A Supercomputer Analyzed Covid-19 — and an Interesting New Theory Has Emerged

A closer look at the Bradykinin hypothesis

Earlier this summer, the Summit supercomputer at Oak Ridge National Lab in Tennessee set about crunching data on more than 40,000 genes from 17,000 genetic samples in an effort to better understand Covid-19. Summit is the second-fastest computer in the world, but the process — which involved analyzing 2.5 billion genetic combinations — still took more than a week.

When Summit was done, researchers analyzed the results. It was, in the words of Dr. Daniel Jacobson, lead researcher and chief scientist for computational systems biology at Oak Ridge, a "eureka moment." The computer had revealed a new theory about how Covid-19 impacts the body: the bradykinin hypothesis.

The hypothesis provides a model that explains many aspects of Covid-19, including some of its most bizarre symptoms. It also suggests 10-plus potential treatments, many of which are already FDA approved. Jacobson's group published their results in a paper in the journal *eLife* in early July.

According to the team's findings, a Covid-19 infection generally begins when the virus enters the body through ACE2 receptors in the nose, (The receptors, which the virus is known to target, are abundant there.) The virus then proceeds through the body, entering cells in other places where ACE2 is also present: the intestines, kidneys, and heart. This likely accounts for at least some of the disease's cardiac and GI symptoms.

But once Covid-19 has established itself in the body, things start to get really interesting. According to Jacobson's group, the data Summit analyzed shows that Covid-19 isn't content to simply infect cells that already express lots of ACE2 receptors. Instead, it actively hijacks the body's own systems, tricking it into upregulating ACE2 receptors in places where they're usually expressed at low or medium levels, including the lungs.

In this sense, Covid-19 is like a burglar who slips in your unlocked second-floor window and starts to ransack your house. Once inside, though, they don't just take your stuff — they also throw open all your doors and windows so their accomplices can rush in and help pillage more efficiently.

The renin–angiotensin system (RAS) controls many aspects of the circulatory system, including the body's levels of a chemical called bradykinin, which normally helps to regulate blood pressure. According to the

team's analysis, when the virus tweaks the RAS, it causes the body's mechanisms for regulating bradykinin to go haywire. Bradykinin receptors are resensitized, and the body also stops effectively breaking down bradykinin. (ACE normally degrades bradykinin, but when the virus downregulates it, it can't do this as effectively.)

The end result, the researchers say, is to release a bradykinin storm — a massive, runaway buildup of bradykinin in the body. According to the bradykinin hypothesis, it's this storm that is ultimately responsible for many of Covid-19's deadly effects. Jacobson's team says in their paper that "the pathology of Covid-19 is likely the result of Bradykinin Storms rather than cytokine storms," which had been previously identified in Covid-19 patients, but that "the two may be intricately linked." Other papers had previously identified bradykinin storms as a possible cause of Covid-19's pathologies.

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As bradykinin builds up in the body, it dramatically increases vascular permeability. In short, it makes your blood vessels leaky. This aligns with recent clinical data, which increasingly views Covid-19 primarily as a vascular disease, rather than a respiratory one. But Covid-19 still has a massive effect on the lungs. As blood vessels start to leak due to a bradykinin storm, the researchers say, the lungs can fill with fluid. Immune cells also leak out into the lungs, Jacobson's team found, causing inflammation.

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And Covid-19 has another especially insidious trick. Through another pathway, the team's data shows, it increases production of hyaluronic acid (HLA) in the lungs. HLA is often used in soaps and lotions for its ability to absorb more than 1,000 times its weight in fluid. When it combines with fluid leaking into the lungs, the results are disastrous: It forms a hydrogel, which can fill the lungs in some patients. According to Jacobson, once this happens, "it's like trying to breathe through Jell-O."

This may explain why ventilators have proven less effective in treating advanced Covid-19 than doctors originally expected, based on experiences with other viruses. "It reaches a point where regardless of how much oxygen you pump in, it doesn't matter, because the alveoli in the lungs are filled with this hydrogel," Jacobson says. "The lungs become like a water balloon." Patients can suffocate even while receiving full breathing support.

The bradykinin hypothesis also extends to many of Covid-19's effects on the heart. About one in five hospitalized Covid-19 patients have damage to their hearts, even if they never had cardiac issues before. Some of this is likely due to the virus infecting the heart directly through its ACE2 receptors. But the RAS also controls aspects of cardiac contractions and blood pressure. According to the researchers, bradykinin storms could create arrhythmias and low blood pressure, which are often seen in Covid-19 patients.

The bradykinin hypothesis also accounts for Covid-19's neurological effects, which are some of the most surprising and concerning elements of the disease. These symptoms (which include dizziness, seizures, delirium, and stroke) are present in as many as half of hospitalized Covid-19 patients. According to Jacobson and his team, MRI studies in France revealed that many Covid-19 patients have evidence of leaky blood vessels in their brains.

