The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can result in a new disease called long-COVID or post-acute COVID-19 syndrome (PACS). Individuals diagnosed with PACS experience persistent cardiac manifestations, such as palpitations, tachycardia, and exercise intolerance. Several mechanisms are thought to be involved in the pathogenesis of PASC-cardiovascular syndrome (PASC-CVS), including inflammation, immune activation, latent virus reactivation, and microvascular or autonomic nervous system dysfunction. However, the pathophysiological mechanisms underlying PASC-CVS are still unknown. In this study, the authors from China investigated the role of SARS-CoV-2 spike (S) protein in activating cardiac β-adrenergic receptors (β-ARs) as one of the possible mechanisms underlying PASC-CVS.

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus. Its genome encodes four structural proteins, namely the spike (S), envelope (E), nucleocapsid (N), and membrane (M) protein. The S protein is a glycosylated homotrimer with each monomer composed of subunits S1 and S2, separated by host cell proteases. The receptor binding domain (RBD) in the S1 subunit recognizes human angiotensin-converting enzyme 2 (ACE2) and is responsible for attachment to host cells.

Interestingly, in 2021, Yapici-Eser et al. hypothesized that mimicry between human proteins and SARS-CoV-2 proteins may have a role in neurobiological pathways that underlie the manifestations of COVID-19 and long COVID syndrome. They utilized a computational methodology (Host-Microbe Interaction PREDiction Algorithm) and detected that SARS-CoV-2 proteins mimic 12 proteins linked with the muscarinic acetylcholine receptor 1 and 3 signaling pathway, 12 proteins linked with the muscarinic acetylcholine receptor 2 and 4 signaling pathway, 9 proteins linked with the beta1 adrenergic receptor signaling pathway, 9 proteins linked with the beta2 adrenergic receptor signaling pathway, 6 proteins linked with the beta3 adrenergic receptor signaling pathway, 5 proteins linked with the alpha-adrenergic receptor signaling pathway, and many other proteins. (Yapici-Eser et al. Neuropsychiatric Symptoms of COVID-19 Explained by SARS-CoV-2 Proteins' Mimicry of Human Protein. Front Hum Neurosci 2021 15:656313.) https://www.frontiersin.org/journals/human-neuroscience/articles/10.3389/fnhum.2021.656313/full

Additionally, a recent *in vitro* study that investigated the effects of mRNA-1273 and BNT162b2 vaccines on the function, structure, and viability of isolated rat left ventricular cardiomyocytes showed that the BNT162b2 vaccine significantly increased protein kinase A

(PKA) activity, the intensity and dynamics of calcium transients in BNT162b2-treated myocytes, and all contraction parameters tested. The authors stated that cell contraction pattern and sustained PKA activation that developed after the BNT162b2 application were largely consistent with the functional changes found in cardiomyocytes (or myocardium) after the catecholamine stimulation and could correspond histopathologically to catecholamine-induced cardiomyopathy.
https://discovermednews.com/cardiotoxic-effects-mrna-1273-bnt162b2-induce-disturbances-of-contractile-function-in-rat-cardiomyocytes/

About the study

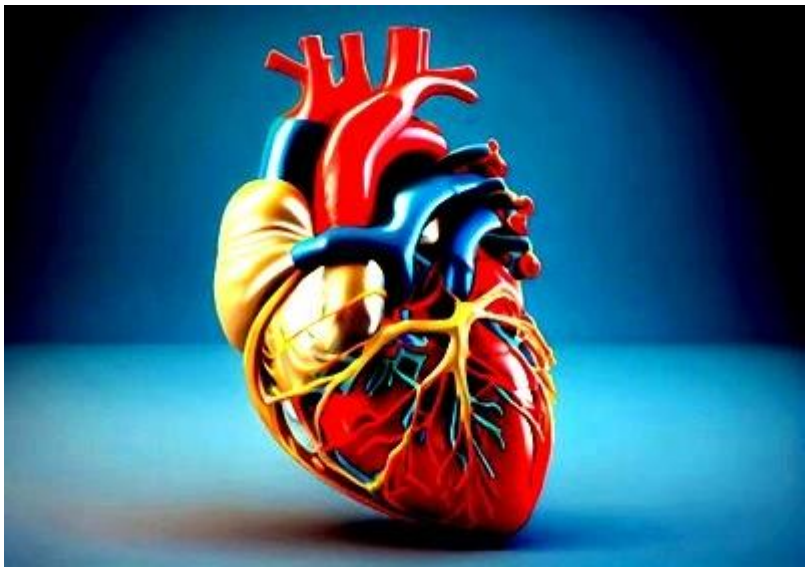
Patients recovered from asymptomatic or mild COVID-19 infection were enrolled in the study 40±10 days after recovery. Current COVID-19 infection, medical history of cardiovascular diseases, antiarrhythmic drug therapy, specifically β-blockers, and severe complications in major organs were the criteria for exclusion.

All participants underwent evaluation, including plasma troponin levels, electrocardiogram (ECG), echocardiography, and coronary computed tomography (CT) angiography. A 24-hour ECG monitoring was performed on patients who were experiencing palpitations. All patients with symptoms of dyspnea, cough, or fatigue underwent chest CT scans to rule out pulmonary diseases.

The resting heart rate (HR), the HR variability (HRV), spectral components, like very low frequency (VLF), low frequency (LF), and high frequency (HF), as well as normalized low frequency (NLF) of HRV were assessed.

