



Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms

Stephane Heymans¹✉ and Leslie T. Cooper²

The risk of acute myocarditis associated with COVID-19 mRNA vaccination has garnered intense (social) media attention. However, myocarditis after COVID-19 mRNA vaccination is rare and usually resolves within days or weeks. Moreover, the risks of hospitalization and death associated with COVID-19 are greater than the risk associated with COVID-19 vaccination. Therefore, COVID-19 vaccination should be recommended in adolescents and adults.

Acute myocarditis most commonly results from a viral infection¹, including infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19). Although rare, acute myocarditis can also occur after vaccination, such as with the vaccine against smallpox or, as seen more recently, the vaccines against COVID-19, in particular those based on mRNA technology (Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273). The risks of acute myocarditis associated with SARS-CoV-2 infection and after COVID-19 mRNA vaccination have garnered intense social media attention. A consistent point in these heated arguments is that the risks of hospitalization and death associated with COVID-19 are greater than the risks linked with the vaccine. Furthermore, COVID-19 vaccination reduces the relative risk of myocarditis and arrhythmia manifold, and myocarditis related to COVID-19 mRNA vaccination occurs mostly in young adults and is mild in most cases. Therefore, given that post-mRNA-vaccine myocarditis is rare and usually resolves within a few days or weeks, COVID-19 vaccination should be recommended in adolescent and adult populations.

Clinical observations

In patients with severe myocarditis, the diagnosis is often established by heart biopsy. In patients with mild myocarditis, the diagnosis is based on compatible clinical findings and confirmed by elevated levels of blood markers or an electrocardiogram (ECG) indicative of cardiac injury, with presence of new abnormalities on echocardiography or cardiac MRI. When non-histological criteria are used, the cause of myocarditis is usually not proven¹. Before the emergence of COVID-19, the estimated global incidence of acute myocarditis was 1–10 cases per 100,000 people per year¹ (TABLE 1). Similarly, the overall incidence of COVID-19 mRNA-vaccine-related

myocarditis seems to be low, estimated as 0.3–5.0 cases per 100,000 vaccinated people in case-series studies from the USA and Israel^{2–5} (see the Supplementary information for the full list of published reports on myocarditis and pericarditis after COVID-19 vaccination). The highest incidence of myocarditis occurred after the second vaccination and mostly in young men (83 of 117 patients were aged ≤30 years and only 15 of 117 patients were women)³. Most of the cases arose within the first week, typically 3–4 days after the vaccination. In myocarditis unrelated to COVID-19 or COVID-19 vaccination, >80% of patients will spontaneously recover, although those hospitalized for myocarditis have an approximately 4–5% risk of death or heart transplantation in the first year after diagnosis⁶. In COVID-19 mRNA-vaccine-associated myocarditis, >90% of patients will functionally completely recover, usually after a chest pain syndrome (see Supplementary information). To date, only eight deaths owing to COVID-19 mRNA-vaccine-associated myocarditis have been reported (>99% survival) (see Supplementary information).

By contrast, the incidence of COVID-19-associated cardiac injury or myocarditis is estimated to be 100 times higher (1,000–1,400 per 100,000 people with COVID-19) than that of COVID-19 mRNA-vaccine-related myocarditis⁷. Moreover, in contrast to the overall mild presentation and good outcome of vaccine-associated myocarditis, COVID-19 is associated with a major risk of cardiovascular complications⁸. Among patients with COVID-19, 10% of outpatients and 40% of hospitalized patients have clinically significant myocardial injury, mostly in the absence of clinically significant coronary artery disease⁹. Advanced age and pre-existing comorbidities (obesity, diabetes mellitus, hypertension or renal dysfunction) are the main predisposing factors for cardiovascular complications in patients with COVID-19.

¹Maastricht University Medical Centre, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, Netherlands.

²Department of Cardiovascular Medicine, Mayo Clinic in Florida, Jacksonville, FL, USA.

✉e-mail: s.heyman@maastrichtuniversity.nl
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Table 1 | Characteristics of COVID-19-associated myocarditis and myocarditis after COVID-19 mRNA vaccination

Myocarditis type	Incidence	Survival (%)	Potential mechanisms
'Common' viral myocarditis	1–10 per 100,000 people per year	>80	Myocardial injury Genetic (variants in genes encoding HLA, desmosomal, cytoskeletal or sarcomeric proteins) Immune crossreactivity Sex-related factors
COVID-19-associated myocarditis and cardiac injury	1,000–4,000 per 100,000 people with SARS-CoV-2 infection	30–80	Endothelial injury and microthrombosis Genetic (variants in genes encoding HLA, desmosomal, cytoskeletal or sarcomeric proteins) Sepsis and shock
Myocarditis after COVID-19 mRNA vaccination	0.3–5.0 per 100,000 vaccinated people	>99	Hypersensitivity reaction Genetic (variants in genes encoding HLA, desmosomal, cytoskeletal or sarcomeric proteins) Immune crossreactivity Sex-related factors

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Sepsis and shock, hypoxia and haemodynamic instability owing to severe COVID-19 pneumonia and its complications, and direct COVID-19-mediated microvascular injury and thrombosis can all cause myocardial damage (assessed by the presence of increased troponin levels in the plasma), ECG changes, heart failure and arrhythmias⁸.

