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Research shows commonly prescribed medications could have adverse effects

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A research team with the Faculty of Medicine & Dentistry at the University of Alberta reported findings that significantly improve understanding of how widely used drugs in Pulmonary Arterial Hypertension (PAH) affect the heart health of treated patients.

The research shows that medications often prescribed for PAH could block the function of an important hormone in the heart, decreasing the strength of contraction of the right heart chambers, a potentially important and yet unrecognized adverse effect.

PAH is a disease that affects the blood vessels of the lungs, causing a progressive narrowing and restriction of the blood flow through the lungs. This narrowing puts a significant strain in the right chamber (right ventricle) of the heart that pushes the blood through the lungs. Eventually the right ventricle fails, causing heart failure and death.

One of the causes of the narrowing of the lung blood vessels is the increased levels of endothelin in the lungs, a hormone that constricts blood vessels throughout the body. Commonly used and very expensive drugs that block the actions of endothelin, which are called endothelin receptor antagonists, or ERAs, are now used throughout the world to treat PAH patients. However, the effects of these drugs in the right ventricle had not previously been studied, until now.

Led by cardiologist Evangelos Michelakis and cardiac surgeon Jayan Nagendran's in a laboratory setting, a multidisciplinary team of

cardiologists, cardiac surgeons, pathologists and scientists at the U of A studied human hearts from 50 PAH patients and laboratory models. The team showed that, while in the normal hearts, ERAs do not have significant effects because the endothelin levels are quite low, this is not the case in the diseased hearts of PAH patients. In the thickened right ventricles from PAH patients, the levels of endothelin are significantly increased.

This new finding suggests that this increase may be beneficial for hearts impacted by PAH, since endothelin is known to increase the strength of contraction of the heart muscle. In other words, as the right ventricle has to work harder pushing blood through the narrowed blood vessels, endothelin may help it function better, but this may be blocked by ERAs. The research team also showed that, as expected, ERAs decrease the strength of contraction of the diseased right ventricles.

"These new findings—that ERAs have direct effects on the right chambers of the heart—have important implications for treated patients" said Nagendran. "For example, PAH patients treated with ERAs can develop fluid retention (swelling), which is currently treated with diuretics. As fluid retention can be a result of decreased right ventricle function, the new findings suggest that this could be a previously unrecognized important adverse effect of these drugs."

In other words, while ERAs may have a beneficial effect on the lung blood vessels, they may also have unwanted effects on the heart.

"While this does not mean that PAH patients should stop using these drugs, this new research sheds more light on the overall mechanism of action of these drugs in PAH patients," said Michelakis. "It may also help physicians to better approach the treatment of PAH patients and design clinical studies to validate these new findings in large populations."

PAH tends to mostly affect younger women, although both sexes of all ages can be affected. The survival of PAH patients is similar to that of patients with metastatic breast cancer, but the yearly cost of treatment can be more than double compared to that of metastatic breast cancer, and can exceed $200,000 per patient.

More information: The study is published in the Jan. 18 issue of *Circulation Research*, a journal of the American Heart Association.

Provided by University of Alberta Faculty of Medicine & Dentistry