

Researchers work to take the pressure off newborns' lungs

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Children born with heart defects that pummel their lungs with up to three times the normal blood volume quickly find their lungs in jeopardy as well.

Georgia Health Sciences University researchers are working to take the pressure off by augmenting a natural recycling system that enables blood vessels to temporarily handle the extra workload until the [heart problem](#) is resolved.

They've found that system isn't getting enough energy to generate sufficient nitric oxide, the powerful blood vessel dilator. But drugs called PPAR agonists, already in use for adult lung injury and to lower [blood glucose](#) and lipids in diabetes, may provide the boost small, fragile blood vessels need.

"Our goal is to help protect the babies' lungs until their heart defect can be corrected," said Dr. Shruti Sharma, [molecular biologist](#) at GHSU's Vascular Biology Center. About 1 percent of newborns have a heart defect with half requiring surgery. Improved surgical and medical treatments have increased [survival rates](#) but the risk of related lung disease also can be deadly as the high blood flow turns flexible pulmonary blood vessels into narrow, rigid pipes. The result, [pulmonary hypertension](#), also puts additional strain on the heart.

Sharma is principal investigator on a four-year [American Heart Association](#) grant to better define key steps of the [recycling system](#) and

whether increasing PPAR signaling can help restore optimal functioning of the system when it's needed most.

It's known that the amino acid arginine interacts with nitric oxide synthase to form nitric oxide and while these babies have plenty of arginine, they can't access it. Studies at GHSU and elsewhere have shown that the arginine found in the [endothelial cells](#) which line blood vessels are most important for nitric oxide generation. That's where recycling comes in.

Under normal conditions, arginine helps nitric oxide synthase produce nitric oxide as well as the byproduct citrulline which interacts with two enzymes that convert it back to arginine, repeating the process anew. Sharma's early findings show that high pressures from the heart defect disrupts the cell's powerhouse, or mitochondria. That means insufficient amounts of the energy source ATP are produced, hindering the function of the molecular chaperone, HSP90, which helps the enzymes do their job.

"Upstream you can see one thing getting disrupted and downstream all the molecules it's regulating are affected," Sharma said.

That's where PPAR agonists come in. Dr. Stephen Black, a cell and molecular physiologist at the Vascular Biology Center who co-directs the Cardiovascular Discovery Institute, has shown that PPAR signaling falters in their animal model of pulmonary hypertension, impairing the cell powerhouse. In fact by blocking PPAR signaling, the researchers have produced the negative effects on the blood vessels without the heart defect.

"We hope that adding a PPAR agonist will improve mitochondrial activity and function and downstream help improve arginine recycling and nitric oxide production," Sharma said. She is retracing the recycling

process to see how the agonist impacts each known step as well as the desired bottom line of improved nitric oxide production.

"We're optimistic that we can get these two enzymes back to doing what they are supposed to."

Provided by Georgia Health Sciences University

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