Devastating heart condition can be reversed, study shows for the first time

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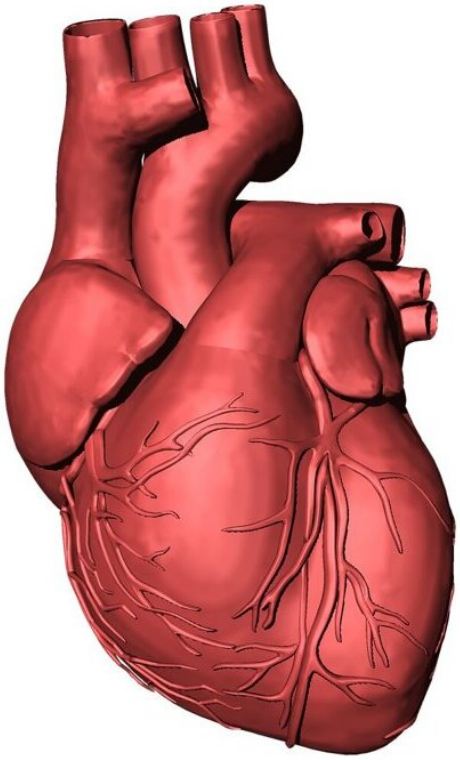

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Three men who had heart failure caused by the build-up of sticky, toxic proteins are now free of symptoms after their condition spontaneously reversed in an unprecedented case described by a team at UCL

(University College London) and the Royal Free Hospital.

The condition, a form of amyloidosis affecting the heart, is progressive and has until now been seen as irreversible, with half of patients dying within four years of diagnosis.

The new study, published as a letter in *The New England Journal of Medicine*, reports on three men, aged 68, 76 and 82, who were diagnosed with transthyretin cardiac amyloidosis but who later recovered. Their own reports of symptoms improving was confirmed by objective assessments including cardiovascular magnetic resonance (CMR) scans showing that the build-up of amyloid proteins in the heart had cleared.

Lead author Professor Marianna Fontana (UCL Division of Medicine) said, "We have seen for the first time that the heart can get better with this disease. That has not been known until now and it raises the bar for what might be possible with new treatments."

The researchers also found evidence of an immune response in the three men that specifically targeted amyloid. The amyloid-targeting antibodies were not found in other patients whose condition progressed as normal.

Senior author Professor Julian Gillmore (UCL Division of Medicine), Head of the UCL Centre for Amyloidosis, based at the Royal Free Hospital, said, "Whether these antibodies caused the patients' recovery is not conclusively proven. However, our data indicates that this is highly likely and there is potential for such antibodies to be recreated in a lab and used as a therapy. We are currently investigating this further, although this research remains at a preliminary stage."

Transthyretin (ATTR) amyloidosis is caused by amyloid deposits composed of a blood protein called transthyretin (TTR). It can be hereditary or non-hereditary ("wild-type"). The build-up of these protein

deposits in the heart is called ATTR amyloid cardiomyopathy (ATTR-CM).

Current treatments on the NHS aim to relieve the symptoms of heart failure (which may include fatigue, swelling in the legs or abdomen, and shortness of breath with activity), but do not tackle the amyloid (although a number of "gene-silencing" therapies are currently being trialed which reduce TTR protein concentration in the blood and thereby slow ongoing amyloid formation).

Advances in imaging techniques—some of which were pioneered at the UCL Centre for Amyloidosis—has meant substantially more people being diagnosed with the disease than was the case 20 years ago. Previously, diagnosis needed a biopsy (involving tissue taken from the heart).

The imaging techniques also mean the burden of amyloid on the heart, and consequently the progression of the disease, can be more precisely monitored, making it easier to detect cases where the condition has reversed, rather than merely remaining stable.

The latest study, supported by the Royal Free Charity, began when one man aged 68 reported his symptoms improving. This prompted the research team to look through records of 1,663 patients diagnosed with ATTR-CM. Out of these patients, two more cases were identified.

The three men's recoveries were confirmed via blood tests, several imaging techniques including echocardiography (a type of ultrasound), CMR scans and scintigraphy (a nuclear medicine bone scan), and, for one patient, an assessment of exercise capacity. CMR scans showed heart structure and function had returned to a near-normal state and amyloid had almost completely cleared.

An in-depth look at the records and assessments for the rest of the 1,663 cohort indicated that these three patients were the only ones whose condition had reversed.

One of the three men underwent a heart muscle biopsy that revealed an atypical inflammatory response surrounding the amyloid deposits (including white blood cells known as macrophages), suggesting an immune reaction. No such inflammatory response was detected in 286 biopsies from patients whose disease had followed a normal progression.

Investigating this further, the researchers found antibodies in the three patients that bound specifically to ATTR amyloid deposits in mouse and human tissue and to synthetic ATTR amyloid. No such antibodies were present in 350 other patients in the cohort with a typical clinical course.

If these antibodies could be harnessed, they could be combined with new therapies being trialed that suppress TTR protein production, enabling clinicians to clear away amyloid as well as preventing further amyloid deposition.

One such promising therapy is a single intravenous infusion of NTLA-2001, a novel gene-editing therapy based on CRISPR/Cas9. Early results of the trial, led by Professor Gillmore, indicate it may stop disease progression.

The UCL Centre for Amyloidosis is one of the world's leading centers for amyloid research. It includes the NHS National Amyloidosis Centre, the only center in the UK specializing in amyloidosis.

Jon Spiers, chief executive of the Royal Free Charity, said, "As an NHS charity, we are proud to be supporting this research. Our priority is to drive early-stage research that brings innovative treatments to patients sooner."

"This work not only represents a major breakthrough in our understanding of cardiac amyloidosis, but crucially opens up new possibilities for more effective treatment options. It's a hugely significant development that we welcome on behalf of all patients of the National Amyloidosis Centre and their families, many of whom have contributed to our research funding with their own fundraising efforts."

More information: Antibody associated reversal of ATTR amyloidosis cardiomyopathy, *New England Journal of Medicine* (2023). www.nejm.org/doi/10.1056/NEJMc2304584

Provided by University College London