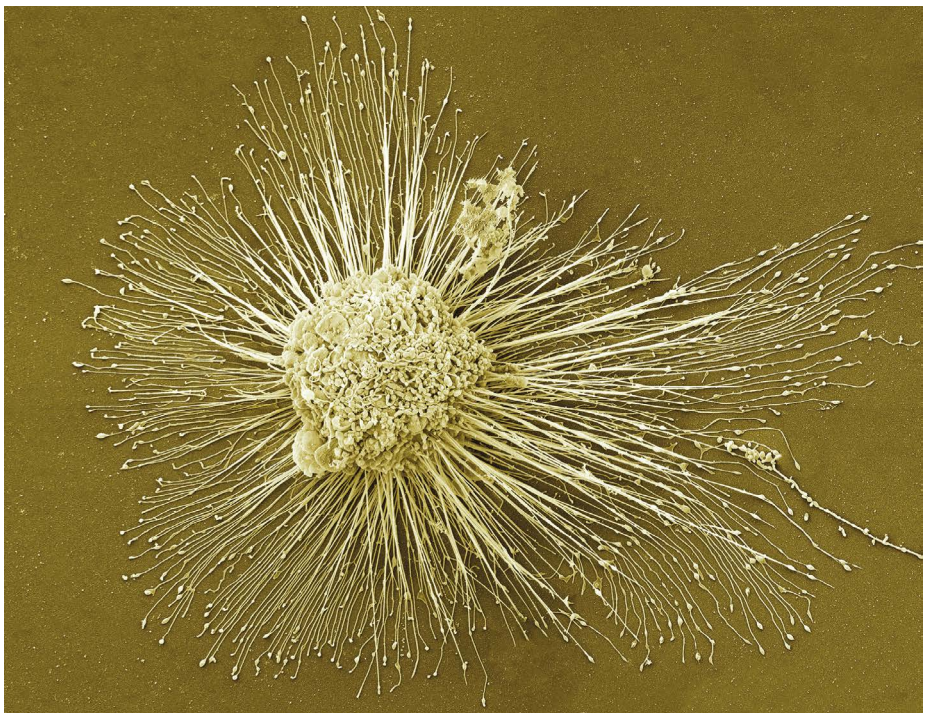

THOMAS DEERINCK, NCMIR/SPL

Heart muscle derived from induced pluripotent stem cells.

'REPROGRAMMED' STEM CELLS FOR HEART DISEASE TESTED IN CHINA

But there is no way to confirm that the unpublished trial using induced pluripotent stem cells works.

By Smriti Mallapaty

Two men in China were the first people in the world to receive an experimental treatment for heart disease based on 'reprogrammed' stem cells, and they have recovered successfully one year later, says the cardiac surgeon who performed the procedures. In May last year, the men were injected with heart muscle cells derived from induced pluripotent stem (iPS) cells, the surgeon told *Nature* – the first known clinical application of iPS-cell technology for treating damaged hearts.

No results have yet been published, so researchers not involved in the work have cautioned that there is no way to confirm whether the treatment works, including whether the reported benefits are due to the iPS-derived cells or simply to the heart bypass that accompanied the treatment.

But the surgeon, Wang Dongjin at Nanjing Drum Tower Hospital, spoke to *Nature* in detail about the procedure and about the patients' conditions. And one of the men – Han Dayong, a 55-year-old electrician from Yangzhou in eastern China who received the treatment alongside a heart bypass – says he is very satisfied with the outcome. Before the surgery, Dayong remembers being tired and often out of breath. Now he can go for walks, climb stairs and sleep through the night. "It was beyond my expectations," he says.

The team behind the treatment plans to publish the results from the two recipients later this year, says Wang Jiaxian, who heads HELP Therapeutics,a biotechnology company based in Nanjing that supplied the heart muscle cells, known as cardiomyocytes, used in the study. The group also has approval to expand its study to include a further 20 patients, he says.

The trial in China is not the only one that is ongoing. In January, a cardiac surgeon in Japan, Yoshiki Sawa, introduced iPS-derived cardiomyocytes designed to treat heart disease into a patient. His team is using an alternative approach in which sheets of cells are grafted onto the heart rather than injected.

