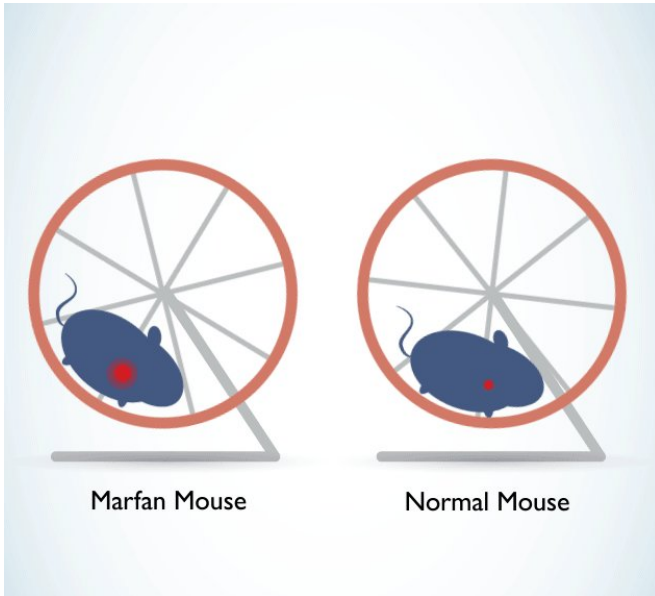


Researchers reverse heart failure in Marfan mice

14 November 2017



Marfan hearts fail when exposed to stress levels well-tolerated by normal mice. Johns Hopkins Medicine researchers were able to reverse this heart failure with drug therapies. Credit: Johns Hopkins Medicine

In experiments with mice that have a rodent form of Marfan syndrome, Johns Hopkins researchers report that even modestly increasing stress on the animals' hearts—at levels well-tolerated in normal mice—can initiate heart failure.

The findings, described August 4 in the *Journal of Clinical Investigation Insight*, revealed a novel cellular pathway in heart tissue that leads to [heart failure](#) and may serve as a model for a new standard of treatment for children with this aggressive form of Marfan syndrome.

Marfan syndrome is a genetic disorder that affects connective tissue throughout the body, elongating limbs, fingers and toes, for example. However, its worst effects are in the heart's blood vessels and valves. Aortic enlargement, heart valve leaks and

heart [failure](#)—marked by heart enlargement and weakened pumping action—are all potentially life-threatening.

The Hopkins team's interest in the mouse model grew out of the clinical experience of children with Marfan seen at The Johns Hopkins Hospital over decades.

"There is a small population of children with particularly aggressive and early onset symptoms of Marfan syndrome, who show dramatic signs of heart failure with only a relatively modest amount of valve leakage," says Hal Dietz, M.D., the Victor A. McKusick Professor of Genetics and Medicine, and professor of pediatrics at the Johns Hopkins University School of Medicine, whose research in Marfan syndrome's causes and treatment spans decades.

Studying heart failure in humans with Marfan syndrome is complicated in part because it is unclear whether the genetic defect in heart muscle is itself to blame, or whether stresses on the organ normally tolerated by healthy hearts—such as a modest increase in blood pressure—are present to trigger it, according to Rosanne Rouf, M.D., director of the outpatient heart failure program at the Johns Hopkins Bayview Medical Center and assistant professor of medicine at the Johns Hopkins University School of Medicine.

To address some of that complexity, Rouf, Dietz and their colleagues induced stress on the hearts of both wild-type and Marfan [mice](#) using a technique called transverse aortic constriction (TAC), which slightly tightens the aorta of experimental mice, mimicking raised blood pressure and inducing a precisely measureable amount of stress to the heart.

Researchers observed the mice's response to very mild TAC over the course of five weeks. The Marfan mice showed profound heart failure within

one week, while the wild-type mice did not fail at all by the end of five weeks.

Using echocardiograms, the researchers observed that the TAC Marfan mouse hearts had dramatically increased in size, weighing an average of 200 milligrams, compared to control mice, weighing an average of 75 milligrams—a sign of profound heart failure in both mice and humans.

"The difference between Marfan mice and healthy mice was striking," says Rouf. "If we expose Marfan hearts to just slight stress, they are in heart failure within one week, whereas normal mice tolerate this level of stress with no problems."

The researchers then studied what was happening within the [heart tissue](#) of TAC Marfan mice to induce heart failure. They found that the muscle cells of the heart were becoming enlarged because they were receiving abnormal growth chemical signals from neighboring support cells called fibroblasts, which make up the structural framework of the heart.

By tracking the signals among cells, the researchers found that one of the affected pathways was a protein called transforming growth factor beta, which is believed to be increased in people with Marfan syndrome and the source of many of the condition's symptoms, Dietz says.

Using this knowledge, Rouf and the research team repeated their experiments, but this time introduced drug therapies that inhibited the growth factor's signaling pathway. Specifically, they gave the mice losartan, a drug currently on the market for treating hypertension, and refametinib, an experimental drug in clinical trials for cancer, a disorder marked by abnormal cell growth. The researchers were able to reverse heart failure in all TAC Marfan mice.

Current treatments for heart failure in Marfan patients are limited to complicated surgeries at specialized centers to fix valve leaks, but patients do not always regain heart function as expected.

"This research shows that, rather than taking a one-size-fits-all approach, we need to be much more proactive in figuring out which children may have

earlier than usual signs of heart failure and operate before there is any decline in heart function to spare their hearts further stress."

The new studies also suggest that drugs such as losartan and the experimental anti-cancer medicine may one day be shown to reverse [heart](#) failure in children with the most aggressive form of Marfan. But, Dietz emphasized that much more animal and human research would be needed to demonstrate their value.

About 1 in 5,000 people have Marfan syndrome, [according to The Marfan Foundation](#). This includes men and women of all ethnic groups. There is a 50 percent chance that a person with Marfan syndrome will pass along the genetic mutation to their children.

More information: Rosanne Rouf et al. Nonmyocyte ERK1/2 signaling contributes to load-induced cardiomyopathy in Marfan mice, *JCI Insight* (2017). [DOI: 10.1172/jci.insight.91588](https://doi.org/10.1172/jci.insight.91588)

Provided by Johns Hopkins University School of Medicine

APA citation: Researchers reverse heart failure in Marfan mice (2017, November 14) retrieved 23 June 2018 from <https://medicalxpress.com/news/2017-11-reverse-heart-failure-marfan-mice.html>

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