Enzyme-linked immunosorbent assay (ELISA) was used to measure plasma levels of the S1 subunit of the SARS-CoV-2 S protein. The microscale thermophoresis (MST) assay was used to investigate the interactions of the S protein with the β-adrenergic receptors β1-AR and β2-AR, and the D1-dopamine receptor (DRD1).

Activation of downstream β-AR signaling, detected by increased cyclic adenosine monophosphate (cAMP) production, and the effects of recombinant S-trimer, epinephrine, METO (β1-AR blocker), and ICI118551 (β2-AR blocker) on cAMP levels were investigated in cultured neonatal mouse cardiomyocytes.



Results

The study included 45 individuals with PASC-CVS, 45 without PASC-CVS (non-PASC-CVS), and 15 healthy controls matched for age, sex, and vaccination status.

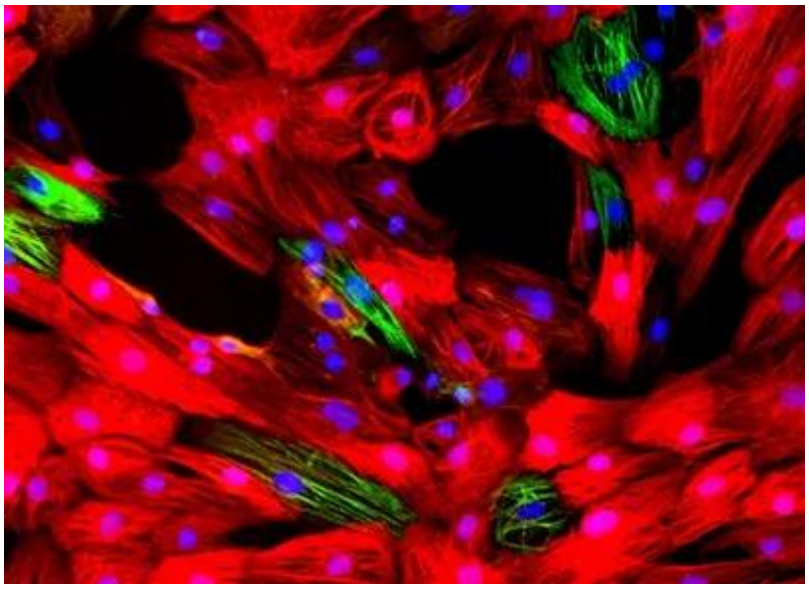
Patients diagnosed with PASC-CVS had significantly higher circulating levels of the S1 subunit of the SARS-CoV-2 S protein compared to individuals without PASC-CVS or healthy controls.

Patients with PASC-CVS also had higher HR and NLF of HRV, which reflect the sympathetic tone, than non-PASC-CVS individuals or healthy controls. Plasma S1 levels positively correlated with HR and NLF. Patients with elevated HR and NLF of HRV had higher plasma S1 levels.

MST assay showed that S-trimers bound to β1- and β2-AR, but not to DRD1, with *K*D values of 21.7 pmol/L and 90.4 nmol/L, respectively. According to the authors, the binding efficiency of S protein to β1-AR, which was significantly higher than that to ACE2, suggests that the accumulation of S protein in the myocardium may lead to activation of cardiac β-ARs. The prolonged β-AR activation may lead to ventricular tachycardia and heart failure.

METO (an β1-AR blocker) and ICI118551 (an β2-AR blocker) blocked the interaction of the S protein with β1- and β2-ARs.

Molecular docking studies and the MST assay of β-AR mutants revealed that the ACE2-binding region in the RBD of the S protein interacted with the extracellular loop 2 (ECL2) of both β-ARs. Because the S protein bound to the same ECL2 region in both β-ARs and the ECL2 region is critical for β-AR activation, the authors proposed that binding of the S protein to the ECL2 region activates cardiac β-ARs in patients with PASC-CVS.



Treatment with recombinant S-trimers activated β-AR downstream signaling in cultured neonatal mouse cardiomyocytes in a dose-dependent manner, as indicated by an increased cyclic adenosine monophosphate (cAMP) production. Pretreatment with METO (an β1-AR blocker) and ICI118551 (an β2-AR blocker) blocked the S protein-induced accumulation of cAMP, suggesting that β-blockers allosterically interfere with S protein binding.

Importantly, the S-trimer increased cAMP production induced by epinephrine in a dose-dependent manner. This suggests that S protein acts as an allosteric β-AR agonist in the presence of epinephrine.

Conclusion

The authors noted that this study is the first to show that the SARS-CoV-2 spike protein acts as an allosteric agonist of β1- and β2 adrenergic receptors. It activates β-adrenergic receptors in cardiomyocytes and contributes to cardiac sympathetic hyperactivity. In addition, the S protein increased activation of downstream β-AR signaling induced by epinephrine. Since the activation of β-AR downstream signaling induced by the S protein was blocked by treatment with β1- and β2-AR blockers, it explains the efficacy of β-blocker therapy for symptomatic relief in individuals diagnosed with PASC-CVS.

Of note, a recent study that analyzed differences in autoantibodies against receptors involved in autonomic regulation between individuals diagnosed with post-COVID-19 vaccination syndrome (PCVS) and vaccinated healthy subjects found higher levels of autoantibodies against six receptors, including β2 adrenergic receptors in individuals with PCVS.
https://discovermednews.com/autoantibodies-against-elements-of-autonomic-regulation-post-covid-vaccination-syndrome/

As sustained β-AR activation may lead to ventricular tachycardia and heart failure, the authors of the present study concluded that blocking the interaction between the S protein and the β-ARs may have potential for the treatment of cardiovascular symptoms in patients with long-COVID.

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Journal Reference

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