How Does COVID-19 Affect The Heart? New Clues Arise

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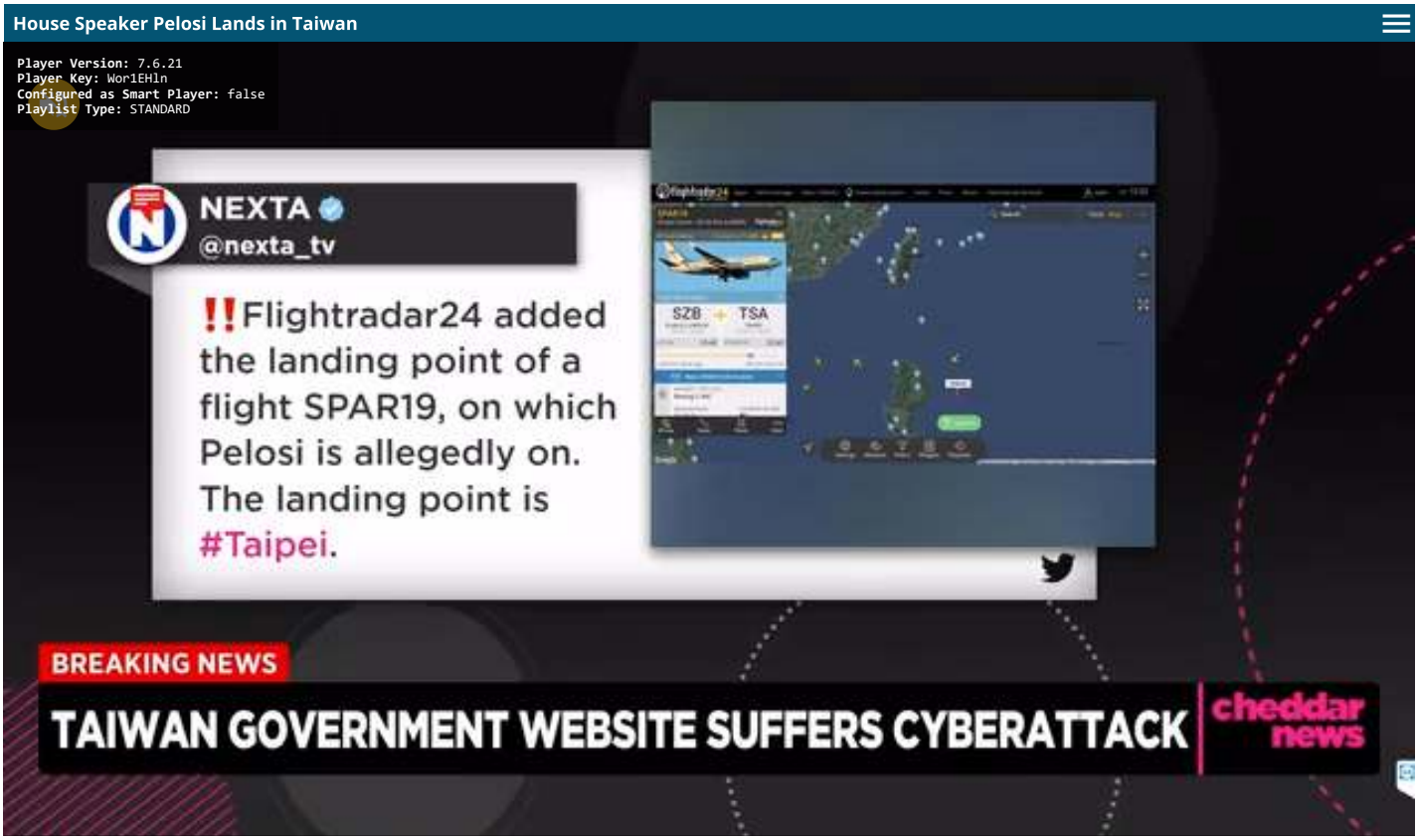
Studies show that up to 62% of patients hospitalized with COVID-19 experience cardiac injury.



Other research shows that individuals who have contracted COVID-19- even if they were not hospitalized- are at an increased risk of cardiovascular conditions.

Knowing more about how SARS-CoV-2 affects the heart could help develop new treatments to protect cardiac health.

Recently, researchers conducted a series of experiments that suggested SARS-CoV-2's spike protein can lead to heart muscle injury through an inflammatory process.

