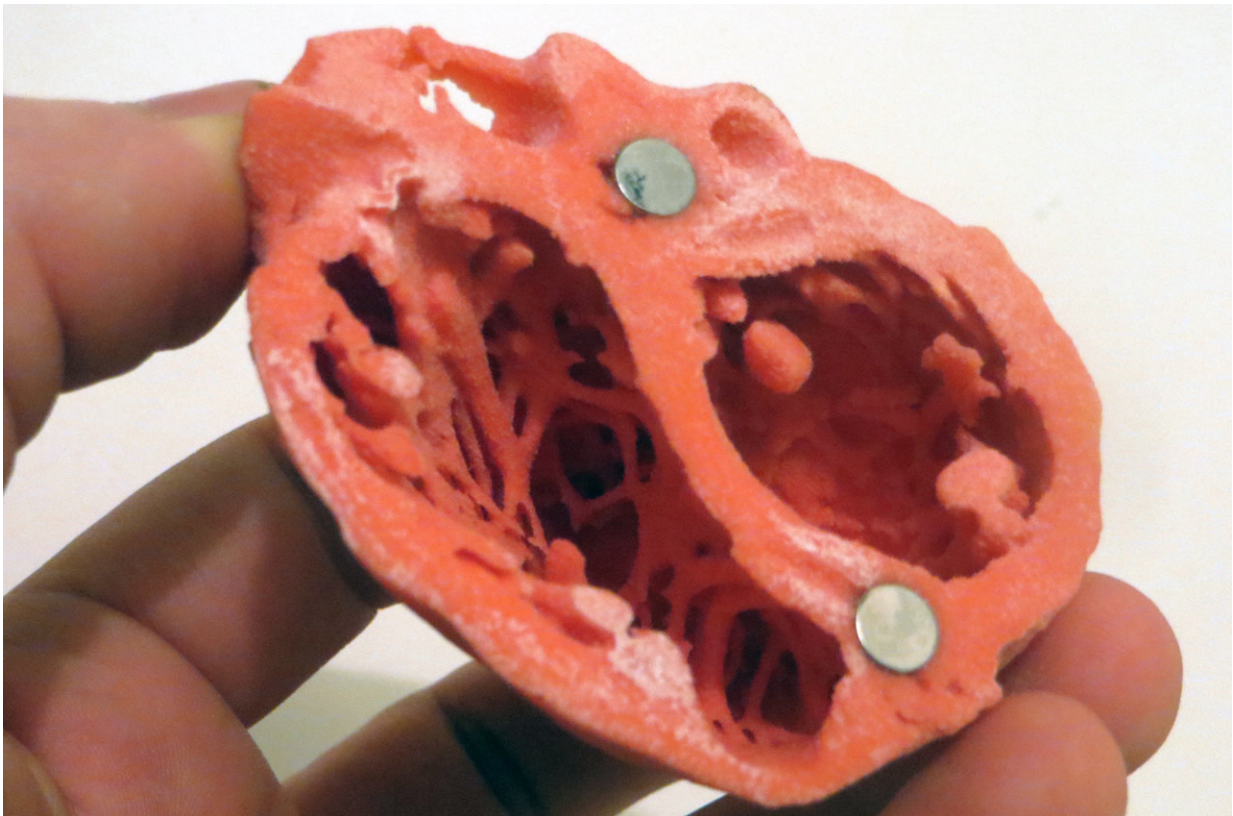


# Study homes in on possible cause of sudden cardiac deaths

March 3 2020, by Jennifer Brown

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3D Model of the heart by Dr. Matthew Bramlet. Credit: NIH

By studying the sick hearts removed from four patients undergoing heart transplants, researchers have identified a protein and a signaling pathway that may contribute to sudden death in an inherited form of heart

disease.

The patients were receiving new hearts to treat Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), a rare genetic disease that causes [abnormal heart rhythms](#) (arrhythmias) and increases the risk of sudden cardiac death, particularly during exercise or emotional excitement. ARVC affects between 1 in 1,000 and 1 in 1,250 people and is a leading cause of [sudden death](#) among young athletes who have no prior symptoms or cardiovascular disease diagnosis.

"We have identified a new pathway in heart cells that explains how arrhythmias occur in patients with ARVC," says Long-Sheng Song, MD, professor of internal medicine at the University of Iowa Carver College of Medicine and one of the leaders of the study team that included researchers from the UI and the Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College in Beijing, China. "We hope that new drugs targeting this pathway can now be developed, which might help us treat this devastating, progressive disease more effectively."

The team led by Song at the UI and Shihua Zhao, MD, at the Chinese Academy of Medical Sciences and Peking Union Medical College in China published their findings March 3 in the journal *Circulation*.

Current treatment of ARVC involves using medication or implantable cardioverter defibrillator devices to prevent the dangerous arrhythmias. However, because the molecular mechanisms that cause the arrhythmias are not well understood, there are no treatments that target the underlying problem.

By comparing cellular proteins in the hearts removed from the ARVC patients to proteins in healthy hearts, Song and his colleagues discovered a significant reduction in the levels of a protein called [integrin](#)  $\beta$ 1D in

ARVC heart muscle cells. This difference was not seen in other types of heart disease such as hypertrophic cardiomyopathy and ischemic heart disease.

To study the role of integrin  $\beta$ 1D, the researchers created genetically modified mice that lacked the protein in their heart muscle cells. At rest, the mice appeared to have normal heart function, but under stress or exertion, mice lacking integrin  $\beta$ 1D were more likely to develop arrhythmias.

Overall, the study found that loss of integrin  $\beta$ 1D prevents the mouse heart muscle cells from properly controlling the calcium levels that are critical for maintaining normal heartbeat. Increased heart rate or stress made the faulty calcium control worse in the mouse hearts. The team found that integrin  $\beta$ 1D helps control normal calcium signaling by stabilizing another important heart protein called RyR2. Gene mutations that disrupt the RYR2 protein cause many heart conditions that involve arrhythmias and lead to heart failure.

The findings implicate the loss of the integrin  $\beta$ 1D protein as a possible cause of ventricular arrhythmias in ARVC patients.

The team was also able to connect the loss of the integrin protein to a set of genetic mutations that cause ARVC in people. These mutations affect a so-called desmosomal protein that helps to form tight end-to-end contacts between [heart](#) muscle cells. The new study suggests that ARVC-causing mutations in a desmosomal protein result in the activation of a [signaling pathway](#), which in turn leads to the loss of the integrin beta 1D [protein](#).

"Our findings suggest that preventing the loss of integrin  $\beta$ 1D using existing or new drugs to inhibit this signaling pathway might provide a way to treat ARVC," Song says.

The next step for the research team will be to use their mouse model to identify compounds that target the signaling pathway and alter integrin  $\beta$ 1D levels and calcium control and see if these compounds can also block or prevent the development of ARVC.

**More information:** Yihui Wang et al. Integrin  $\beta$ 1D Deficiency-Mediated RyR2 Dysfunction Contributes to Catecholamine-Sensitive Ventricular Tachycardia in ARVC. *Circulation* 3 Mar 2020.

Provided by University of Iowa

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