Medical News & Perspectives

Researchers Investigate What COVID-19 Does to the Heart

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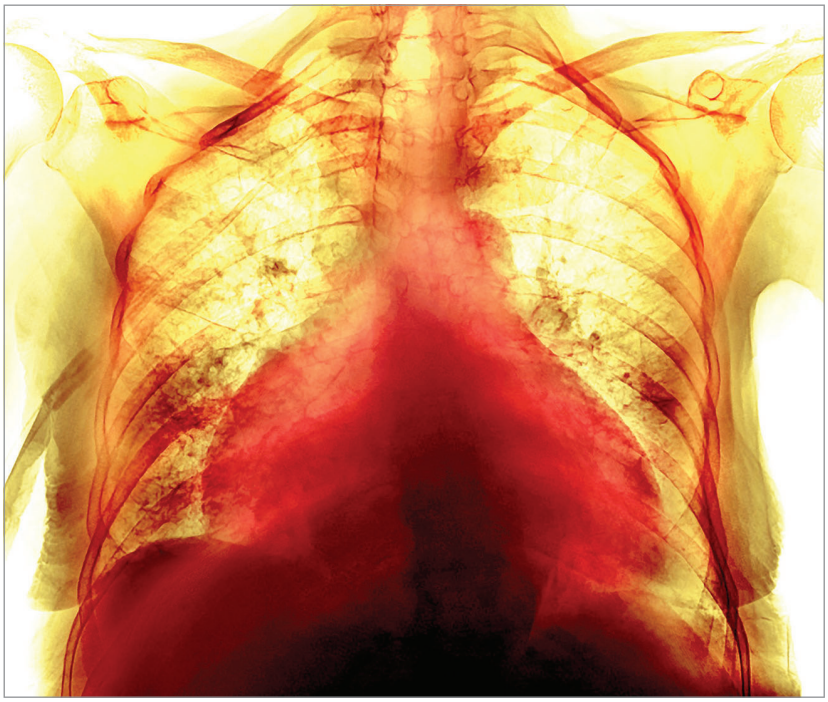


Philip Marazzi, MD/sciencesource.com

The first sign of heart damage was in their blood. In early case reports from Wuhan, China, where the novel coronavirus emerged, an unexpected number of patients hospitalized with the respiratory infection had elevated levels of cardiac troponin, a marker of myocardial—heart muscle—injury. Next came the echocardiograms suggesting functional abnormalities in many patients' hearts. Soon it was obvious that myocardial injury heralded poor prognosis for patients hospitalized with coronavirus disease 2019 (COVID-19).

Multimedia

"It was quite clear that people that came into the hospital sick that had heart injury were the ones that were at greatest risk of requiring mechanical ventilation and, ultimately, at the greatest risk of dying," said Aaron Baggish, MD, director of the cardiovascular performance program at Massachusetts General Hospital.

It wasn't surprising that patients with preexisting cardiovascular issues—prior heart failure, coronary artery disease, hypertension—were more likely to fare poorly, based on other respiratory illnesses. But so were those without a history of heart problems who had elevated troponin levels.

Physicians and scientists wondered then, as now: How common is heart injury across the spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, from asymptomatic cases to critical disease?

Researchers are also working to explain the cardiac damage, with recent attention shifting from viral myocarditis to systemic inflammation. But experts said that the most important question is the clinical one: What will COVID-19–associated heart injury mean, over the short-term and long-term, for the tens of millions of people around the world infected with the virus?

A Usual Suspect

Early in the pandemic, as reports documented elevated troponin levels in severe COVID-19 cases, suspicion quickly turned to myocarditis, an inflammatory disease in the heart muscle. Most often triggered by a virus, myocarditis usually resolves on its own as the infection wanes. But it can cause serious acute outcomes, including arrhythmias, heart failure, cardiac arrest, and sudden death.

Although a few case reports have emerged of fulminant myocarditis with cardiogenic shock—the most sudden and extreme form—during acute SARS-CoV-2 infection, the finding has been rare. Arrhythmias, which can be fatal, appear to be more common among hospitalized patients, although it's unclear how frequently they're related to myocarditis. Some reports have also included heart failure.

The effects of cardiac inflammation in COVID-19 are wide-ranging and, for some, appear to be the infection's main feature. In March, physicians in Italy determined that inflammation of the heart muscle and sac, known as myopericarditis, was likely behind extreme fatigue in an otherwise healthy 53-year-old woman with a positive SARS-CoV-2 test who had mild respiratory symptoms and fever a week earlier.

Experts haven't reached consensus on how long viral myocarditis takes to resolve, in part because sophisticated imaging tools and protocols for accurately diagnosing it are relatively new; in addition, the duration of clinical symptoms may not match serological or imaging biomarkers. This unknown has made it hard to interpret some findings from recovered patients.

