Coronavirus May Be a Vascular Disease, Which Explains Everything

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Coronavirus May Be a Blood Vessel Disease, Which Explains Everything

Many of the infection's bizarre symptoms have one thing in common

In April, blood clots emerged as one of the many mysterious symptoms attributed to Covid-19, a disease that had initially been thought to largely affect the lungs in the form of pneumonia. Quickly after came reports of young people dying due to coronavirus-related strokes. Next it was Covid toes — painful red or purple digits.

What do all of these symptoms have in common? An impairment in blood circulation. Add in the fact that 40% of deaths from Covid-19 are related to cardiovascular complications, and the disease starts to look like a vascular infection instead of a purely respiratory one.

Months into the pandemic, there is now a growing body of evidence to support the theory that the novel coronavirus can infect blood vessels, which could explain not only the high prevalence of blood clots, strokes, and heart attacks, but also provide an answer for the diverse set of head-to-toe symptoms that have emerged.

"All these Covid-associated complications were a mystery. We see blood clotting, we see kidney damage, we see inflammation of the heart, we see stroke, we see encephalitis [swelling of the brain]," says William Li, MD, president of the Angiogenesis Foundation. "A whole myriad of seemingly unconnected phenomena that you do not normally see with SARS or H1N1 or, frankly, most infectious diseases."

"If you start to put all of the data together that's emerging, it turns out that this virus is probably a vasculotropic virus, meaning that it affects the [blood vessels]," says Mandeep Mehra, MD, medical director of the Brigham and Women's Hospital Heart and Vascular Center.

In a paper published in April in the scientific journal *The Lancet*, Mehra and a team of scientists discovered that the SARS-CoV-2 virus can infect the endothelial cells that line the inside of blood vessels. Endothelial cells protect the cardiovascular system, and they release proteins that influence everything from blood clotting to the immune response. In the paper, the scientists showed damage to endothelial cells in the lungs, heart, kidneys, liver, and intestines in people with Covid-19.

“The concept that’s emerging is that this is not a respiratory illness alone, this is a respiratory illness to start with, but it is actually a vascular illness that kills people through its involvement of the vasculature,” says Mehra.

> A respiratory virus infecting blood cells and circulating through the body is virtually unheard of.

A one-of-a-kind respiratory virus

SARS-CoV-2 is thought to enter the body through ACE2 receptors present on the surface of cells that line the respiratory tract in the nose and throat. Once in the lungs, the virus appears to move from the alveoli, the air sacs in the lung, into the blood vessels, which are also rich in ACE2 receptors.

“[The virus] enters the lung, it destroys the lung tissue, and people start coughing. The destruction of the lung tissue breaks open some blood vessels,” Mehra explains. “Then it starts to infect endothelial cell after endothelial cell, creates a local immune response, and inflames the endothelium.”

A respiratory virus infecting blood cells and circulating through the body is virtually unheard of. Influenza viruses like H1N1 are not known to do this, and the original SARS virus, a sister coronavirus to the current infection, did not spread past the lung. Other types of viruses, such as Ebola or Dengue, can damage endothelial cells, but they are very different from viruses that typically infect the lungs.

Benhur Lee, MD, a professor of microbiology at the Icahn School of Medicine at Mount Sinai, says the difference between SARS and SARS-CoV-2 likely stems from an extra protein each of the viruses requires to activate and spread. Although both viruses dock onto cells through ACE2 receptors, another protein is needed to crack open the virus so its genetic material can get into the infected cell. The additional protein the original SARS virus requires is only present in lung tissue, but the protein for SARS-CoV-2 to activate is present in all cells, especially endothelial cells.

“In SARS1, the protein that’s required to cleave it is likely present only in the lung environment, so that’s where it can replicate. To my knowledge, it doesn’t really go systemic,” Lee says. “[SARS-CoV-2] is cleaved by a protein called furin, and that’s a big danger because furin is present in all our cells, it’s ubiquitous.”

Endothelial damage could explain the virus' weird symptoms

An infection of the blood vessels would explain many of the weird tendencies of the novel coronavirus, like the high rates of blood clots. Endothelial cells help regulate clot formation by sending out proteins that turn the coagulation system on or off. The cells also help ensure that blood flows smoothly and doesn't get caught on any rough edges on the blood vessel walls.

"The endothelial cell layer is in part responsible for [clot] regulation, it inhibits clot formation through a variety of ways," says Sanjum Sethi, MD, MPH, an interventional cardiologist at Columbia University Irving Medical Center. "If that's disrupted, you could see why that may potentially promote clot formation."

Endothelial damage might account for the high rates of cardiovascular damage and seemingly spontaneous heart attacks in people with Covid-19, too. Damage to endothelial cells causes inflammation in the blood vessels, and that can cause any plaque that's accumulated to rupture, causing a heart attack. This means anyone who has plaque in their blood vessels that might normally have remained stable or been controlled with medication is suddenly at a much higher risk for a heart attack.

