Stem Cells and Space

What Microgravity Can Teach Us About the Human Heart

BY AMY THOMPSON, *Staff Writer*

NASA Astronaut Kate Rubins examines iPSC-derived cardiomyocytes grown within a fully enclosed cell culture plate.

NASA

The musical "Rent" famously calculated 525,600 minutes in a year, but how do you measure a year in heartbeats? The human heart is a small but mighty muscular organ that sends oxygen-rich blood throughout the body as it beats more than 30 million times a year. But not all our hearts function as they are supposed to. When you measure a year in terms of lives lost to cardiovascular disease, the number is staggering. With nearly 18 million people dying from heart disease each year, the World Health Organization says this condition is the number one cause of death globally.

Cardiovascular disease damages heart muscle; once this tissue is damaged, there's no cure or means to restore its function. But what if the affected tissue could be fully regenerated? Induced pluripotent stem cells (iPSCs), which can transform into many different cell types—including heart cells, are at the forefront of regenerative medicine research. A team of investigators from Stanford University took cardiac iPSC research where it had never gone before: the International Space Station (ISS).

The team sent human cardiac cells derived from iPSCs to space to study heart function at the cellular level. Previous experiments have shown that spaceflight induces physiological changes in cardiac function, including reduced heart rate, lowered arterial pressure, and increased cardiac output. But most cardiovascular studies in space have been at the organ level, with little data on how microgravity affects the heart and its functionality at the cellular level.

Arun Sharma explains his experiment ahead of its launch on the SpaceX CRS-9 mission.

Arun Sharma

Joseph Wu of Stanford University's School of Medicine and Arun Sharma, a former Stanford graduate student and current assistant professor at the Cedars-Sinai Medical Center, set out to change that. As part of their ISS National Laboratory-sponsored investigation, they transformed iPSCs into specialized heart muscle cells called cardiomyocytes and examined microgravity-induced changes in those cells' contraction, growth, and gene expression. Through their findings, published in Stem Cell Reports, the team sought insights that could improve cardiovascular disease modeling and drug screening and lead to new cell replacement therapies to treat damaged heart muscle tissue.

"Our study is unique because it is the first to use human induced pluripotent stem cells to study the effects of spaceflight on human heart function," Wu said. "Space-based research may provide insight into cellular mechanisms that could not only benefit astronaut health during long-duration spaceflight but also lay the foundation for new insights into improving heart health on Earth."

From a Dream to Reality

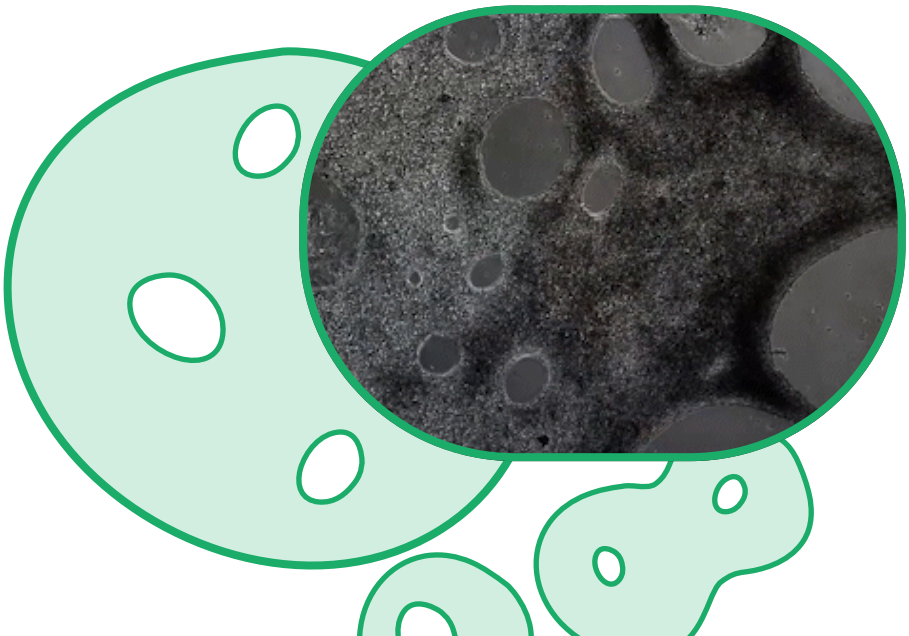
Growing up as a child in Huntsville, Alabama, Sharma's head was among the stars as he dreamt of exploring space. Today, he has his own research lab at Cedars-Sinai, where he creates models of the heart using iPSCs to study cardiovascular disease. A few years ago, an opportunity to leverage the ISS National Lab for cardiac stem cell research brought his childhood dreams of space to life.

