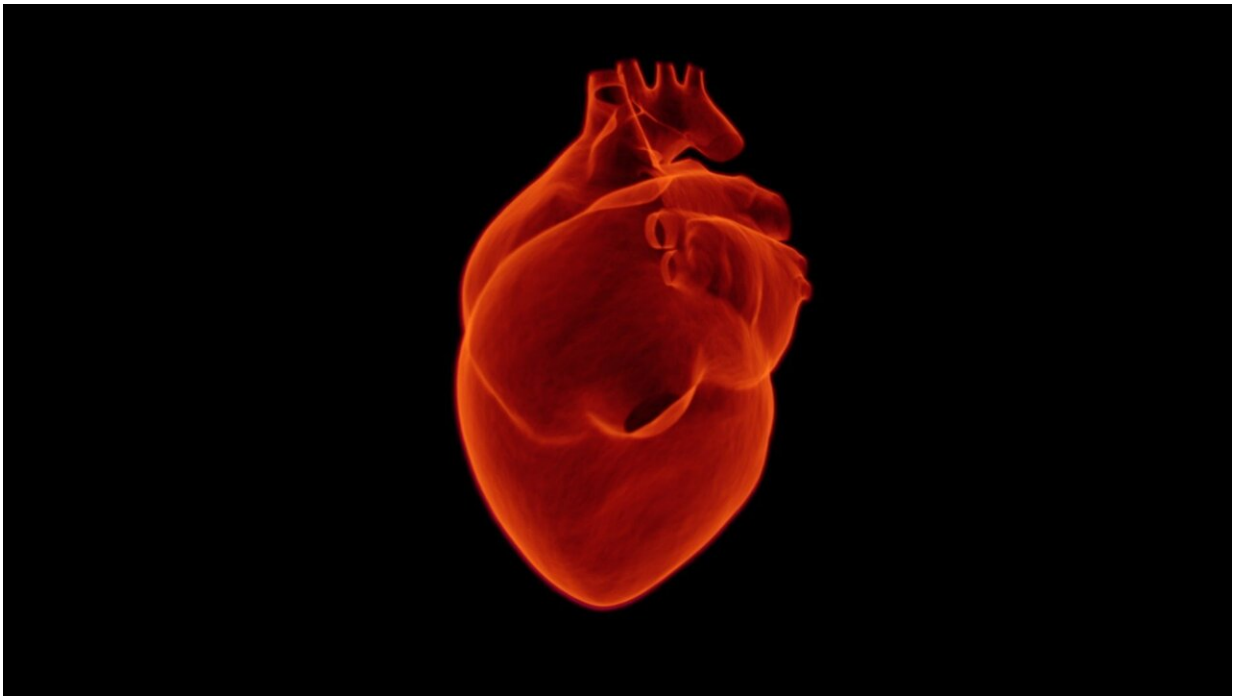
Gene-based therapy may slow development of life-threatening heart condition

January 30 2024



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A new study in mice shows that replacement of a dysfunctional gene could prolong survival in some people with arrhythmogenic right ventricular cardiomyopathy (ARVC), a rare inherited disorder in which the muscular walls of the heart progressively weaken and put patients at risk of dangerous irregular heartbeats.

The research is published in the journal *Circulation: Genomic and Precision Medicine*.

The investigational treatment targets the loss of function of a gene implicated in many cases of ARVC, plakophilin-2 (PKP2). The PKP2 gene provides instructions for making a protein that holds heart tissues together. When the gene—one of several thought to contribute to the disease —is defective and fails to make a functional protein, fibrous and fatty tissue builds up within the heart's walls, causing them to weaken. The heart can also beat irregularly without any warning and sometimes stop working. While current therapies can help restore the heart's normal rhythm and control symptoms, they fail to provide a cure.

In a collaboration between researchers at NYU Grossman School of Medicine and scientists at Rocket Pharmaceuticals (a biotechnology company), the new work revealed that untreated mice engineered to lose PKP2 gene function died within six weeks after the gene was silenced. However, all but one of those that received a single dose of a gene therapy, carrying the normal version of the gene, lived for more than five months. Mice that received the replacement gene also saw a 70% to 80% reduction in fibrous tissue buildup, depending on the dose.

"Our findings offer experimental evidence that gene therapy targeting plakophilin-2 can interrupt the progression of a deadly heart condition," says study co-lead author Chantal van Opbergen, Ph.D., a postdoctoral research fellow at NYU Langone Health.

According to the study authors, the most advanced stages of ARVC are marked by irreversible heart damage, sometimes requiring a heart transplant. Researchers have long sought to slow the disease and prevent as much tissue loss as possible.

In earlier research from the NYU Langone team, the authors explored

the mechanisms by which defects in the PKP2 gene can cause the unexpected occurrence of a life-threatening irregular heartbeat (arrhythmias), similar to that observed in some patients with ARVC.

For the new study, the team used a mouse model of ARVC in which the genetic makeup was altered to render the PKP2 gene not functional. For proof-of concept in the present work, they used an adeno-associated viral vector as the delivery mechanism to transfer the healthy gene into the cardiac cells, thereby delivering the needed PKP2 protein therapy.

These viral vectors are small, non-replicating particles that ferry the desired gene into target cells by taking advantage of their natural infection process, namely their ability to invade a cell and take up residence there. However, unlike infectious viruses, the viral vectors do not multiply after their genetic material is transferred to the heart cells, which—with the healthy gene in place—now produce the normal protein. Rocket Pharmaceuticals designed and developed the viral vector that was used in the study.

According to the findings, the experimental treatment reduced episodes of arrhythmia in the mice by as much as 50%, slowed the deterioration of the heart's walls, and maintained their ability to pump blood effectively.

"These results suggest that this gene-therapy method may combat arrhythmogenic right ventricular cardiomyopathy in both early and more advanced stages of the condition," said study co-senior author Mario Delmar, MD, Ph.D. Delmar is the Patricia M. and Robert H. Martinsen Professor of Cardiology in the Department of Medicine at NYU Langone Health and a professor in its Department of Cell Biology.

"Such promising findings in animal models pave the way towards exploring this treatment option in humans," said study co-senior author

and cardiologist Marina Cerrone, MD.

Based in part on the current study data, Rocket Pharmaceuticals has initiated a Phase 1 clinical trial to test the safety of the experimental treatment in ARVC patients with disease-causing PKP2 mutations, notes Cerrone, a research associate professor in the Department of Medicine at NYU Langone.

That said, Cerrone cautions that while targeting PKP2 affects one of the most common causes of ARVC, further experiments will be needed to correct other genetic mutations known to contribute to the disease.

More information: Chantal J.M. van Opbergen et al, AAV-Mediated Delivery of Plakophilin-2a Arrests Progression of Arrhythmogenic Right Ventricular Cardiomyopathy in Murine Hearts: Preclinical Evidence Supporting Gene Therapy in Humans, *Circulation: Genomic and Precision Medicine* (2024). DOI: 10.1161/CIRCGEN.123.004305

Provided by NYU Langone Health