-pandemic levels as normality marches into our lives. Declining mental health is predicted to improve, and vital hospital resources may now be diverted to other patients in need of medical attention. The finish line is finally visible as nations seek to build herd immunity through vaccine mandates. But will there be barriers in this final phase of the pandemic? The answer is complex and multifactorial, with vaccine hesitancy expected to play a critical role.

Of the many vaccines, messenger RNA (mRNA) vaccine, a relatively new mode of inducing immunity, has been remarkably resilient in protecting against new versions of the virus. The superiority of mRNA vaccines has been particularly visible in the context of the Omicron SARS-CoV-2 variant, a highly contagious variant shown to efficiently evade both natural and induced immunity in individuals (particularly in non-mRNA vaccine recipients). The trouble with mRNA vaccines, however, is the risk of myocarditis, an emerging focus of public concern generating arguments in favour of vaccine refusal and hesitancy.

Reassuringly, numerous epidemiological studies have confirmed that myocarditis following mRNA vaccines is rare. In a recent Danish study by Husby et al (1), the incidence of myopericarditis following BNT162b2 in 3.5 million people was 1.4 per 100,000 vaccinated individuals and that following mRNA-1273 was 4.2 per 100,000. An Israeli study of 9.2 million residents noted an overall rate of myocarditis of 2.35 per 100,000 in individuals vaccinated with

BNT162b2 after the second dose. By contrast, the risk of myocarditis secondary to coronavirus diseases (COVID-19) has been shown to be at least four-to-five-fold higher in two studies (2, 3). Furthermore, risks of other complications such as pericarditis, arrhythmia, deep-vein thrombosis, pulmonary embolism, myocardial infarction, intracranial haemorrhage, and thrombocytopenia were also substantially higher post-acute COVID-19 when compared to vaccine-related adverse events.

While the prevalence of mRNA vaccine-associated myocarditis is now reasonably well characterised, the pattern and extent of myocardial injury compared to other forms of myocarditis remain poorly understood. To address these gaps, in this issue of *Radiology*, Fronza and colleagues evaluated the extent of myocardial injury seen with vaccine-associated myocarditis and compared them to COVID-19 and non-COVID-19/non-vaccine related myocarditis (4). Cardiac magnetic resonance imaging (MRI) findings from 92 consecutive patients with suspected myocarditis were retrospectively assessed as part of this study. Sixty-one percent of cases were non-COVID-19/non-vaccine related myocarditis (including post-infectious, autoimmune, drug induced, hyper-eosinophilic, idiopathic cases), 23% were mRNA vaccine-associated myocarditis and 11% COVID-19 related-myocarditis. A little over half of the vaccine-linked cases received the mRNA-1273 vaccine and 43% BNT162b2 vaccine. Previous studies (5-7) have reported clinical and MRI findings from post-vaccine myocarditis in selected cohorts of hospitalised patients, though none of them had a control group.

In line with prior studies, individuals with vaccine-associated myocarditis were predominantly male (81%) and younger (mean age of 31 ± 14 years) (4). Chest pain or myocarditis symptoms were

reported at a median of 3 days from the second dose in 81% of cases or in 12% of cases following the first dose. Cardiac MRI from both hospitalised and non-hospitalised patients with vaccine-associated myocarditis were also uniquely assessed in this study. The authors observed that non-hospitalised myocarditis patients had MRI abnormalities comparable to those needing hospital admission for vaccine-associated myocarditis. Patients with vaccine-associated myocarditis frequently had subepicardial fibrosis, a pattern similar to myocarditis secondary to COVID-19 and other aetiologies. However, mid wall fibrosis was notably less frequent and left ventricular impairment less common in vaccine-associated myocarditis. Even the extent of late gadolinium enhancement (focal fibrosis) in the post-vaccine group was lower and abnormalities on tissue characterisation (T1 and T2 mapping) although common (affecting 67-79% of cases) were less severe in magnitude relative to the other groups. The outcome at short-term follow up (22 days (7-49 days) of individuals with vaccine-associated myocarditis showed no major adverse events. In contrast, patients with COVID-19 associated myocarditis had 3 major adverse cardiovascular events (MACE) and those with myocarditis of other aetiologies had 5 MACE at a median of 211 days and 195 days, respectively.

The main findings highlighted by the authors were as follows: First, vaccine-associated myocarditis tended to be mild both in clinical presentation and extent of injury. This is in keeping with other case series and cohort descriptions of vaccine-associated myocarditis (5-7). The second was that post-vaccine myocarditis fibrosis was predominantly subepicardial in distribution, a pattern linked to better outcomes in a prior study of myocarditis (8). Third, while previous publications focussed on more severe cases of myocarditis (such as those needing hospital admission), in this study, even individuals with mild forms of myocarditis were seen to have

abnormalities on detailed cardiac evaluation. This finding highlights the need for surveillance of those with suspected myocardial involvement post-mRNA vaccine. Finally, short-term follow up of a small group of vaccine-related myocarditis was relatively uneventful. This hints toward a possible benign prognosis, though follow-up duration of comparator groups (post-COVID and other myocarditis group) were much longer limiting the validity of this conclusion.

