Drug that improves blood flow may help find cause of exercise intolerance in cystic fibrosis

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Study participant Dana Curry, Research Associate Nichole Seigler, Dr. Ryan Harris, (foreground) and Pulmonary Fellow Dr. Justin Gregg. Credit: Phil Jones

A little white pill may help scientists learn why patients with cystic fibrosis have less exercise capacity than their peers, even if their lungs are relatively healthy.

The researchers hope the drug sildenafil – marketed as Revatio to treat pulmonary hypertension and Viagra for erectile dysfunction – as well as a cocktail of over-the-counter antioxidants will help them identify the

root of the blood vessel dysfunction that makes exercise difficult for these patients.

"We want to understand why these patients have blood vessel dysfunction and exercise intolerance even though there are all these new therapies improving their lung function," said Dr. Ryan A. Harris, clinical exercise physiologist at the Georgia Prevention Institute at the Medical College of Georgia at Georgia Regents University.

His previous studies have shown that it's leg fatigue rather than lung capacity that limits the exercise capacity of patients age 8-18 and evidence suggests that insufficient levels of blood and oxygen to their muscles could be to blame.

Harris is Principal Investigator on three new grants that should help resolve the dilemma. Grantors include the National Institutes of Health, the Cystic Fibrosis Foundation, as well as Vertex Pharmaceuticals Inc., makers of a new series of gene therapies, which appear to address genetic problems that produce the thick, sticky mucus that is a disease hallmark.

Harris and colleague Dr. Katie T. McKie, a pediatrician and Director of the Pediatric Cystic Fibrosis Center at GRU's Children's Hospital of Georgia, were the first to report blood vessel dysfunction and exercise intolerance in young cystic fibrosis patients in 2012 in *CHEST* Journal. Data indicates that cystic fibrosis patients who exercise live longer, Harris noted.

In cystic fibrosis, dehydrated mucus, which McKie equates to glue, becomes a bacteria magnet, producing inflammation, which further increases stickiness, McKie said. Mucus, which is supposed to provide a protective barrier, instead spurs chronic inflammation and clogs up healthy organ function, including the lungs, liver, pancreas, intestines,

and reproductive tract. In a decade of caring for these patients, McKie has seen huge strides in the laundry list of treatments these patients require including mechanical clearance of the thick mucus, inhaling hypertonic saline to hydrate and thin mucus, anti-inflammatory medication, and inhaled antibiotics. Most recently, gene therapies are coming online that more directly address the dysfunction of chloride channels, which are supposed to hydrate the mucus. These drugs should help normalize the consistency of the mucus, minimize lung damage, and enable improved nutrition, McKie said.

With life expectancy now at about age 40 compared with age 5 in the 1950s, longer-term consequences, such as the disease's impact on the cardiovascular system, are coming to the forefront, Harris said. "All the existing therapies are primarily tied to lung function," Harris said. "We are bringing a new dimension to the table."

Data suggests exercise could further reduce medical problems, improving quality and longevity of life. "They are going to feel better, have less pulmonary exacerbations, less infections, less systemic disease," Harris said.

The blood vessel or endothelial dysfunction Harris and McKie found in these young patients is essentially the reduced ability of blood vessels to respond to important cues, such as dilating when exercise or stress increase the body's demand for blood and oxygen. The dysfunction may be linked to chronic inflammation and oxidative stress, which, in turn, impair the body's ability to use nitric oxide, a major blood vessel dilator.

Sildenafil, known to relax muscles and increase blood flow and exercise capacity in other patients, should help further parse the role of blood flow and endothelial dysfunction. In a group of adult patients, they are measuring endothelial function and exercise capacity, giving patients either a single dose of sildenafil or a placebo, then retesting them. In a

related study, they are giving a lower-dose of sildenafil multiple times daily over four weeks before retesting. The single dose should open the "flood gates" of blood flow, Harris said. He expects that lower doses of sildenafil taken over more days, like exercise, will retrain blood vessels to respond more normally. "There is evidence in others who use it that blood vessels improve," Harris said.

Another study is using a cocktail of over-the-counter antioxidants in patients with high levels of oxidative stress, which ties into their chronic state of inflammation. As with the single dose of sildenafil, Harris expects to see an immediate – although temporary – improvement in exercise capacity in these patients.

"Right now we are looking at mechanisms that may be contributing to these problems but we also need to develop treatments that will provide sustained improvement," Harris said. While sildenafil and antioxidants may eventually help provide a solution, these studies won't answer that question, he noted.

The researchers also are beginning to get baseline measures of endothelial function and exercise capacity in patients who will qualify for a combination gene therapy that should be available next year so they can eventually assess the impact of the newest drugs on blood flow and exercise capacity.

More than 1,000 mutations of the cystic fibrosis transmembrane conductance regulator gene have been identified in patients. About half of patients could benefit from the new combination of lumacaftor and ivacaftor: lumacaftor helps move defective CFTR protein to the cell surface, and ivacaftor improves its function once there, according to the Cystic Fibrosis Foundation.

Harris and McKie have shown that even though patients can take in

oxygen well, they are not as good as their healthy counterparts at using it. At rest, oxygen saturation in the patients' blood was lower. During peak exercise, the amount of oxygen they consumed was 14 percent lower while expelled air had higher oxygen levels, indicating that their muscles were not as efficient at using it.

Another telltale sign was the fact that their blood vessels simply didn't dilate as well. The researchers put a cuff on the lower arm to increase blood flow through the brachial artery, a major vessel in the bicep. How much the artery dilates in response to the increased flow when the cuff is released depends on how much nitric oxide is available, and it was significantly less in patients versus controls.

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