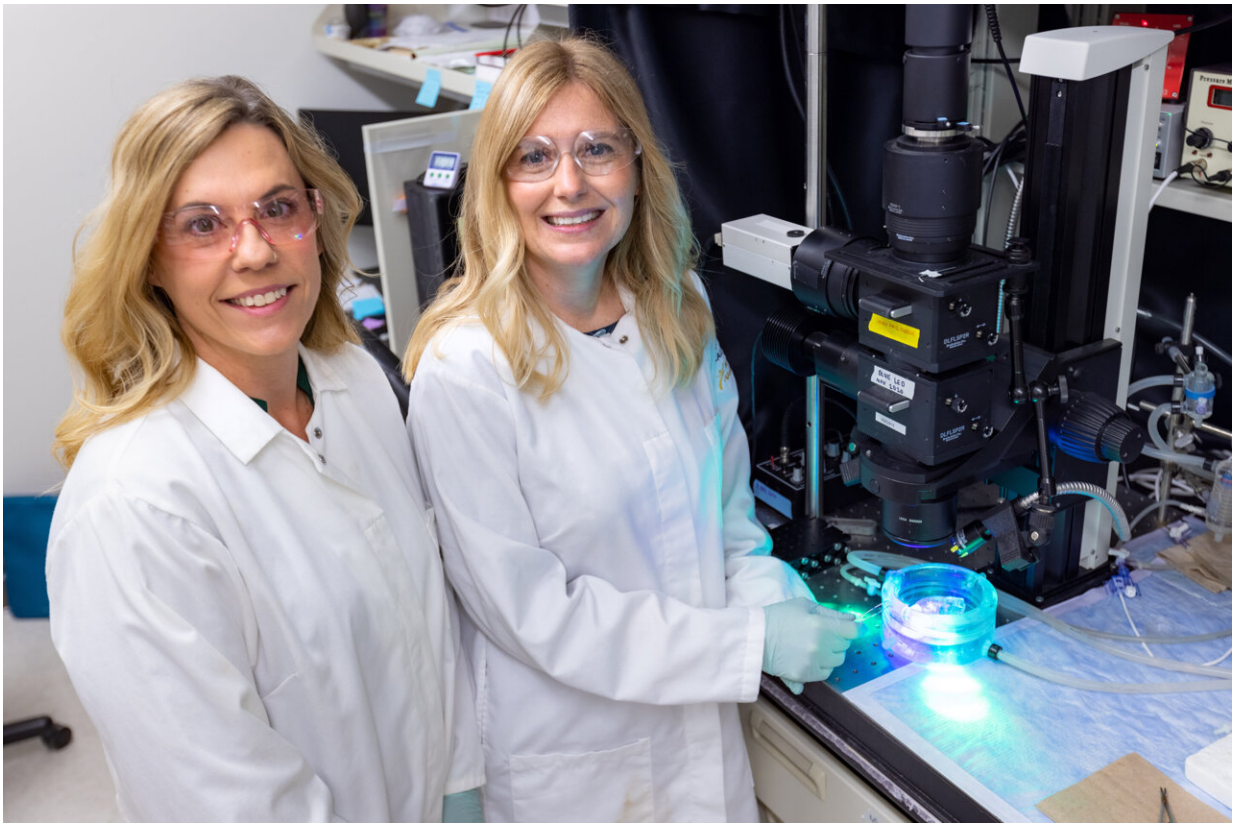


Female and male hearts respond differently to stress hormone in mouse study

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Professor Crystal M. Ripplinger (left) and Post-Doctoral Scholar Jessica L. Caldwell (right), UC Davis School of Medicine Department of Pharmacology. Credit: UC Davis

A [new study](#) published in *Science Advances* shows female and male

hearts respond differently to the stress hormone noradrenaline. The study in mice may have implications for human heart disorders like arrhythmias and heart failure and how different sexes respond to medications.

