Finding triggers of birth defects in an embryo heart

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Researchers at Case Western Reserve University have found a way to create three-dimensional maps of the stress that circulating blood places on the developing heart in an animal model – a key to understanding triggers of heart defects.

The team has begun testing the technology to uncover how alcohol, drugs and other factors set off events that result in defects found in newborn humans.

Passing blood cells drag on the endothelial cells that line the growing heart, a phenomenon called shear stress, which has been linked to changes in gene expression that results in defects, most often in the valves. But precisely how they're connected is unclear.

"Alcohol exposure may affect shear stress by modulating the heart rate, but it may also involve vigor and/or timing of the contraction," said Andrew Rollins, associate professor of biomedical engineering and senior author of the new study. "Now that we have the tool, we can start to figure that out."

"We're analyzing early and late development of the heart and trying to make the connections that result in valve dysfunction," said Lindsy M. Peterson, a PhD student in Rollins' lab and lead author. Their work is published in the current online issue of the Optical Society of America's journal Biomedical Optics *Express*.

The pair teamed with research assistant professor Michael W. Jenkins; senior research associate Shi Gu; Lee Barwick, an undergraduate researcher now at Brigham Young University; and Michiko Watanabe, a professor of pediatrics at Case Western Reserve School of Medicine.

To look at the structure of the developing heart and blood flow, the researchers modified a technology called Doppler optical coherence tomography. Called OCT for short, they shine an infrared laser on the heart.

The reflections measured at various depths are used to create a three-dimensional image in much the same manner submariners use sonar to picture their surroundings in the deep sea. But the researchers add the dimension of time, creating movies of blood flow through the structures, needed to map shear stress.

They take their first images at two days, during a stage of heart development called cardiac looping. This is when the simple straight tube that's an embryo heart turns clockwise into a helix, forming the beginnings of two atria and two ventricles. They take more images at three days and again at eight days, when the septum, the wall between the left and right sides of the heart, has formed.

Working with Ganga Karunamuni, a pediatrics research associate at the school of medicine, the team is now pursuing a slate of experiments testing the quail heart model's response to alcohol exposure and will also test exposure to mental health drugs called selective serotonin receptor inhibitors. Alone or together, they can alter shear stress.

They are exposing the model to alcohol at a stage called gastrulation, when the embryo changes from two sheets of cells to a multi-layered organism.

This is a critical stage for induction of birth defects, Peterson said. In humans, it's an early stage when a woman may not know that she is pregnant.

Rollins said clinical applications are a long way off but the team has begun talking about possibilities.

"If it became feasible to screen a fetus for abnormal heart function," he said, "it might be possible to intervene with drugs, with gene therapy." Or, by using non-invasive pulses of infrared light to make the heart contract on demand – another technology the team is developing with clinical colleagues in Pediatric Cardiology– to prevent or treat defects before birth.

Provided by Case Western Reserve University