While the study by Fronza et al (4) had some novel findings, there were several limitations, some of which were acknowledged by the authors. This includes its limited sample size, retrospective nature making it susceptible to reporting bias, short follow up duration of the post-vaccine group and heterogeneity in patient populations. Inconsistent imaging protocols (e.g. use of 1.5 and 3T scans) and variable scan intervals from symptom onset across groups can also be problematic, as native T1 and T2 mapping are highly sensitive to field strength, effects of co-morbidities and timing of scan from acute insult. Although the authors attempt to adjust for some of these differences statistically and by using Z-scores, imperfections in covariates and normal ranges may still result in residual confounding. Prospective cohort studies with larger sample size, consistent imaging protocols and longer follow up duration are therefore needed to validate these findings in the future.

Despite the numerous reports of mRNA vaccine-associated myocarditis, underlying pathophysiological mechanisms that contribute to presentations are still unknown and present an important area of research. Three possible explanations for myocarditis have been put forward by experts but are lacking consistent confirmatory evidence. These include mRNA immunogenic response, cross-reactivity of spike antibodies with myocardial contractile proteins and hormonal

differences in immune response. Foreign RNA molecules are typically highly immunogenic and shown to activate the innate immune system leading to the early destruction of RNA molecules before they enter the cells. Nucleoside modifications of mRNA is a revolutionary approach shown to considerably reduce this immunogenicity (9), making it possible to safely and effectively administer mRNA vaccines to millions of people protecting them against serious illness secondary to COVID-19. However, in certain genetically predisposed individuals, inappropriate activation of the innate and acquired immune response can still occur, leading to the release of proinflammatory cytokines and immunologic activation and subsequent myocardial injury.

Another mechanism considered plausible is the cross reactivity of SARS-CoV-2 spike glycoprotein antibodies and cardiac self-antigens (10). Molecular mimicry between the spike glycoprotein and structurally identical protein sequences including myosin heavy chain may trigger an autoimmune response to cardiac antigens and potentially induce myocardial inflammation. Finally, the strong predisposition for males to develop mRNA-induced myocarditis implies that hormonal differences in immune response may be a driver for myocardial inflammation. Indeed, T helper cell response is favourably promoted by testosterone, which also inhibits other anti-inflammatory cells. By contrast, oestrogen has many anti-inflammatory properties and therefore protects against numerous inflammatory diseases before the onset of menopause.

The risk of myocarditis linked to mRNA vaccine has been a major source of public anxiety, though several studies have confirmed the rarity of this complication. In this work by Fronza and colleagues (4), we are once again reassured that myocarditis secondary to mRNA vaccine is most

likely mild and self-limiting, and may have minimal short term consequences, though larger studies with longer term follow up are needed. In comparison, COVID-19 associated myocardial injury, hospitalisation and death continue to pose a real threat to the unvaccinated population and vital lifeline of hospital resources. Global efforts to promote vaccine equity and education will be necessary to bridge the gaps in population immunity against COVID-19.

References

1. Husby A, Hansen JV, Fosbøl E, Thiesson EM, Madsen M, Thomsen RW, et al. SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study. *BMJ*. 2021;375:e068665.
2. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. *New England Journal of Medicine*. 2021;385(12):1078-90.
3. Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. *Nature Medicine*. 2021.
4. Fronza M, Thavendiranathan P, Chan C, et al. Myocardial Injury Pattern at MRI in COVID-19 Vaccine-associated Myocarditis. *Radiology* In Press.
5. Marshall M, Ferguson ID, Lewis P, Jaggi P, Gagliardo C, Collins JS, et al. Symptomatic Acute Myocarditis in 7 Adolescents After Pfizer-BioNTech COVID-19 Vaccination. *Pediatrics*. 2021;148(3).
6. Rosner CM, Genovese L, Tehrani BN, Atkins M, Bakhshi H, Chaudhri S, et al. Myocarditis Temporally Associated With COVID-19 Vaccination. *Circulation*. 2021;144(6):502-5.
7. Montgomery J, Ryan M, Engler R, Hoffman D, McClenathan B, Collins L, et al. Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. *JAMA Cardiology*. 2021;6(10):1202-6.
8. Gräni C, Eichhorn C, Bière L, Murthy VL, Agarwal V, Kaneko K, et al. Prognostic Value of Cardiac Magnetic Resonance Tissue Characterization in Risk Stratifying Patients With Suspected Myocarditis. *Journal of the American College of Cardiology*. 2017;70(16):1964-76.
9. Karikó K, Buckstein M, Ni H, Weissman D. Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. *Immunity*. 2005;23(2):165-75.
10. Vojdani A, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. *Clinical Immunology (Orlando, Fla)*. 2020;217:108480.



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