National table tennis player Juliane Wolf has now also overcome long COVID.

Photo: Binh Truong/DBS

The heart after COVID-19

Not all long-term damage disappears without treatment

By Anne Hardy

Even young and healthy individuals can still suffer myocardial inflammation weeks after recovering from a COVID-19 infection. Pioneering work in Frankfurt using high-resolution magnetic resonance imaging has now corroborated this. Frankfurt scientists are currently heading research work into the reasons behind it as well as the therapies which could protect and heal the heart.

Top athlete Juliane Wolf, national table tennis player and fourth in the world rankings in para table tennis, was in fact very lucky. Although she contracted SARS-CoV-2 in November 2020, she had hardly any symptoms – a mild course of the disease, as is frequently the case among young people. However, she remained very tired and developed a headache if she looked at a monitor for a long time. It was at University Hospital Frankfurt that she was diagnosed with something she had not expected: myocarditis. The 33-year-old was shocked. "At that time, I was just about to start my proper training again, but instead everything ground to a halt. That was particularly hard to get my head round in the run-up to Tokyo," she explains. Wolf is not only an athlete but also works as a research associate at the Faculty of Educational Sciences. No drugs have yet been tested for this mild form of myocardial inflammation. Instead, she was urged to avoid stress.

Heart damage like in chronic diabetes

Julia Wolf's medical examination was part of a study by Professor Eike Nagel, Dr Valentina Puntmann and their team at the Institute for Experimental and Translational Cardiovascular Imaging at University Hospital Frankfurt. In the framework of this study, the physicians are looking at the long-term effects of a COVID-19 infection on the heart.

In most COVID-19 patients, only severe courses of heart muscle inflammation, that is, myocarditis, have so far come to attention. "As far as mild cases are concerned, we're seeing a grey zone that we think is underestimated, although we don't yet have any exact figures based on epidemiological studies," says Professor Nagel. His group specialises in detecting myocarditis at an early stage. The researchers have developed their own magnetic resonance imaging (MRI) methods that are more accurate and less error-prone than the standard programmes offered by the equipment manufacturers. To date, these methods are not used routinely.

Together with his colleague Dr Valentina Puntmann back in July 2020, Nagel was one of the first researchers worldwide to look at long-term heart damage following a COVID-19 infection. The results of the study, which appeared in the scientific journal JAMA Cardiology, caused a sensation: In 78 per cent of the test persons, changes in the heart were detectable two months after the onset of the infection. 60 per cent suffered from inflammation of the heart muscle cells.

"This doesn't mean that 78 per cent of the participants in the study will develop a heart problem as a result of COVID, since changes in the heart muscle were also seen in a control group without COVID that has the same risk factors, such as smoking," Nagel stresses. What stands out, however, is that in the post-COVID group the changes are far greater. "More than half the patients show signs of damage that is more pronounced than in people with chronic diabetes or high blood pressure."

Cardiac insufficiency will increase after COVID

The second important finding was that 22 per cent of the participants in the study displayed increased amounts of water in the heart muscle, which indicates slight to moderate inflammation. Seen from a purely statistical perspective, these patients have an increased risk of developing cardiac insufficiency or arrhythmias in the course of their life. That is why Nagel considers it important to recognise these early stages. Without declaring people sick because of it. "My aim is to keep people as healthy as possible," he says.

What is thought-provoking is the fact that myocardial inflammation also occurred in people

LONG-TERM HEART DAMAGE FROM COVID

In principle, three types of long-term damage can occur: As a result of the infection, plaque can break off and clog coronary vessels, causing a heart attack. There is also an increased risk of this with influenza. Or patients suffer microinfarcts, which in general cannot be detected with standard imaging methods because only small regions are affected. This seems to occur frequently in COVID-19 infections and makes the heart less resilient. The third possibility is diffuse myocarditis, which can be triggered by immune cells fighting the virus or from autoimmune reactions. This also causes heart muscle cells to die and tissue to scar.

who had only experienced a mild bout of COVID, like national table tennis player Juliane Wolf. Most of the test persons suffered from non-specific symptoms such as shortness of breath and fatigue.

Nagel advises caution: "People always say: You'll be alright. With young people who are fit that's indeed the case. But they still display measurable damage nonetheless. Perhaps their performance is only 98 per cent. Top athletes notice this quickly. But they're trained to give it their best at all times and try to compensate for this through harder training. That's not necessarily the best thing to do if you still have some slight inflammation."