"Inflammation and endothelial dysfunction promote plaque rupture," Sethi says. "Endothelial dysfunction is linked towards worse heart outcomes, in particular myocardial infarction or heart attack."

Blood vessel damage could also explain why people with pre-existing conditions like high blood pressure, high cholesterol, diabetes, and heart disease are at a higher risk for severe complications from a virus that's supposed to just infect the lungs. All of those diseases cause endothelial cell dysfunction, and the additional damage and inflammation in the blood vessels caused by the infection could push them over the edge and cause serious problems.

The theory could even solve the mystery of why ventilation often isn't enough to help many Covid-19 patients breathe better. Moving air into the lungs, which ventilators help with, is only one part of the equation. The exchange of oxygen and carbon dioxide in the blood is just as important to provide the rest of the body with oxygen, and that process relies on functioning blood vessels in the lungs.

"If you have blood clots within the blood vessels that are required for complete oxygen exchange, even if you're moving air in and out of the airways, [if] the circulation is blocked, the full benefits of mechanical ventilatory support are somewhat thwarted," says Li.

A new paper published last week in the *New England Journal of Medicine*, on which Li is a co-author, found widespread evidence of blood clots and infection in the endothelial cells in the lungs of people who died from Covid-19. This was in stark contrast to people

who died from H1N1, who had nine times fewer blood clots in the lungs. Even the structure of the blood vessels was different in the Covid-19 lungs, with many more new branches that likely formed after the original blood vessels were damaged.

“We saw blood clots everywhere,” Li says. “We were observing virus particles filling up the endothelial cell like filling up a gumball machine. The endothelial cell swells and the cell membrane starts to break down, and now you have a layer of injured endothelium.”

Finally, infection of the blood vessels may be how the virus travels through the body and infects other organs — something that’s atypical of respiratory infections.

“Endothelial cells connect the entire circulation [system], 60,000 miles worth of blood vessels throughout our body,” says Li. “Is this one way that Covid-19 can impact the brain, the heart, the Covid toe? Does SARS-CoV-2 traffic itself through the endothelial cells or get into the bloodstream this way? We don’t know the answer to that.”

> In another paper that looked at nearly 9,000 people with Covid-19, Mehra showed that the use of statins and ACE inhibitors were linked to higher rates of survival.

If Covid-19 is a vascular disease, the best antiviral therapy might not be antiviral therapy

An alternative theory is that the blood clotting and symptoms in other organs are caused by inflammation in the body due to an over-reactive immune response — the so-called cytokine storm. This inflammatory reaction can occur in other respiratory illnesses and severe cases of pneumonia, which is why the initial reports of blood clots, heart complications, and neurological symptoms didn’t sound the alarm bells. However, the magnitude of the problems seen with Covid-19 appear to go beyond the inflammation experienced in other respiratory infections.

“There is some increased propensity, we think, of clotting happening with these [other] viruses. I think inflammation in general promotes that,” Sethi says. “Is this over and above or unique for SARS-CoV-2, or is that just because [the infection] is just that much more severe? I think those are all really good questions that unfortunately we don’t have the answer to yet.”

Anecdotally, Sethi says the number of requests he received as the director of the pulmonary embolism response team, which deals with blood clots in the lungs, in April 2020 was two to three times the number in April 2019. The question he’s now trying to answer is whether that’s because there were simply more patients at the hospital during that month, the peak of the pandemic, or if Covid-19 patients really do have a higher risk for blood clots.

“I suspect from what we see and what our preliminary data show is that this virus has an additional risk factor for blood clots, but I can’t prove that yet,” Sethi says.

The good news is that if Covid-19 is a vascular disease, there are existing drugs that can help protect against endothelial cell damage. In another *New England Journal of Medicine* paper that looked at nearly 9,000 people with Covid-19, Mehra showed that the use of statins and ACE inhibitors were linked to higher rates of survival. Statins reduce the risk of heart attacks not only by lowering cholesterol or preventing plaque, they also stabilize existing plaque, meaning they're less likely to rupture if someone is on the drugs.

"It turns out that both statins and ACE inhibitors are extremely protective on vascular dysfunction," Mehra says. "Most of their benefit in the continuum of cardiovascular illness — be it high blood pressure, be it stroke, be it heart attack, be it arrhythmia, be it heart failure — in any situation the mechanism by which they protect the cardiovascular system starts with their ability to stabilize the endothelial cells."

Mehra continues, "What we're saying is that maybe the best antiviral therapy is not actually an antiviral therapy. The best therapy might actually be a drug that stabilizes the vascular endothelial. We're building a drastically different concept."