A study published in May, for example, examined 26 patients discharged from a Wuhan hospital after recovering from moderate to severe COVID-19. The patients had had symptoms including chest pain and palpitations for a median of 47 days by the time they underwent cardiac magnetic resonance (CMR) imaging. Fourteen patients had edema—fluid retention, which is the key sign of active inflammation on CMR. Many of them also had indicators of scarring and decreased right ventricle function.

The most alarming report to suggest lingering heart injury appeared in July in *JAMA Cardiology*. Researchers in Germany

examined data from 100 patients thought to have recovered based on a negative nasal swab. Two to 3 months after their COVID-19 diagnosis, 60 of the individuals had indications of myocardial inflammation on CMR, and even more had elevated troponin levels. Three individuals with severe abnormalities underwent biopsies that confirmed active inflammation in their heart muscle tissue. Compared with a control group, the recovered patients had greater left ventricular volume and lower ejection fraction, signs that their hearts were enlarged and pumping less efficiently.

A few things besides the frequency of aberrations were cause for concern. Unlike the study published in May, two-thirds of patients in this report didn't require hospitalization, and some were even asymptomatic. What's more, the patients were relatively young (49 years old, on average), and their COVID-19 severity, preexisting health conditions, and time since diagnosis didn't affect their likelihood of having an abnormal heart scan.

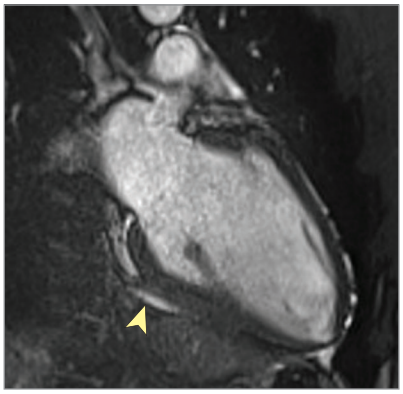
The results suggested that scores of otherwise healthy people who recovered from COVID-19—even those who didn't get very sick—could have potentially harmful inflammation smoldering in their hearts months later.

The health implications are still an open question. "This may be clinically inconsequential, or it could lead to chronic effects," Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), said of the findings at an American Heart Association (AHA) conference in November.

Connie Tsao, MD, MPH, who directs clinical CMR research at the Beth Israel Deaconess Medical Center in Boston, agreed. "The detection of findings on cardiovascular imaging does not always directly translate to clinical symptoms, either acutely or chronically," she cautioned in an email.

Sports in the Spotlight

In September, another imaging report grabbed headlines. It investigated myocarditis among younger recovered individuals. Of 26 male and female competitive athletes at The Ohio State University, 4 had CMR findings consistent with myocarditis and 8 others had evidence of scarring on their hearts, although none had elevated troponin levels. All the players in the study, which was published in *JAMA Cardiology*, had asymptomatic or nonsevere SARS-CoV-2 infections and were scanned 11 to 53 days after quarantining for 2 weeks.



Cardiac magnetic resonance imaging shows pericardial effusion (indicated by arrow) in an Ohio State University competitive athlete recovering from coronavirus disease 2019.

In a blog post, National Institutes of Health Director Francis Collins, MD, PhD, said the results raised concerns despite the study's small size. The findings, he noted, "add more evidence" to the German study "that suggested subtle cardiac consequences of SARS-CoV-2 infection may be common in adults."

Those consequences could be fatal during physical activity, which puts a strain on the heart. Myocarditis, while not frequent, triggers up to 12% of sudden cardiac deaths among young adults and is an established cause of death for competitive athletes. Over the past year, sports cardiologists like Baggish, who works with the New England Patriots and several other professional, college, and Olympic teams, worried about athletes with COVID-19 getting back in the game too soon. To protect athletes, the American College of Cardiology (ACC) published COVID-19 return-to-play guidelines in May, which recommended cardiac imaging and other tests before they could resume sports.

Myocarditis has sidelined some players during the pandemic, including Boston Red Sox pitcher Eduardo Rodriguez, whose condition was discovered on a scan in July. But Baggish said he hasn't seen a lot of concerning heart profiles among athletes who had very mild COVID-19.

"What we saw in June, July, and August when professional sports came back online, and followed closely thereafter by college, is that we were doing a lot of testing and we weren't finding much," he said. "The people we were finding things in…were the ones that were really sick with COVID infection—sick enough to be home in bed for several days or hospitalized." Based on that, updated ACC guidelines, which Baggish helped revise, reserve return-to-play cardiac testing for athletes who had moderate or severe infections.