"It's already known from the clinical side that COVID-19 infection can induce heart injury, however, what we don't know is the mechanistic details of how this occurs. What we suspect is that the spike protein has unknown pathological roles," said Dr. Zhiqiang Lin, lead author of the study and an assistant professor at the Masonic Medical Research Institute in Utica, New York.

"Our data show that the spike protein from SARS-CoV-2 causes heart muscle damage. That's why it's important to get vaccinated and prevent this disease," he added.

The researchers presented their findings at the American Heart Association's Basic Cardiovascular Sciences Scientific Sessions 2022.

The role of the spike protein

SARS-CoV-2 enters healthy cells via its spike protein, located on its surface. The spike protein works by latching onto receptors known as angiotensin-converting enzyme 2 (ACE2) on healthy cells, so it may then enter them.

HCoV-NL63 is also a coronavirus that enters cells by attaching to ACE2 receptors. While it causes moderate respiratory symptoms, it does not lead to cardiac injury.

"Host natural immunity is the first line of defense against pathogen invasion, and heart muscle cells have their own natural immune machinery. Activation of the body's immune response is essential for fighting against virus infection; however, this may also impair heart muscle cell function and even lead to cell death and heart failure," explained Dr. Lin.

In the present study, the researchers hypothesized that SARS-CoV-2 may damage the heart via immune responses that are independent of ACE2. To test their hypothesis, they compared the ability of both viruses to cause cardiac injury.

They found that while SARS-CoV-2 activated the TLR4 signaling pathway — a major part of the natural immune response — while HCov-NL63 did not.

To understand more about how activation of TLR4 signaling may affect the heart, the researchers cloned the SARS-CoV-2 spike protein and the NL63 spike protein, and delivered them to mice via an adeno-associated viral vector.

They found that the SARS-CoV-2 spike protein, and not the NL63 protein, led to heart dysfunction, hypertrophic remodeling— or in other words, cellular enlargement—and cardiac inflammation.

In vitro experiments with rat cardiac muscle cells also led to hypertrophic remodeling and increased levels of inflammatory markers.

Heart damage from the spike protein

The researchers next examined heart biopsies from a deceased patient with COVID-19-associated myocarditis, a patient who died of mRNA-vaccine-associated myocarditis, and a healthy heart. Myocarditis occurs when the heart muscle becomes inflamed.

Whereas both the spike protein and the TLR4 protein were detected in cardiac muscle cells and other cell types in the COVID-19 patient, neither protein was detected in the healthy heart.

"That means once the heart is infected with SARS-CoV-2, it will activate TLR4 signaling. Besides directly damaging the heart muscle cells, the spike protein itself is very inflammatory and may cause systemic inflammation that indirectly causes heart problems," noted Dr. Lin.

Meanwhile, the researchers detected only a small fraction of spike protein in the cardiac muscle cells of the mRNA vaccine patient and no obvious signs of TLR4.

This, they noted, means that mRNA vaccines are unlikely to cause myocarditis via cardiac muscle cells.

The researchers concluded that the SARS-CoV-2 spike protein might damage the heart via TLR4 inflammatory pathways, independently of ACE2.

Study limitations

When asked about possible limitations to the study, Dr. Ziyad Al-Aly, chief of research and development at VA Saint Louis Health Care System, told *MNT*: "This is preliminary data in the form of an abstract, so it is hard to evaluate without seeing the full paper. Having said that, I think this line of inquiry is important to help us understand how SARS-CoV-2 affects the heart, and what role, if any, spike proteins may play."

"It also helps us understand what the mechanisms of injury may be. Understanding these mechanisms will help design preventive and therapeutic strategies," he added.

Dr. James Lo, assistant professor at Weill Cornell Medicine Graduate School of Medical Sciences, agreed that it is difficult to comment on the study's limitations without seeing the full paper.

He nevertheless called the findings "intriguing," and noted:

> *"WHAT IS STILL UNKNOWN IS HOW THE SPIKE PROTEIN WOULD ACTIVATE INFLAMMATORY PATHWAYS SUCH AS TLR4. WE STILL HAVE A LONG WAY TO GO IN TERMS OF UNDERSTANDING WHY A SMALL MINORITY OF PATIENTS WITH COVID-19 DEVELOP CARDIAC INJURY OR MYOCARDITIS."*

Moving forward, the researchers intend to investigate how SARS-CoV-2 spike proteins cause inflammation in the heart.

So far, they have outlined two potential ways this may happen. The first possibility is that the spike protein directly activates inflammation in virus-infected heart muscle cells.

The second possibility is that the spike protein is shed into the bloodstream and damages the heart as it circulates.

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