Potential mechanisms

Myocarditis that results from enterovirus or human herpesvirus (HHV4 and HHV6) infection is generally more severe with younger age and male sex. This type of myocarditis can be associated with an immune-genetic background that increases the likelihood of developing acute myocarditis after viral injury, such as genetic variants in genes encoding HLA factors and, in a minority of patients, genetic variants in genes encoding desmosomal, cytoskeletal or sarcomeric proteins¹. The generation of autoantibodies and hormone-related factors contribute to the sex-specific differences observed in both COVID-19 mRNA-vaccination-related myocarditis and in non-COVID-19 viral myocarditis. Publications in the past year describe similar factors predisposing to acute myocarditis after COVID-19 mRNA vaccination⁹.

mRNA vaccines against COVID-19 contain nucleoside-modified mRNA that encodes the viral spike glycoprotein of SARS-CoV-2 and is encapsulated in lipid nanoparticles, but do not contain live virus or DNA. The viral spike protein, once produced in the cell after mRNA-vaccine entry, induces an adaptive immune response to identify and destroy viruses that express the spike protein. Vaccine-induced spike-protein IgG antibodies prevent the attachment of SARS-CoV-2 to the host cell (which occurs via spike-protein binding to the angiotensin-converting enzyme 2 receptor) and thereby neutralize the virus. The three main mechanisms by which COVID-19 mRNA vaccines might induce hyperimmunity⁹ are mRNA immune reactivity, antibodies to SARS-CoV-2 spike glycoproteins cross-reacting with myocardial contractile proteins, and

hormonal differences. All of these mechanisms can be influenced by immune-genetic background, age and sex.

The immune system might detect the mRNA in the vaccine as an antigen, resulting in the activation of pro-inflammatory cascades and immunological pathways in the heart. Although nucleoside modifications of mRNA reduce their innate immunogenicity, the immune response to mRNA might still drive the activation of an aberrant innate and acquired immune response, which can explain the stronger immune response seen with mRNA vaccines than with other types of COVID-19 vaccine. However, this hypothesis is not supported by the lack of immune-related adverse effects in other organs in which the mRNA vaccine is being uptaken. Molecular mimicry between the spike protein of SARS-CoV-2 and cardiac self-antigens is another possible mechanism. Antibodies directed to SARS-CoV-2 spike glycoproteins might cross-react with structurally similar human protein sequences, including myocardial α -myosin heavy chain⁹. These autoantibodies might be innocent bystanders resulting from myocardial inflammation and injury, or might reflect a certain immune-genetic background that predisposes to developing hyperimmunity and myocarditis upon any trigger. Finally, given the increased incidence among male patients, differences in hormone signalling might be involved in the pathophysiology of COVID-19 mRNA-vaccination-related myocarditis. Testosterone can inhibit anti-inflammatory immune cells and promote a more aggressive T helper 1 cell-type immune response¹. By contrast, oestrogen has inhibitory effects on pro-inflammatory T cells, resulting in a decrease in cell-mediated immune responses¹.

Vaccinations: the way to go!

As in 'common' viral myocarditis, myocarditis associated with COVID-19 mRNA vaccination mainly occurs in young adults within 1 week of viral antigen-induced immune activation, but can sometimes occur in vaccine recipients with immune and genetic susceptibility to myocarditis. The risk ratio of myocarditis in a large study

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from Israel was 3.24 in the first 42 days after the first dose of the Pfizer-BioNTech mRNA vaccine². By contrast, the risk ratio of myocarditis associated with COVID-19 was estimated to be 18.28 (REF.²). Importantly, most of the patients admitted to hospital with post-mRNA-vaccine myocarditis survived and recovered cardiac function within 1–5 weeks after an initial hospitalization of 3–5 days^{2–5}. In addition, the higher proactive surveillance and public awareness in vaccinated people owing to intense media attention, and the reporting of unrelated myocarditis cases weeks to months after vaccination, might have resulted in an overestimation bias of this surplus risk compared with more passively collected historical data.

Despite these rare cases of self-limited myocarditis, the benefit–risk assessment for COVID-19 (mRNA) vaccination underscores a very strong favourable balance for all age and sex groups. Vaccines against COVID-19 have proved to be highly effective at preventing symptomatic disease in clinical trials and real-world reports. Vaccination flattens the epidemiology curve and strongly reduces the risk of COVID-19-related hospitalization, intensive care admission and death in both young and elderly individuals¹⁰. COVID-19 vaccination also reduces the risk of COVID-19-associated acute kidney injury, arrhythmia and thrombosis¹⁰. Moreover, with COVID-19 vaccination, the risk of myocardial injury and myocarditis decreases 1,000-fold in the general population, with a minor 1–5-fold increased risk of

mild myocarditis in young adults. Therefore, COVID-19 vaccination has an extremely favourable risk ratio for myocarditis and should be recommended in adolescent and adult populations.

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Competing interests

The authors declare no competing interests.

Supplementary information

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