For decades, researchers have been trying to treat heart disease – a leading cause of death worldwide – using adult stem cells. They hoped that the cells would morph into muscle cells once inserted into the heart.

But after trials in people proved inconclusive, researchers turned to iPS cells. These are created by inducing adult cells to revert to an embryonic-like state, from which they can develop into other cell types, such as cardiomyocytes.

Evidence in rodents and monkeys suggests that introducing iPS-cell-derived cardiomyocytes directly into the heart does regenerate muscle tissue and improve the organ's function[1]. Researchers hope that the first trials in people will reveal the same.

"These are really exciting times," says Wolfram-Hubertus Zimmermann, a pharmacologist at the University Medical Centre Göttingen in Germany.

As well as the iPS-cell pilot study under way in Japan, several others are planned in France and the United States. Zimmermann is also planning one in Germany.

Safety first

That there is a trial ongoing in China came as a surprise to many, who didn't know that researchers there had overcome one of the field's biggest challenges – the need to produce large numbers of iPS-cell-derived cardiomyocytes that are pure enough to be used in people. This takes a lot of time and effort to get right, so very few companies or research groups have successfully done it, says Charles Murry, a pathologist at the University of Washington in Seattle who also plans to inject cells into people's hearts.

Wang Jiaxian says that his company has been developing the cells for almost four years.

Wang Dongjin told *Nature* that he injected some 100 million cardiomyocytes, derived from iPS cells created using cells donated by a healthy person, around the damaged heart tissue of his two patients. At the same time, both men, who had severe heart disease, underwent a coronary-artery bypass operation, in which vessels from elsewhere in the body are transplanted onto the artery to improve blood flow.

Wang says his goal was to assess the safety of the cell injections, and that he was encouraged when his patients' heart function improved significantly after the operations. Neither patient has developed tumours, he adds, which can be a risk of using pluripotent stem cells.

To prevent the body from attacking the cardiomyocytes, Wang says, both patients took immunosuppressant drugs. One took them for a month; the other had to stop after a week owing to side effects.

Wang also says that the procedure did not cause sustained dysfunction in heart rhythm. Zimmermann says that is a sign that it's safe, but it needs to be tested in more people.

Murry adds that the health benefits that the

patients have reported cannot be attributed to the reprogrammed cells alone, because the men also received a coronary bypass. "If you do two things to somebody and they get better, you can't say which one caused it," he says.

Researchers are divided on the best way to introduce cardiomyocytes into the heart. Injecting them is typically less intrusive than grafting sheets of cells, because it doesn't require surgery, although the Chinese patients did have bypass operations. Proponents of injections also argue that in animals, the procedure has allowed the tissue to better integrate into the heart and produce new muscle[2].

But Philippe Menasché, a cardiac surgeon at the University of Paris, says that the injections puncture the heart in multiple locations, which might damage the tissue.

In January, Sawa, a surgeon at Osaka University in Japan, trialled the alternative approach; grafting sheets of 100 million cardiac muscle cells onto a patient's diseased heart. Sawa says the recipient moved out of intensive care within a few days. He plans to conduct the procedure in a further eight people.

Work in animals shows that more cells tend to survive being transplanted in sheets or patches than survive injection. But studies have also found that such grafted cells do not beat in synchrony with the heart[3].

1. Liu, Y.-W. *et al. Nature Biotechnol.* **36**, 597–605 (2018).
2. Gerbin, K. A., Yang, X., Murry, C. E. & Coulombe, K. L. *PLoS ONE* **10**, e0131446 (2015).
3. Zimmermann, W.-H. *Curr. Opin. Physiol.* **14**, 70–77 (2020).

CORONAVIRUS BLOOD-CLOT MYSTERY INTENSIFIES

Research begins to pick apart the mechanisms behind a deadly COVID-19 complication.

By Cassandra Willyard

Purple rashes, swollen legs, clogged catheters and sudden death — blood clots, large and small, are a frequent complication of COVID-19, and researchers are just beginning to untangle why.