Baggish and collaborators at the University of Washington, along with the AHA and the American Medical Society for Sports Medicine, have launched the Outcomes Registry for Cardiac Conditions in Athletes to track National Collegiate Athletic Association players' heart health and fitness as they return to sports after a COVID-19 diagnosis. "I think, within the next several months, we're going to see studies that really help us to define whether or not we have a problem or whether this was a lot of smoke and very little fire," he said.

Recent data from one Big Ten Conference school suggests the latter. In January, University of Wisconsin-Madison athletics reported that only 2 of its 145 student athletes recovering from asymptomatic to moderate COVID-19 had myocarditis based on CMR.

A Red Herring?

In fact, data from endomyocardial biopsies and autopsies suggest that virus-mediated myocarditis—which requires an infection in the myocardium for pathological diagnosis—may not be common in COVID-19. "It turns out there's a lot less myocarditis than we originally thought there would be," Northwestern Medicine cardiologist Donald Lloyd-Jones, MD, president-elect of the AHA, said in an interview.

To confirm viral myocarditis in a patient's heart, a pathologist typically looks for the virus, as well as specific immune cells and injured heart muscle cells. Although RNA from SARS-CoV-2 has been detected in hearts, this combination of infection, immune response, and damaged myocytes has not been frequent.

In one report, a substantial amount of the virus was found in 16 of 39 autopsied hearts, but although 15 of the organs had increased proinflammatory genes, none had immune cells indicative of myocarditis. "Whether changes in gene expression might translate into inflammation later on needs to be studied," the study's senior

JAMA Cardiology. 2021;6(1):116-118.

author, Dirk Westermann, MD, of the University Heart & Vascular Centre Hamburg, said in an email.

Even some autopsy-confirmed cases likely were not true myocarditis, according to a review of published reports. Some pathologists may not use sufficiently strict criteria because no formal myocarditis definition for autopsies exists, the authors said. Published clinical and imaging studies that suggested SARS-CoV-2 myocarditis was common may have also biased pathologists' findings.

Experts have noted that the CMR studies themselves have been small and may not reflect the broader population of COVID-19 survivors. Without the benefit of data from baseline scans, it's possible that intense training, not COVID-19, explains the Ohio State players' scarring, for example.

As for the German study, the participants weren't randomly selected. Many of them experienced shortness of breath, exhaustion, heart palpitations, and chest pain, which may have led them to volunteer for imaging. That means the study may have skewed toward patients with cardiac manifestations.

A critical editorial in *Circulation* also pointed out an overlap in the range of inflammation-related imaging values among the recovered COVID-19 patients and a control group with similar risk factors in the study. For most of the patients, "they were very mild abnormalities," Patricia Bandettini, MD, a senior research physician at the National Heart, Lung, and Blood Institute, confirmed. "But," she added, "that doesn't mean that they weren't real."

It also isn't known how these studies' troponin and CMR findings compare with other viral infections or acute illnesses for which such tests aren't routinely conducted, the editorialists noted. Michael Sneller, MD, an immunoregulation researcher at the NIAID, said he'd like to use CMR to investigate how many patients who have recovered from influenza have signs of heart inflammation. "I wish I could see if this is anything specific for this coronavirus or whether it's something that you can see with any virus," he said.

Matthias Friedrich, MD, chief of cardiovascular imaging at the McGill University Health Centre in Montreal, said there is something unique about the novel coronavirus: its affinity for the angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 is found on cells in the lungs, heart, and other organs and on endothelial cells lining the body's blood vessels. When SARS-CoV-2 binds to ACE2 to gain cell entry, it blocks many of the receptor's functions, such as maintaining appropriate vascular permeability.

During a bout with COVID-19, ACE2 is downregulated, Friedrich explained. Blood vessels, including in the heart, become more permeable, allowing excess fluid to flow into the myocardium's interstitial space. According to Friedrich, mild edema is a common CMR finding in published reports and among COVID-19 outpatients he is studying. Both leaky blood vessels and systemic inflammation can cause the swelling, which in some cases has lasted as long as 12 weeks. "Edema probably plays a huge role in cardiac injury in COVID," he said, and could help to explain some patients' ongoing fatigue.

If leaky blood vessels cause edema, dexamethasone, which maintains the endothelial cell barrier and is used to reduce brain swelling, has the potential to help, Friedrich said. In a recent article, he and colleagues hypothesized that the glucocorticoid's ability to treat edema in tissues including the myocardium could, in part, explain how it reduced mortality among hospitalized patients receiving respiratory support in a recent practice-changing COVID-19 trial.