Myocardial inflammation often goes undetected

When would Eike Nagel recommend an MRI scan? When a patient complains of palpitations, does not feel particularly fit and his or her troponin levels are slightly increased. Troponin-T is a protein that performs an important function in the contraction of the heart muscle cells. If these are damaged or die off, more troponin-T is released into the blood. "The level doesn't have to be as high in early myocarditis as in a heart attack because in early myocarditis some of the cells are only damaged and the damaged cells release less troponin than the dying ones. On the basis of the data available so far, we can't yet say what the threshold is."

The MRI scan then makes it possible to identify areas where scar tissue has formed because heart muscle cells have died off (T1 value). Unlike after a heart attack, the scarred (fibrotic) tissue is distributed diffusely in the heart muscle. In addition, the accumulation of fluid in the heart muscle (T2 value) can be seen, which indicates inflammation. In an acute case, such as that of athlete Juliane Wolf, the heart can recover again as soon as the water disappears out of the tissue. Some cells, however, do not recover, as can be deduced from the T1 value once the inflammation has gone. If it is still high, the damage is irreversible.

Studies in the planning for the treatment of long-term damage

No drugs for this early form of myocarditis have yet been approved. That is why Nagel is planning a multicentre study with partners at the German Centre for Cardiovascular Research. If microinfarcts are presumed to be the cause, vasodilative strategies might be the answer. Low-dose ACE inhibitors (in higher doses they lower blood pressure) could be used to counter the formation of scar tissue. Researchers such as Professor Stefanie Dimmeler, director of the Institute of Cardiovascular Regeneration, are currently pinning a lot of hope on anti-inflammatory therapy, for instance with cortisone: "Cortisone attacks inflammation on a broad

ABOUT STEFANIE DIMMELER AND EIKE NAGEL

Professor Stefanie Dimmeler, born in 1967, studied biology and earned her doctoral degree at the University of Konstanz. After three years at the University of Cologne, she joined the Department of Cardiology at Medical Clinic III of University Hospital Frankfurt and Goethe University, where she has headed the "Molecular Cardiology Working Group" since 1997 and earned her post-doctoral degree (Habilitation) in 1998. Stefanie Dimmeler has been professor of molecular cardiology at Goethe University since 2001 and director of the Institute of Cardiovascular Regeneration at the Centre for Molecular Medicine since 2008. She is spokesperson of the managing board of the German Centre for Cardiovascular Research e. V. and of the Cardio-Pulmonary Institute cluster of excellence.

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Professor Eike Nagel, born in 1967, studied medicine at the University of Cologne and earned his doctoral degree there on the topic of magnetic resonance imaging. He trained as a cardiologist and specialist in internal medicine in Kiel, Zurich and at the German Heart Center Berlin. Having completed his post-doctoral degree (Habilitation), he was professor and head of the Department of Cardiovascular Imaging at King's College London from 2007 to 2015. Since 2015, he has headed the Institute for Experimental and Translational Cardiovascular Imaging at University Hospital Frankfurt and holds a professorship of the German Centre for Cardiovascular Research at Goethe University. Eike Nagel is one of the founding members of the Society for Cardiovascular Magnetic Resonance (SCMR).

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scale and in so doing also protects the heart and the blood vessels," she says.

The institute is also currently testing various cardiac drugs to see what protective effect they have on the heart. In addition, studies are being conducted on how to prevent thromboses in order, in turn, to prevent infarcts.

How does the virus enter the heart?

Biologist Professor Stefanie Dimmeler has been studying the effects of SARS-CoV-2 on the heart at cell and tissue level since the beginning of the pandemic. Back in February 2020, she was already working with Professor Sandra Ciesek, head of virology at University Hospital Frankfurt, who had isolated the virus from people returning from Wuhan. First, Dimmeler infected heart muscle cells and endothelial cells, with which the walls of the blood vessel are lined, in cell cultures. The next step was to examine infected 3-D heart cultures. Such tissue-like cultures beat or twitch in the test tube like little hearts. As Dimmeler observed: "The beat rate rises steeply when cultures are infected, indicating that the cells are under severe stress. They die off within three days."

The next step was to examine tissue sections from human hearts obtained during organ transplantations. For this, Stefanie Dimmeler travelled during the first lockdown – with special permission from the Chancellor – to the Medical Centre of LMU Munich. There, she placed thin slices of heart tissue immediately after removal into the incubator she had brought with her and in which electrical impulses stimulated the tissue slices to continue contracting. "It was very exciting," she remembers, "because we didn't know whether the heart tissue would survive transportation back to our lab undamaged."