COVID-19's impact on the respiratory system has gained much attention. But for weeks, reports have been pouring in of the disease's effects throughout the body, many of which are caused by clots. "This is like a storm of blood clots," says Behnood Bikdeli, a cardiologist at Columbia University in New York City. Anyone with a severe illness is at risk of developing clots, but people hospitalized with COVID-19 seem to be even more susceptible.

Scientists have a few plausible hypotheses to explain the phenomenon, and they are just beginning to launch studies aimed at gaining mechanistic insights. But with the death toll rising, they are scrambling to test clot-curbing medications.

Double whammy

Blood clots, jelly-like clumps of cells and proteins, are the body's mechanism to stop bleeding. It's not just their presence that has puzzled scientists: it's how they show up. "There are so many things about the presentations that are a little bit unusual," says James O'Donnell, director of the Irish Centre for Vascular Biology at the Royal College of Surgeons in Dublin.

Blood thinners don't reliably prevent clotting in people with COVID-19, and young people are dying of strokes caused by the blockages in the brain. And many people in hospital have drastically elevated levels of a protein fragment called D-dimer, which is generated when a clot dissolves. High levels of D-dimer seem to be a powerful predictor of mortality in hospitalized people infected with coronavirus (L. Zhang *et al. J. Thromb. Haemost.* https://doi.org/dv34; 2020).

"This is not what you'd expect to see in someone who just has a severe infection."

Researchers have also observed miniature clots in the body's smallest vessels. "This is not what you'd expect to see in someone who just has a severe infection," says Jeffrey Laurence, a haematologist at Weill Cornell Medicine in New York City. It's a "double hit", says O'Donnell. Pneumonia, which can be caused by COVID-19, clogs the tiny sacs in the lungs with fluid or pus, and microclots restrict oxygenated blood from moving through them.

Why this clotting occurs is still a mystery. One possibility is that SARS-CoV-2, the coronavirus responsible for COVID-19, is directly attacking the endothelial cells that line the blood vessels. Endothelial cells harbour the same ACE2 receptor that the virus uses to enter lung cells. And there is evidence that endothelial cells can become infected: researchers at University Hospital Zurich in Switzerland and Brigham and Women's Hospital in Boston, Massachusetts, observed SARS-CoV-2 in endothelial cells inside kidney tissue (Z. Varga *et al. Lancet* **395**, 1417–1418; 2020).

In healthy individuals, the blood vessel is "a very smoothly lined pipe", says Peter Liu, chief scientific officer at the University of Ottawa Heart Institute in Canada. The lining actively stops clots from forming. But viral infection can damage these cells, prompting them to churn out proteins that trigger the process.

The virus's effects on the immune system could also affect clotting. In some people, COVID-19 prompts immune cells to release a torrent of chemical signals that ramps up inflammation, which is linked to coagulation and clotting through a variety of pathways. And the virus seems to activate a defence mechanism that sparks clotting, known as the complement system. Laurence's group found that small, clogged vessels in lung and skin tissue from people with COVID-19 were studded with proteins. All these systems — complement, inflammation, coagulation — are interrelated, says Agnes Lee, director of the Hematology Research Program at the University of British Columbia in Vancouver, Canada. "In some patients with COVID, all of those systems are kind of in hyperdrive."

Race to new therapies

Even as researchers begin to unravel how clotting occurs in people with COVID-19, they're sprinting to test new therapies aimed at preventing and breaking up clots.

At Columbia University, researchers are launching a clinical trial to compare the standard clot-preventing doses of blood thinners with a higher dose in people who are critically ill with COVID-19. Similar trials are planned for Canada and Switzerland. And scientists at Beth Israel Deaconess Medical Center in Boston have begun enrolment for a clinical trial to evaluate an even more powerful clot-busting medication called tissue plasminogen activator, or tPA.

Scientists hope that these trials and others will provide the data necessary to help physicians to make difficult treatment decisions. Lee worries about the amount of 'reactionary medicine' happening. "People are changing their therapeutic approach in reaction to their local and personal experience," she says. She understands the impetus, "but we have to remember the main thing is first do no harm".