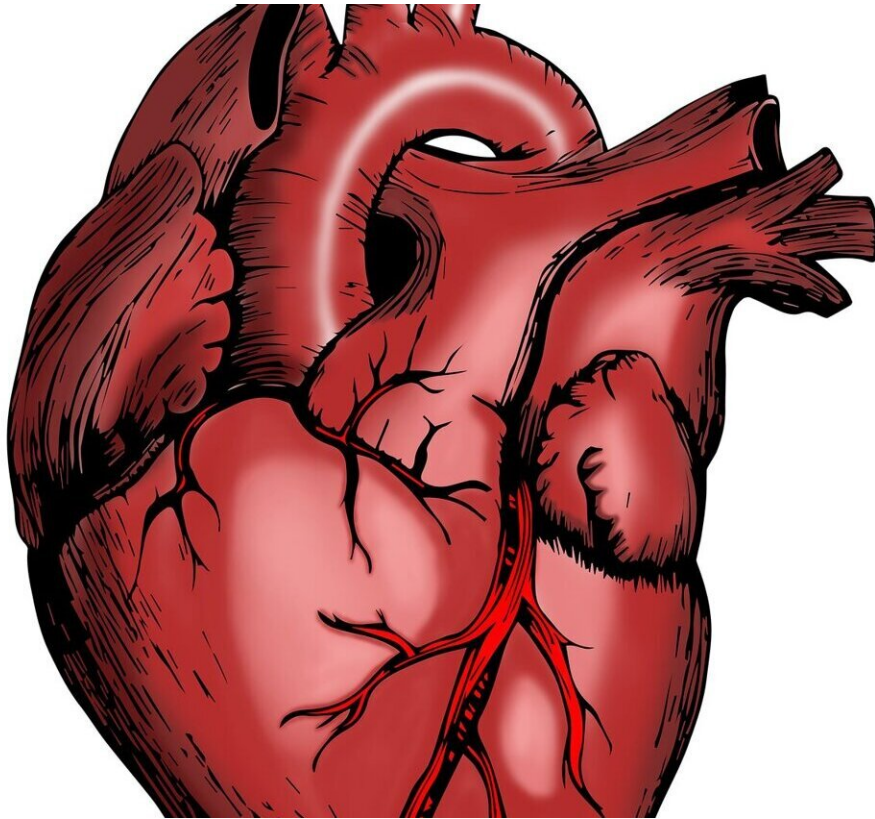


# Defining the role of HDAC6 in regulating heart stiffness

May 16 2022, by Greg Glasgow

---



Credit: Pixabay/CC0 Public Domain

Researchers at the University of Colorado School of Medicine have discovered an enzyme that regulates heart stiffness, setting the stage for developing novel treatments for heart failure.

The enzyme, histone deacetylase 6 (HDAC6), has been studied in the context of many diseases, including [heart disease](#), but CU School of Medicine researchers Timothy McKinsey, Ph.D., professor of medicine in the Division of Cardiology, and Kathleen Woulfe, Ph.D., assistant professor of medicine in the Division of Cardiology, recently discovered a new role for HDAC6 in the regulation of myofibrils, the contractile units of the heart. The research was published May 16 in the *Journal of Clinical Investigation*.

"When your heart is pumping and relaxing optimally, it's at a certain stiffness," McKinsey says. "Stresses—including aging, hypertension, and obesity—can cause the heart to become too stiff, preventing it from relaxing and filling with blood efficiently, which leads to something called [diastolic dysfunction](#). In other instances, the heart is not stiff enough, so it can't pump effectively, which leads to systolic dysfunction. Both conditions are life-threatening."

## **The role of titin**

The CU researchers found evidence that HDAC6 acts on titin, a massive myofibril protein that contributes to heart stiffness. HDAC6 appears to remove a chemical modification known as acetylation from titin. When HDAC6 is inhibited, titin causes the heart to become stiffer; when HDAC6 is activated, the heart becomes less stiff. In the future, once cardiologists determine which type of dysfunction a patient has, it might be possible to therapeutically adjust HDAC6 [enzymatic activity](#) or levels to help the heart to pump and relax at an optimal stiffness.

"Heart failure is still a huge problem that affects millions of people worldwide," McKinsey says. "Even though there are medications to treat [heart failure](#), people with the condition still often have poor quality of life and die at an alarming rate. We think this discovery could provide a novel avenue for treating heart failure through a distinct mechanism."

The progress of therapeutically manipulating HDAC6 to treat heart failure is helped along by the fact that HDAC6 inhibitors are actively being developed to treat other conditions, including neurodegeneration and cancer, though McKinsey cautions that the heart needs to be monitored more carefully in people receiving HDAC6 inhibitors.

"Our data suggest that in some cases, if you inhibit this enzyme, the heart might get too stiff," McKinsey says. "Nevertheless, we firmly support continued clinical development of HDAC6 inhibitors, since this class of compounds holds great promise for treating a variety of devastating diseases, including certain forms of heart failure."

## **The research continues**

The CU researchers plan to continue to study the role of HDAC6 in heart stiffness, including testing HDAC6 inhibitors in preclinical models of systolic heart failure where titin is too "compliant," and developing [gene therapy](#) to provide activated HDAC6 to hearts that are too stiff. Much of their work takes place in Woulfe's laboratory, which is one of a handful of labs in the world that can isolate and study myofibril mechanics.

"We are able to isolate proteins that direct contraction and relaxation in the heart in a way that preserves the mechanical function," Woulfe says. "We can do this from tissue that's frozen, from our human heart bank, or from animals. We take away everything else except for those proteins that contract and relax. They are the fundamental basis of the function of the heart. This system enabled us to discover that HDAC6 directly regulates myofibril stiffness, most likely by deacetylating titin."

"We think this is a major finding, and there's still a lot more to do," McKinsey adds. "Scientific discovery is a series of building blocks, and we believe this is a key building block that allows us to understand the

mechanics of the heart better at a [molecular level](#), and also suggests therapeutic potential. We're going to keep vigorously working on the details of HDAC6 action in the [heart](#)."

**More information:** Ying-Hsi Lin et al, HDAC6 modulates myofibril stiffness and diastolic function of the heart, *Journal of Clinical Investigation* (2022). [DOI: 10.1172/JCI148333](https://doi.org/10.1172/JCI148333)

Provided by CU Anschutz Medical Campus

Citation: Defining the role of HDAC6 in regulating heart stiffness (2022, May 16) retrieved 11 May 2024 from <https://medicalxpress.com/news/2022-05-role-hdac6-heart-stiffness.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.