HOW THE VIRUS ATTACKS HEART CELLS

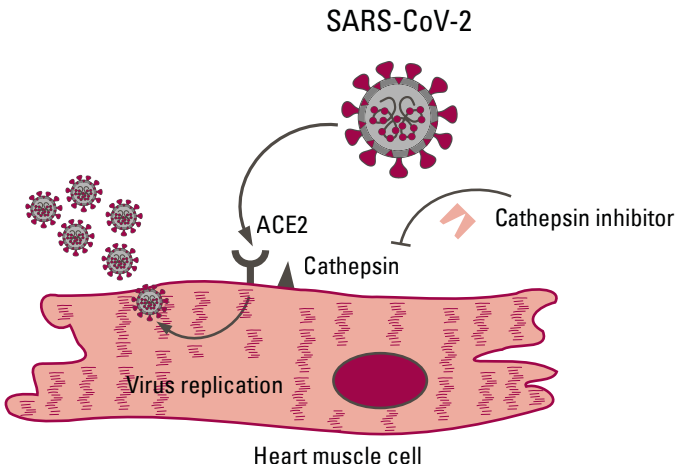

Diagram: Julian Wagner; adapted by Peter Kiefer

In order to penetrate heart cells, SARS-CoV-2 needs the ACE-2 receptor as well as the cellular molecule cathepsin. In the laboratory, cathepsin inhibitors were able to stop the virus from multiplying in heart muscle cells.

MRI images for research: Cardiologist Dr Valentina Puntmann looks after a study participant at the Institute for Experimental and Cardiovascular Imaging at University Hospital Frankfurt.

Photo: Uwe Dettmar

Further information

https://www.cardiac-imaging.org/in-the-media

One important finding from these experiments: Heart muscle cells are infected via a slightly different route than lung cells. Heart muscle cells have only small amounts of the protease TMPRSS2, via which the coronavirus enters lung cells. Instead, the virus uses the protein cathepsin, which is found in large quantities in the heart. In the laboratory trials, cathepsin-inhibiting agents were able to stop the virus from replicating. These agents could be used in future in the acute stage of a COVID-19 infection – to date no inhibitors have been approved.

Damaged hearts and blood vessels are more vulnerable

"With COVID-19 infections, we have the chicken-and-egg dilemma, meaning we don't know whether the heart problems can be traced back directly to the attack by the virus or whether they're the result of immune-related inflammatory reactions that also damage the endothelium," explains Dimmeler. In a healthy person, the endothelium, which lines the walls of the blood vessels, prevents viruses from entering the heart muscle via the blood. The coronavirus is not able to overcome this vascular barrier either, as Dimmeler's team was able to prove through experiments on five different types of endothelium: "Although the endothelial cells in the heart can absorb the virus, it doesn't survive in them. This means that the endothelium is a protective shield for the heart." However, people with vascular diseases or pre-damaged hearts are at risk, since in their case the virus can take a firm hold in the heart.

And why then can myocarditis occur as a long-term effect in people whose heart was previously healthy? Stefanie Dimmeler suspects that the endothelium is attacked by immune reactions and that this destroys its barrier function.

Dimmeler and her team also used cell cultures to study the effect of remdesivir, the virostatic agent that has been the first approved treatment for COVID-19 in the United States since November 2020. They showed that remdesivir stops the virus from replicating in cells – irrespective of whether it is a lung or heart muscle cell. However, clinical trials with the drug have so far not been particularly convincing. Dimmeler assumes that the virostatic agent is only effective if administered at an early stage of an infection. "Once the virus has attacked the organs, it's probably too late," she says.

What can be done in the acute phase?

Whether the heart is damaged during an acute COVID infection and administering a drug such as remdesivir or cathepsin inhibitors is promising could be decided with the help of high-resolution MRI. However, it is not possible simply to wheel COVID patients from the hermetically sealed wing of an intensive care unit through the hospital to an MRI machine, especially if they are on a ventilator. This would require changing hospital infrastructure and making an MRI scanner available exclusively for COVID patients. "It takes two hours after the procedure before the machine is aerosol-free again," explains Eike Nagel. This is extremely laborious both for routine hospital operations as well as for research.

National table tennis player Juliane Wolf's heart has meanwhile recovered without therapy. During a second MRI scan in mid-March, it looked healthy again. "I only started training again slowly after the long break nonetheless," she says. ●

IN A NUTSHELL

- COVID infections have long-term effects on the heart, which could often lead to cardiac insufficiency later on.
- High-resolution MRI can be used to detect myocardial inflammation at an early stage.
- Pre-damaged hearts and blood vessels as well as autoimmune inflammatory reactions as a result of a COVID-19 infection increase the risk of myocardial inflammation.
- If cardiac function is impaired or pathological biomarkers such as troponin-T increase, extreme physical exertion should be avoided.

The author

Dr Anne Hardy,
born in 1965, studied physics and earned her doctoral degree in history of science. As a freelance science journalist, she specialises in natural science and medical topics.

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