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].

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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".

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