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Research may yield improved treatment for diseased lungs

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A multi-institutional team of engineers, scientists and clinicians from the University of Wisconsin-Madison will study large-artery biomechanics that could play a role in heart failure in patients with pulmonary arterial hypertension.

Patients who have the disease may have narrowed, thickened pulmonary arteries in which scar tissue accumulates, blood flow is blocked and tiny blood clots form. There are treatments, but no cure, for pulmonary arterial hypertension.

Naomi Chesler, a UW-Madison assistant professor of biomedical engineering, is leading the project, which is supported by roughly $2 million in grants from the National Institutes of Health National Heart Lung and Blood Institute. She says the research team hopes to create improved diagnostic tools that enable them to track stiffening of large and small arteries and link these measurements with impaired ventricular function.

Currently, researchers believe pulmonary arterial hypertension is tied mostly to narrowing of the small blood vessels that carry oxygen-poor blood from the right ventricle of the heart to the pulmonary arteries in the lungs. "That reduction in diameter increases resistance, and that increase in resistance overloads the right heart, because it has to produce more pressure," says Chesler.

But in this process, she says, researchers have downplayed the role of

stiffness in the much larger pulmonary arteries, which also contributes to the right heart load.

For example, on the left side of the circulation, where oxygen-rich blood from the lungs flows to the head, limbs and major organs, researchers just recently have begun to understand that the properties of large "conduit" arteries are important to left-ventricle function.

"Changes can occur to large vessels that alter the way that pulse waves travel in the circulation and can end up overloading the left ventricle - not by increasing the mean pressure, but by altering the wave patterns," says Chesler. "So a goal of this project is to investigate whether that occurs also on the right side. If it does, it'll open up all sorts of new treatment possibilities, because we haven't been treating the large arteries because we haven't been thinking of them as part of the problem."

Researchers have measured impedance, which is like resistance but takes into account arterial stiffness, in human pulmonary circulation since the 1960s. But while these measurements show that large-artery stiffening occurs, the data don't show whether that stiffness affects ventricular function, says Chesler.

She, too, will measure impedance in the pulmonary circulation, focusing specifically on the role of a particular protein, collagen, in arterial stiffening. A key innovation in molecular biology will enable Chesler to use transgenic mice to explore the physical role of collagen-mediated large-artery stiffening in pulmonary arterial hypertension. She will induce large-artery stiffness in the mice in a process that mimics scleroderma, a disease in which the body produces too much collagen, the body's ubiquitous fibrous structural protein that strengthens blood vessels.

Patients with certain kinds of scleroderma also contract a kind of pulmonary hypertension that is particularly resistant to most treatments. So in a limited series of studies in such patients, Chesler also will investigate whether excess collagen negatively affects heart health. "My hypothesis is that patients with scleroderma do particularly poorly because all this excess collagen is stiffening the large and smaller vessels," she says. "We're not addressing that with modern treatments, and so we need to look at effects of stiffness on blood flow patterns and ventricular function in this context."

Chesler's collaborators include UW-Madison cardiology associate scientist Timothy Hacker; biostatistics and medical informatics associate scientist Jens Eickhoff; medicine assistant professors James Runo and Nancy Sweitzer; radiology and biomedical engineering assistant professor Scott Reeder; and Medical College of Wisconsin assistant professor Robert Molthen.

Also participating as research consultants are David Riley, University of Medicine and Dentistry of New Jersey professor of pulmonary and critical care medicine; and David Kass, Johns Hopkins University professor of cardiology, medicine and biomedical engineering.

Source: University of Wisconsin-Madison