The team built a new type of [fluorescence imaging](#) system that allows them to use light to see how a mouse [heart](#) responds to hormones and neurotransmitters in real time. The [mice](#) were exposed to noradrenaline, also known as norepinephrine. Noradrenaline is both a neurotransmitter and hormone associated with the body's "fight or flight" response.

The results reveal that male and female mouse hearts respond uniformly at first after exposure to noradrenaline. However, some areas of the female heart return to normal more quickly than the male heart, which produces differences in the heart's [electrical activity](#).

"The differences in electrical activity that we observed are called repolarization in the female hearts. Repolarization refers to how the heart resets between each heartbeat and is closely linked to some types of arrhythmias," said Jessica L. Caldwell, first author of the study. Caldwell is a postdoctoral scholar in the UC Davis School of Medicine Department of Pharmacology.

"We know that there are sex differences in the risk for certain types of arrhythmias. The study reveals a new factor that may contribute to different arrhythmia susceptibility between men and women," Caldwell said.

Heart disease is the leading cause of death in the US

Heart disease is the leading cause of death for both [men](#) and [women](#) in the United States. It accounted for about 1 in every 4 male deaths and 1 in every 5 female deaths in 2020. Despite the impact on both sexes,

cardiology research has largely been [performed on male subjects](#).

In this study, the researchers were interested in looking at factors that may contribute to arrhythmias. Arrhythmias are a type of heart disorder where the [electrical impulses](#) that control heartbeats don't function properly. They affect somewhere between [1.5% to 5%](#) of the population.

Methods

The novel imaging system uses a mouse, called the CAMPER mouse, that has been genetically modified to emit light during a very specific chemical reaction in the heart—cAMP binding.

The cAMP molecule (an abbreviation of cyclic adenosine 3',5;-monophosphate) is an intermediate messenger that turns signals from hormones and neurotransmitters, including noradrenaline, into action from heart cells.

The light signals from the CAMPER mouse are transmitted by a biosensor that uses [fluorescence resonance energy transfer \(FRET\)](#). This FRET signal can be picked up at high speed and high resolution by a new imaging system specially designed for hearts. This allows the researchers to record the heart's reaction to noradrenaline in real time, along with changes in electrical activity.

This new imaging approach revealed the differences in the breakdown of cAMP in female and male mice and the associated differences in electrical activity.

Including female mice leads to discoveries

The researchers had not planned to study sex-based responses, according to Crystal M. Ripplinger, senior author of the study. But the researchers

started seeing a pattern of different reactions, which led them to realize the differences were sex-based.

Ripplinger, an electrical and biomedical engineer, is a professor in the Department of Pharmacology.

When she started her lab at the UC Davis School of Medicine over a decade ago, she exclusively used male animals. That was the norm for most research at the time. But several years ago, she began including male and female animals in her studies.

"Sometimes the data between the two sexes is the same. But if the data start to show variation, the first thing we do is look at [sex differences](#). Using both male and female mice has revealed clues into differences we would never have suspected. Researchers are realizing you can't extrapolate to both sexes from only studying one," Ripplinger said.

She notes that with the current study, it's not clear what the differences in cAMP and electrical activity may mean.

"The response in the female mice may be protective—or it may not. But simply documenting that there is a measurable difference in the response to a stress hormone is significant. We are hoping to learn more in future studies," Ripplinger said.

Additional authors on the study include I-Ju (Eric) Lee, Lena Ngo, Lianguo Wang, Donald M. Bers, Manuel F. Navedo and Julie Bossuyt from UC Davis; Sherif Bahriz from UC Davis and Mansoura University; Bing (Rita) Xu and Yang K. Xiang from UC Davis and VA Northern California.

More information: Jessica L. Caldwell et al, Whole-heart multiparametric optical imaging reveals sex-dependent heterogeneity in

cAMP signaling and repolarization kinetics, *Science Advances* (2023).
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