

An augmented immune response explains the adverse course of COVID-19 in patients with hypertension

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COVID-19 patients who also suffer from high blood pressure are more likely to fall severely ill with the disease, which also leaves them at greater risk of death. Scientists from the Berlin Institute of Health (BIH) and Charité–Universitätsmedizin Berlin, in collaboration with partners in

Heidelberg and Leipzig, have now found that the immune cells of patients with hypertension are already pre-activated, and that this pre-activation is greatly enhanced under COVID-19. This most likely explains the augmented response of the immune system and the more severe disease progression. However, certain hypertension-reducing drugs known as ACE inhibitors can have a beneficial effect. They not only lower blood pressure, but also counteract immune hyperactivation. The scientists have now published their findings in the journal *Nature Biotechnology*.

More than one billion people worldwide suffer from high blood pressure, or hypertension. Of the more than 75 million people around the world who have become infected with the SARS-CoV-2 virus worldwide so far, more than 16 million also have hypertension. These patients are more likely to become severely ill, which in turn results in an increased risk of death. It was previously unclear to what extent treatment with antihypertensive drugs could be continued during a SARS-CoV-2 infection—and whether they were more likely to benefit or harm the patients. This is because antihypertensives interfere with the exact same regulatory mechanism that the novel [coronavirus](#) SARS-CoV-2 uses to enter the [host cell](#) and trigger COVID-19.

Professor Ulf Landmesser is Medical Director of the CharitéCenter 11 for Cardiovascular Diseases, Director of the Medical Department of Cardiology and BIH Professor of Cardiology on the Charité's Campus Benjamin Franklin in Berlin. He recognized early on that patients with hypertension or cardiovascular diseases often experienced a particularly critical disease progression with COVID-19. "The virus uses the receptor ACE2 as an entry portal into the cells, and the formation of this receptor is potentially influenced by the administration of antihypertensive drugs," explains Landmesser. "We had therefore initially feared that patients receiving ACE inhibitors or [angiotensin receptor blockers](#) might have more ACE2 receptors on their cell surfaces and thus become more

easily infected."

Certain drugs that lower blood pressure could also help with COVID-19

To clarify this suspicion, the scientists analyzed individual cells from the respiratory systems of COVID-19 patients who were also taking medication for high blood pressure. Dr. Sören Lukassen, a scientist in Professor Christian Conrad's group at the BIH Digital Health Center, explains that they were subsequently able to give the all-clear: "We found that the drugs do not seem to cause more receptors to form on the cells. As a result, we do not believe that they make it easier for the virus to enter the cells in this way and thus cause the more severe course of COVID-19." On the contrary, cardiovascular patients taking ACE inhibitors actually displayed a lower risk of becoming severely ill with COVID-19. In fact, they displayed almost the same level of risk as COVID-19 patients without cardiovascular problems.

Severe course of COVID-19 linked to pre-activation of the immune system

The blood of hypertensive patients usually shows elevated levels of inflammation, which can be fatal in the case of a SARS-CoV-2 infection. "Elevated inflammation levels are always a warning signal that COVID-19 will be more severe, regardless of any cardiovascular issues," explains Landmesser. The scientists therefore employed single-cell sequencing methods to investigate the immune response of hypertensive patients with COVID-19.

"We analyzed a total of 114,761 cells from the nasopharynx of 32 COVID-19 patients and 16 non-infected controls, with both groups including cardiovascular patients as well as people without

cardiovascular problems," reports Dr. Saskia Trump, research group leader in the lab of Irina Lehmann, who is BIH Professor for Environmental Epigenetics and Lung Research. "We found that the immune cells of the cardiovascular patients displayed strong pre-activation even before infection with the novel coronavirus," explains Lehmann. "After contact with the virus, these patients were more likely to develop an augmented immune response, which was associated with the severe disease progression of COVID-19. However, our results also showed that treatment with ACE inhibitors, though not with angiotensin receptor blockers, could prevent this augmented immune response following infection by the coronavirus. ACE inhibitors could thus reduce the risk of patients with hypertension from experiencing severe disease progression."

Delayed reduction in viral load

Furthermore, the scientists found that the anti-hypertensive drugs can also impact how quickly the immune system is able to reduce the viral load, i.e., the concentration of the virus in the body. "Here, we observed a clear difference between the different forms of treatment for high blood pressure," notes Roland Eils, Director of the BIH Digital Health Center. "In the patients treated with angiotensin II receptor blockers, the reduction in viral load was significantly delayed, which could also contribute to a more severe course of COVID-19. We did not observe this delay in the patients who were receiving ACE inhibitors to treat their hypertension."

Interdisciplinary collaboration speeds up research

More than 40 scientists have been working at a breakneck pace on this [extensive study](#). "The ability to quickly provide answers to urgent questions during the ongoing pandemic requires interdisciplinary

collaboration among many committed individuals," explains Eils. "COVID-19 is such a complex disease that we brought together experts from cardiology, immunology, virology, pulmonary medicine, intensive care and computer science for this study. Our goal was to provide a scientifically sound answer as quickly as possible to the question of whether simultaneous treatment with ACE inhibitors or angiotensin receptor blockers could have beneficial or even adverse effects during the COVID-19 pandemic."

No evidence of increased risk of infection

Thanks to the study, the teams from the BIH, Charité and collaborating institutions in Leipzig and Heidelberg can now reassure both patients and the physicians treating them: "Our study provides no evidence that treatment with anti-hypertensive drugs increases the risk of infection by the novel coronavirus," says Ulf Landmesser, summarizing the results. "However, treating hypertension with ACE inhibitors could be more beneficial for patients suffering from COVID-19 than treatment with angiotensin II receptor blockers—a hypothesis that is currently being further investigated in randomized trials."

More information: Saskia Trump et al, Hypertension delays viral clearance and exacerbates airway hyperinflammation in patients with COVID-19, *Nature Biotechnology* (2020). [DOI: 10.1038/s41587-020-00796-1](https://doi.org/10.1038/s41587-020-00796-1)

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