When Sharma was a graduate student, he worked in Wu's lab at Stanford. As stem cell biologists, the researchers were pioneering new ways to use stem cells to study the heart when they heard about an opportunity to design stem cell experiments to send to the space station. The space station is home to a cutting-edge research laboratory that enables science not possible on Earth, and the two jumped at the chance to advance their research using this unique platform.

Microgravity induces changes in living organisms, and it is well documented that spaceflight can adversely affect cardiac function. Researchers have also found that long-term exposure to microgravity leads to the weakening of heart muscle tissue and other changes in cardiac function seen in patients with cardiovascular disease. These changes happen more quickly than on Earth, providing an accelerated model of disease progression.

"We wanted to answer the fundamental question of what exactly happens to the cells of the human heart in microgravity," Sharma said. "We had an idea of what happens on the organ level but not on the cellular level."

To this end, Wu and Sharma sought to examine microgravity's effects on the structure and function of cardiomyocytes derived from iPSCs. The benefit of using iPSCs is that they can easily be produced from donor blood or skin samples, and once they are transformed into cardiomyocytes, they are comparable to and share the same DNA as cells from the donor's heart.



A view of the cardiomyocytes beating under a microscope onboard the ISS.

NASA

"Induced pluripotent stem cells can transform into nearly any other cell type in the body, which means they are a prime resource for regenerative medicine because they serve as a single source of cells that could be used to replace those lost to damage or disease," Wu said.

Arun Sharma, NASA astronaut Kate Rubins, and Sarah Wallace of NASA's Johnson Space Center speak with CNN correspondent Rachel Crane at the 2017 International Space Station Research and Development Conference.

ISS National Lab

For the investigation, peripheral blood mononuclear cells from three donors were collected and converted into stem cells that were differentiated into cardiomyocytes before they were sent to space. The team cultured the iPSC-derived cardiomyocytes onboard the space station for a little more than a month and analyzed cellular structure, function, and gene expression.

"We used induced pluripotent stem cells—blood cells that have been reprogrammed—and turned them into beating human heart cells," Sharma said. "And we're hoping to use these cells to predict what's going to happen to a real patient in a clinic who has heart disease."

Long-Duration Cell Culture in Space

Wu and Sharma served as trailblazers in studying iPSC-derived cardiomyocytes in space, but they also paved the way for future long-duration cell culture on the space station. Researchers have been doing cell culture in space for decades, but they were limited by how long a space shuttle could remain in orbit for its mission—typically no longer than two weeks.

With the advent of the International Space Station and the commercial cargo program, researchers could grow cells in space for longer than ever, enabling more in-depth studies into how cells behave in microgravity. But first, facilities, hardware, and processes were needed to keep cells alive in space for more than a month.

"We think of the International Space Station as this permanent presence in low Earth orbit with this state-of-the-art science lab, but at first, we didn't necessarily have the proper cell culture facilities and all the equipment needed to support it," said NASA astronaut Kate Rubins, who worked on Wu and Sharma's investigation while on station. "One of the key things this experiment did was to really pioneer ways to keep the cells in culture long term."

According to Rubins, many technologies supporting the investigation, from the carbon dioxide incubator that housed the cells to the special dishes that the cells would grow on to even the method Rubins used to feed the cells, all needed to be created specifically for this project.

"Coming up with all the equipment and procedures needed for growing these cells for 30 days, it's really quite pioneering and will be the foundation for future stem cell investigations," she said.

While the team's cardiomyocytes were on the orbiting laboratory, Rubins was charged with their care. She ensured they were fed and documented their growth through photos and video captured with a special microscope she installed on station. Rubins said that, terrestrially, most cell culture is not all that thrilling. On Earth, the cells are settled on a plate, and they just sort of stick there and grow, but watching the cardiomyocytes growing and beating in space was more exciting.

"My crewmates laughed at me every time I raved about the microscope I got to use for this experiment as I was installing it," Rubins said. "But then when I was doing the actual imaging, they all came and floated down, huddled around the screen to get a glimpse of the cells beating."

Rubins said the microscope allowed her to document what was going on with the cells during the process, providing a wealth of data for the researchers to analyze spaceflight's effects on the growing cardiomyocytes.

