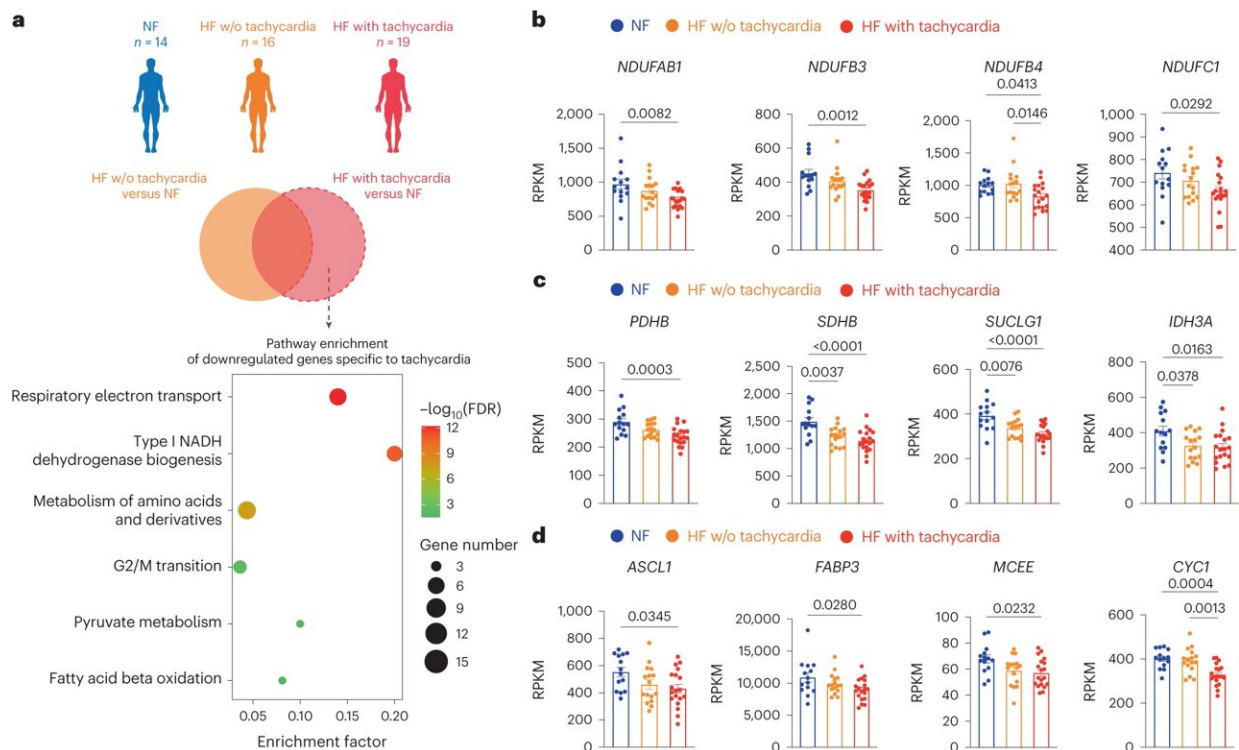


Engineered human heart tissue shows researchers the mechanics of tachycardia

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Tachycardia is associated with the downregulation of OXPHOS, TCA cycle and fatty acid oxidation in patients with HF. a, Transcriptomic analysis of myocardial samples from human patients with non-failing hearts (NF; n = 14, 49.1 ± 8.6 years old, 11 males and 3 females), HF without (w/o) tachycardia (HF; n = 16, 46.5 ± 14.3 years old, 12 males and 4 females) and HF with tachycardia (n = 19, 51.3 ± 11.9 years old, 16 males and 3 females). Genes exclusively downregulated in patients of HF with tachycardia were analyzed for pathway enrichment. Results are shown as a bubble plot. Bubble color and size represent false discovery rate (FDR) and gene number, respectively. b, Expression of OXPHOS genes *NDUFAB1*, *NDUFB3*, *NDUFB4* and *NDUFC1*. c, Expression of TCA

cycle genes PDHB, SDHB, SUCLG1 and IDH3A. d, Expression of fatty acid oxidation genes ACSL1, FABP3, MCEE and CYC1. In b–d, the expression levels are shown in reads per kilobase of transcript per million mapped reads (RPKM). One-way ANOVA with Tukey’s multiple comparisons test. Data are displayed as mean \pm s.e.m. Credit: *Nature Biomedical Engineering* (2023). DOI: 10.1038/s41551-023-01134-x

Heart rates are easier to monitor today than ever before. Thanks to smartwatches that can sense a pulse, all it takes is a quick flip of the wrist to check your heart. But monitoring the cells responsible for heart rate is much more challenging—and it's encouraged researchers to invent new ways to analyze them.