Bradykinin — especially at high doses — can also lead to a breakdown of the blood-brain barrier. Under normal circumstances, this barrier acts as a filter between your brain and the rest of your circulatory system. It lets in the nutrients and small molecules that the brain needs to function, while keeping out toxins and pathogens and keeping the brain's internal environment tightly regulated.

If bradykinin storms cause the blood-brain barrier to break down, this could allow harmful cells and compounds into the brain, leading to inflammation, potential brain damage, and many of the neurological symptoms Covid-19 patients experience. Jacobson told me, "It is a reasonable hypothesis that many of the neurological symptoms in Covid-19 could be due to an excess of bradykinin. It has been reported that bradykinin would indeed be likely to increase the permeability of the blood-brain barrier. In addition, similar neurological symptoms have been observed in other diseases that result from an excess of bradykinin."

Increased bradykinin levels could also account for other common Covid-19 symptoms. ACE inhibitors — a class of drugs used to treat high blood pressure — have a similar effect on the RAS system as Covid-19, increasing bradykinin levels. In fact, Jacobson and his team note in their paper that "the virus… acts pharmacologically as an ACE inhibitor" — almost directly mirroring the actions of these drugs.

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By acting like a natural ACE inhibitor, Covid-19 may be causing the same effects that hypertensive patients sometimes get when they take blood pressure–lowering drugs. ACE inhibitors are known to cause a dry cough and fatigue, two textbook symptoms of Covid-19. And they can potentially increase blood potassium levels, which has also been observed in Covid-19 patients. The similarities between ACE inhibitor side effects and Covid-19 symptoms strengthen the bradykinin hypothesis, the researchers say.

ACE inhibitors are also known to cause a loss of taste and smell. Jacobson stresses, though, that this symptom is more likely due to the virus "affecting the cells surrounding olfactory nerve cells" than the direct effects of bradykinin.

Though still an emerging theory, the bradykinin hypothesis explains several other of Covid-19's seemingly bizarre symptoms. Jacobson and his team speculate that leaky vasculature caused by bradykinin storms could be responsible for "Covid toes," a condition involving swollen, bruised toes that some Covid-19 patients experience. Bradykinin can also mess with the thyroid gland, which could produce the thyroid symptoms recently observed in some patients.

The bradykinin hypothesis could also explain some of the broader demographic patterns of the disease's spread. The researchers note that some aspects of the RAS system are sex-linked, with proteins for several receptors (such as one called TMSB4X) located on the X chromosome. This means that "women… would have twice the levels of this protein than men," a result borne out by the researchers' data. In their paper, Jacobson's team concludes that this "could explain the lower incidence of Covid-19 induced mortality in women." A genetic quirk of the RAS could be giving women extra protection against the disease.

The bradykinin hypothesis provides a model that "contributes to a better understanding of Covid-19" and "adds novelty to the existing literature," according to scientists Frank van de Veerdonk, Jos WM van der Meer, and Roger Little, who peer-reviewed the team's paper. It predicts nearly all the disease's symptoms, even ones (like bruises on the toes) that at first appear random, and further suggests new treatments for the disease.

As Jacobson and team point out, several drugs target aspects of the RAS and are already FDA approved to treat other conditions. They could arguably be applied to treating Covid-19 as well. Several, like danazol, stanozolol, and ecallantide, reduce bradykinin production and could potentially stop a deadly bradykinin storm. Others, like icatibant, reduce bradykinin signaling and could blunt its effects once it's already in the body.

Interestingly, Jacobson's team also suggests vitamin D as a potentially useful Covid-19 drug. The vitamin is involved in the RAS system and could prove helpful by reducing levels of another compound, known as REN. Again, this could stop potentially deadly bradykinin storms from forming. The researchers note that vitamin D has already been shown to help those with Covid-19. The vitamin is readily available over the counter, and around 20% of the population is deficient. If indeed the vitamin proves effective at reducing the severity of bradykinin storms, it could be an easy, relatively safe way to reduce the severity of the virus.

Other compounds could treat symptoms associated with bradykinin storms. Hymecromone, for example, could reduce hyaluronic acid levels, potentially stopping deadly hydrogels from forming in the lungs. And timbetasin could mimic the mechanism that the researchers believe protects women from more severe Covid-19 infections. All of these potential treatments are speculative, of course, and would need to be studied in a rigorous, controlled environment before their effectiveness could be determined and they could be used more broadly.

Covid-19 stands out for both the scale of its global impact and the apparent randomness of its many symptoms. Physicians have struggled to understand the disease and come up with a unified theory for how it works. Though as of yet unproven, the bradykinin hypothesis provides such a theory. And like all good hypotheses, it also provides specific, testable predictions — in this case, actual drugs that could provide relief to real patients.

The researchers are quick to point out that "the testing of any of these pharmaceutical interventions should be done in well-designed clinical trials." As to the next step in the process, Jacobson is clear: "We have to get this message out." His team's finding won't cure Covid-19. But if the treatments it points to pan out in the clinic, interventions guided by the bradykinin hypothesis could greatly reduce patients' suffering — and potentially save lives.