# New tests provide new insight into why patients are in heart failure

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These are Drs. Uzoma Ibebuogu and Inna Gladysheva of the Medical College of Georgia. Credit: Medical College of Georgia

A failing heart makes a lot of a hormone needed to eliminate the excess salt and water bloating the body but not enough of the enzyme needed to activate it, researchers say.

Using novel assays they developed, Medical College of Georgia researchers found people in heart failure have less of the enzyme corin needed to activate pro-ANP, or pro-atrial natriuretic peptide, a hormone made by heart muscle cells that, when active, helps reduce extra sodium and fluid that tax the cardiovascular system.

Low corin levels help explain why the heart's natural attempt to save itself is often thwarted in heart failure and researchers hope the new tests they developed can help identify those people.

"The question is always: If you have so much of this hormone that is supposed to increase diuresis, why are patients still in heart failure with all this fluid in their lungs?" says Dr. Uzoma Ibebuogu, cardiology fellow at the Medical College of Georgia.

Dr. Ibebuogu presented the findings at the American College of Cardiology Congress March 28-31 in Orlando where he was among five finalists for the Young Investigator Award.

When he and colleagues Drs. Guy Reed and Inna Gladysheva compared 14 patients in heart failure to 16 people with healthy hearts, they found those in heart failure had about 80 percent less corin. Their assays enabled measurement of corin as well as active ANP levels instead of only the total pro-ANP levels measured by current technology.

Their findings indicate that low corin levels may be an indicator of heart failure or even people at risk for the condition diagnosed in more than a half million Americans annually, says Dr. Gladysheva, cardiovascular researcher in the MCG School of Medicine.

Heart failure is becoming increasingly common as people survive heart attacks but live with heart muscles that are too weak to contract and/or relax properly. Blood comes into the right side of the heart from the body then to the lungs then back to the left side of the heart which pumps it out to the body. In heart failure, fluid backs up in the lungs and the rest of the body, causing swelling and making it hard to breathe. Patients often require frequent hospitalization and five-year survival rates are about 50 percent.

Treatment includes lifestyle changes such as losing weight, restricting sodium and drug therapy such as diuretics, to help kidneys eliminate excess fluid and sodium. More recently a substance similar to ANP, called brain natriuretic peptide, or BNP, also is being used.

As with pro-ANP, a heart experiencing failure makes more BNP, which scientists believe also plays a role in ridding the body of excess fluid and sodium.

But experience is showing the drug only helps some patients and MCG researchers suspect their new tests can better identify which ones. Because even if patients have enough corin and consequently enough active ANP - or BNP - there can still be problems with activation of downstream signals that ultimately tell the kidneys to increase elimination of salt and fluids.

At the other end of the spectrum, some patients Dr. Ibebuogu sees with weak heart muscles don't experience heart failure symptoms. "Maybe they are making enough corin to take care of themselves," he theorizes. He and Dr. Gladysheva plan to find out by comparing corin levels in these individuals to those with symptoms. They'll also explore whether a damaged heart makes less corin and if a corin substitute could activate more ANP.

MCG researchers also want to use their assays to look at levels of active ANP and corin in a larger number of patients to determine whether corin levels are a good predictor/indicator of heart failure. "Corin levels were low in heart failure patients but we can't say when they dropped," Dr. Gladysheva says. "Was it when they started developing heart failure or is it genetic?"

A recombinant protein also called corin identified in the late 1990s helped solve the mystery of how pro-ANP got cleaved into the active

state. That got Dr. Gladysheva wondering about the natural protein activator. She used antibodies to the recombinant protein to find the natural corin on the surface of heart cells, or cardiomyocytes. She later showed that corin and pro-ANP co-exist in the same heart cells in research published in *Journal of Molecular and Cellular Cardiology* in 2008.

That led to further exploration of why the heart's attempt to save itself from failure seems to fail so often and MCG researchers exploring their theory that corin levels might sometimes be to blame.

Source: Medical College of Georgia