Joseph Wu, M.D., Ph.D., director of the Stanford Cardiovascular Institute and professor of medicine and of radiology, has devised a new stem cell-derived model of heart tissue that provides insight into conditions that crop up when heart cells beat out of control. In particular, Wu is studying a disorder called tachycardia, which increases the [heart rate](#) and can lead to cardiomyopathy, in which the heart loses its ability to pump blood sufficiently in people with otherwise healthy heart structures.

"Tachycardia is probably more common than we think," said postdoctoral scholar Chengyi Tu, Ph.D., who helped lead the work. "It's believed to be underdiagnosed because an increase in heart rate is quite common in different types of heart diseases, and it gets masked."

To study tachycardia-induced cardiomyopathy, the researchers engineered heart cells from [human stem cells](#) to uncover how our body's engine runs when it's in overdrive.

"Modeling tachycardia-induced cardiomyopathy with human stem cell-derived heart tissues allows us to better understand the impact of fast [heart rates](#) on our bodies," said Wu, the Simon H. Stertzer, M.D., Professor who is the senior author of the [study](#). It was published Nov. 27 in *Nature Biomedical Engineering*. Tu is the lead author.

Engineering heart cells

Unlike most types of organ tissues, heart cells are extremely difficult to grow in a lab. Patient heart cells cultured in a dish tend to de-differentiate—or lose their primary function and fail to beat.

"Ideally, you want to take samples of a patient's heart just after disease diagnosis, during illness and after treatment," Tu said. "To validate your discovery, you need a lot of replicates to give you statistical power, but clinically, it's impossible to sample so frequently."

Given the dearth of tissue, Wu and his colleagues grew more than 400 heart tissue samples from stem cells to look at how heart cells function, a process that spanned more than four years.

"Making engineered heart tissue is very different from culturing cells in a dish. The timeline is very long," Tu said. Generating heart cells from stem cells takes about two weeks; putting them together in a 3D tissue and maturing them takes almost two months.

Restoring the chemical balance

Using a wired chamber, the researchers electrically stimulated the cells, inducing tachycardia. They tested whether the cells could recover from tachycardia over the course of 10 days. During the first five days, the cells' ability to contract continuously declined to about 50% of normal

function. But once the researchers stopped the [electrical stimulation](#), the cells made a full recovery in five days.

That tracks with what doctors already know about tachycardia-induced cardiomyopathy—it's mostly reversible. When a person's heart rate slows back down, their heart tissue function returns to normal.

In another experiment, researchers induced tachycardia in a different group of engineered heart tissue. Then, after stopping stimulation, the team supplemented the tissues with NAD—a molecule that supports energy reactions—and saw the [heart cells'](#) function recover more rapidly. The supplemented tissues had recovered 83% of their original function by the first day, while the untreated group showed little improvement.

To validate their findings, the team compared the engineered heart tissues with clinical human data and canine model data. "I was surprised by how well the engineered heart tissues mimic the real human hearts," Tu said.

Uncovering the molecular switch

During tachycardia, the heart may struggle to pump blood to the rest of the body because the fast heart rate prevents the heart's chambers from filling up and contracting fully. If it persists for several days or weeks, which can happen in severe cases, [blood vessels](#) stop supplying enough oxygen to the heart tissue and the rest of the body.

When beating normally, the heart uses fat as an energy source, but breaking down fats requires a lot of oxygen. Without oxygen, the heart's fuel source switches to sugar in a process called metabolic rewiring. The fuel switch and hypoxia, or lack of oxygen, contribute to a decrease in the NAD/NADH ratio, a vital chemical duo that helps maintain the function of a protein in heart [tissue](#) known as SERCA.

"Varying levels of the SERCA protein act like a gas and brake pedal for a car," Tu said. When researchers increase the amount of NAD, the heart's gas pedal is thrust, and the SERCA protein strengthens the heartbeat of the engineered cells. When decreased, the engineered heart tissues hit the brakes, making them beat more weakly.

By giving patients NAD through an off-the-shelf supplement or by IV injection, clinicians believe they can restore the chemical balance and accelerate a patient's recovery.

Alongside a new possible supplement to help patients recover from tachycardia, the research demonstrates the importance of new methods to model disease. Last year, President Joe Biden signed the FDA Modernization Act 2.0 into law, which removed the requirement for animal testing before human drug trials.

"Now, there is more need for non-animal models to complement the animal models," Tu said. "This work proves that it's possible to model complex cardiac conditions using a universal non-animal model to study this disease and test possible therapeutics."

More information: Chengyi Tu et al, Tachycardia-induced metabolic rewiring as a driver of contractile dysfunction, *Nature Biomedical Engineering* (2023). [DOI: 10.1038/s41551-023-01134-x](https://doi.org/10.1038/s41551-023-01134-x)

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