Many Culprits

In December, a case report described elevated troponin, severely depressed left ventricular systolic function, and heart failure symptoms associated with SARS-CoV-2 infection in a 2-month-old infant, who survived the illness. "We think it was acute viral myocarditis that caused heart failure in this baby," Madhu Sharma, MD, an attending pediatric cardiologist who treated the patient at the Children's Hospital at Montefiore in the Bronx, said in an email.

Although direct infection like this can occur, many experts now believe that systemic inflammation originating from the infected lungs or blood vessels, not myocyte infection, explains most myocardial injury findings among patients hospitalized with COVID-19. Immune cell messengers called cytokines circulating through the body could induce heart muscle inflammation. Systemic inflammation could also trigger arrhythmias and destabilize coronary plaques, leading to plaque rupture and type 1 myocardial infarction (MI), or heart attack—the most common cause of elevated troponins.

A recent study involving Rhesus macaques supports the role of systemic inflammation. Researchers at Emory University led by cardiologist Rebecca Levit, MD, discovered more scar tissue in the hearts of monkeys they infected with SARS-CoV-2 two weeks prior than in an uninfected control group. Yet they detected no virus or white blood cells in the infected monkeys' hearts.

"We hypothesize that support cells in the heart, fibroblast, may be responding to the systemic inflammation," Levit said in an email. "The activation of these cells may lead to fibrosis."

Additionally, several other COVID-19 manifestations could injure the heart muscle, including an oxygen supply-and-demand imbalance in the heart (type 2 MI), blood clots, sepsis, stress-induced cardiomyopathy, and multisystem inflammatory syndrome. Troponin levels could also represent COVID-19 severity because a critical illness can hasten preexisting cardiovascular disease.

Sorting out the source of myocardial injury could steer treatments to safeguard the heart. Going forward, novel research tools like stem cell–derived cardiovascular cells will be used to model how SARS-CoV-2 infection causes cardiac damage. Researchers have begun to infect these lab-grown cells to understand the precise mechanisms of heart cell injury.

One such study found that SARS-CoV-2 is toxic to stem cell-derived cardiomyocytes. "Our goal is to molecularly define this cytotoxicity to develop specific cardioprotective therapeutics," researcher Melanie Ott, MD, PhD, director of the Gladstone Institute of Virology in San Francisco, said in an email. "Protecting the heart from direct or indirect effects of the infection appears more and more important."

Tracking Survivors

Researchers are eager to learn what the elevated troponin levels and abnormal imaging findings will mean for patients in the months and years to come—if anything.

New-onset chronic heart failure is one concern. Pumping problems aren't widespread among hospitalized patients, although some studies have identified left

ventricular systolic dysfunction in some of them. There's also evidence of right ventricular abnormalities and left ventricular diastolic dysfunction, which could increase the risk of heart failure with preserved ejection fraction among survivors of severe COVID-19. One study of hospitalized patients with elevated troponin levels discovered high rates of myocarditis-like scarring without edema about a month after they were discharged, a finding that suggests the scars may be permanent.

Some fear that even among patients with milder infections, sustained inflammation could cause future problems like scarring, arrhythmias, and heart failure, but only time will tell. If prolonged, as the German study suggests it can be after SARS-CoV-2 infection, edema could lead to irreversible fibrosis, which "translates into patients with heart failure, 5, 10, 15, 20 years down the road from now," Friedrich said.

In the meantime, many cardiologists suspect that heart abnormalities could contribute to the COVID-19 "long haulers'" lingering symptoms—fatigue, shortness of breath, chest tightness, and heart palpitations. "I'm convinced that it's at least a component," Jeanette Schulz-Menger, MD, a cardiologist at Charité University Medicine and the Helios Clinics, both in Berlin, Germany, said in an interview.

Levit is of a similar mind. "We're seeing clinically that a lot of patients, even months after they recover, are still having shortness of breath and fatigue, and of course there may be lung pathology that is contributing to that," she said. "But I'm worried that potentially there's cardiac toxicity that could be affecting these patients for a long time. Typically, if there's fibrosis in the heart, it doesn't resolve."

Research under way in centers around the world could begin to answer these questions. "We certainly are struggling with understanding what's the underlying mechanism for these COVID long haulers," Lloyd-Jones said. "I think we do want to understand a little bit more about whether there's ongoing targeted inflammation in the myocardium or secondary bystander types of inflammation that may be contributing to those syndromes."

Sneller is the principal investigator of a study that will track the health of hundreds of COVID-19 survivors and a control group over the next 3 years. He said he expects to have data from the first 100 enrollees early this spring. Bandettini, a collaborator, is overseeing CMR imaging to detect inflammation, decreased blood flow, and other changes in the heart muscle. "Will this translate into something in the future? I don't think we know that for sure," she said. ■

Note: Source references are available through embedded hyperlinks in the article text online.