NASA astronaut Kate Rubins examines heart cells onboard the ISS as part of the Effects of Microgravity on Stem Cell-Derived Heart Cells investigation.

NASA

"Through the video microscopy, we can record the images and learn a lot about the cells: cell size, cell morphology, and how it's changing over time," she said. "We could also quantify the strength of the contractions and the timing to compare to ground-based cells."

Understanding Spaceflight-Induced Changes

After the samples returned to Earth, the researchers looked for changes in cell morphology and structure and found no clear differences between the flight and ground control samples. However, functional changes within the cells remained even after the cells were returned to a normal gravity environment. The team also assessed the calcium-handling of the cells as part of their analysis.

Calcium plays a key role in regulating cardiac contractile function. The team discovered that the spaceflight cells not only displayed decreased calcium recycling but also beat irregularly. Additionally, the team performed RNA-sequencing analysis on the samples both during spaceflight and after their return to Earth. Among spaceflight, postflight, and ground control samples, the team discovered changes in the level of gene expression among more than 2,600 genes.

According to Sharma, the changes indicated that the cells adopted a unique gene expression signature while in space, which means they appear to be able to adjust to their environment. What's more, once the cells returned to Earth, they appeared to return to a pattern more similar to ground controls, despite having spent more than a month in space.

"We're surprised about how quickly human heart muscle cells are able to adapt to the environment in which they are placed, including microgravity," Wu said. "Microgravity is an environment that is not very well understood in terms of its overall effect on the human body, and studies like ours could help shed light on how the cells of the body behave in space."

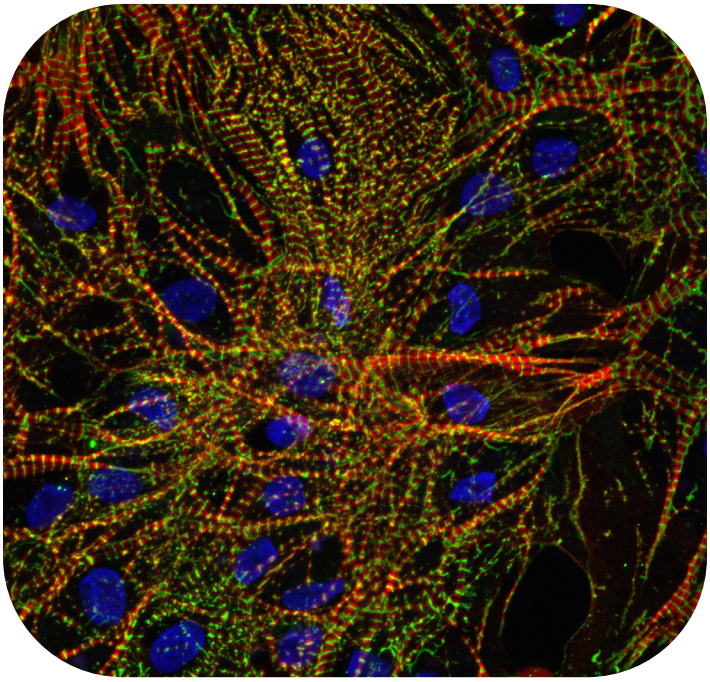
A view of the biocell that housed the heart cells on the space station.

Stanford University

Wu noted that while the changes observed were subtle, they were statistically significant. Additionally, it was difficult to say for sure whether the changes would affect how the heart functioned.

"Keep in mind our study was only five weeks—it's a short time. I don't know what gene changes would be if it was six months," Wu said. "I'm sure if the experiment ran for a longer period, you would see more changes."

But the biggest takeaway from this experiment is that it established the use of iPSCs as an accurate model to study cardiac function in microgravity. "This investigation laid the groundwork for future experiments that can utilize next-generation technologies to make the leap from 2D cells to 3D tissues and even organoids to further improve disease modeling and cardiac function in space," Wu said.



An image of heart cells grown in microgravity onboard the space station.

Stanford University

The project also helped set the stage for more complex types of stem cell experiments in space, including the burgeoning field of tissue chip research. Using iPSCs as a base model, researchers can design experiments to study other organ systems like the brain, kidneys, and more.

"This may seem like science fiction, but we're enabling real science, and other researchers are taking notice, which will hopefully initiate an influx of these types of experiments on the space station," Sharma said. "There are lots of different scientists that are thinking about how to use iPSC-derived cells in space to advance their research."