Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Post RNA-based COVID vaccines myocarditis: Proposed mechanisms

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There have been several reports of myo-(peri-)carditis after vaccination with the SARS-CoV-2 RNA-based vaccines (BNT162b2-mRNA and mRNA-1273) especially after the second dose [1–3]. Despite the tremendous success achieved by these vaccines, however, there remains a rare but significant risk of morbidity which may further augment vaccine hesitancy. Therefore, unravelling the underlying mechanism(s) leading to myo-(peri-)carditis may help with improving the current vaccines and/or raising awareness among clinicians and public health authorities.

The role of pericytes in susceptibility to COVID-19 through the expression of SARS-CoV-2 receptor, *i.e.*, angiotensin-converting enzyme 2 (ACE2) has been demonstrated [4]. Pericytes also play a significant role in repairing cardiac tissue injuries including those of cardiac endothelial cells. This is especially true in young male adults who may happen to more frequently experience subtle cardiac injuries compared with the general population [5]. It has also been shown that after infection with SARS-CoV-2, anamnestic humoral immune responses to previously-encountered common coronaviruses (CoVs) is augmented significantly [6]. Given the commonality among the spike glycoproteins of the latter with that of SARS-CoV-2, after COVID-19 vaccination two types of antibodies appear: one against SARS-CoV-2 spike and a group cross-reactive one against common CoVs' spikes. This phenomenon is even much more pronounced in those who had been previously infected with SARS-CoV-2, even though asymptomatically, as well as in those after the second dose of COVID-19 vaccine. Myo-(peri-)carditis has been reported more frequently after the second dose of the RNA-based COVID-19 vaccines [2]. This brings us to the first hypothesis.

Anti-spike antibodies elicited as a result of past exposure to common CoVs and/or to SARS-CoV-2 spike (be it through prior infection or vaccination), may elicit anti-idiotype antibodies, that is, antibodies directed against the paratope region of anti-spike antibodies. Since the latter is the mirror image of the anti-spike antibodies, it may mimic the spike protein itself and bind ACE2 expressed on cardiac pericytes that express ACE2. This forms an immobilized immune complex on the surface of pericytes. This localized immune complex, in turn, may lead to activation of the complement system through its classical pathway and damage to the target cell.

A more likey mechanism is where the vaccine lipid nanoparticles leak from the injection site and enter circulation where injection practices are not very well observed [7]. Then they reach the heart and can be endocytosed by cardiac tissue including cardiac muscle, pericytes, endothelial cells, and macrophages. Local production of spike protein on the surface of cardiac cells and/or its shedding along with detached cell membranes may recruit neutrophils that also express ACE2 on their surface. Spike-activated

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neutrophils produce neutrophil extracellular traps [8] that subsequently activate alternative pathway of complement *in situ*, damaging cardiac endothelial cells. One may ask that these can simply happen anywhere else in the body, however, the simple answer is in the heart itself, because it is a vital organ, since there is not much wiggle room for immunopathology, clinical manifestations are noticed immediately, therefore, any subtle injuries are brought up faster to medical attention.

All in all, this is a rare phenomenon, and following best practices in vaccine administering may aid in mitigating this adverse effect and vaccine hesitancy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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