Study finds higher levels of common diet-associated microbe elevates heart failure risk

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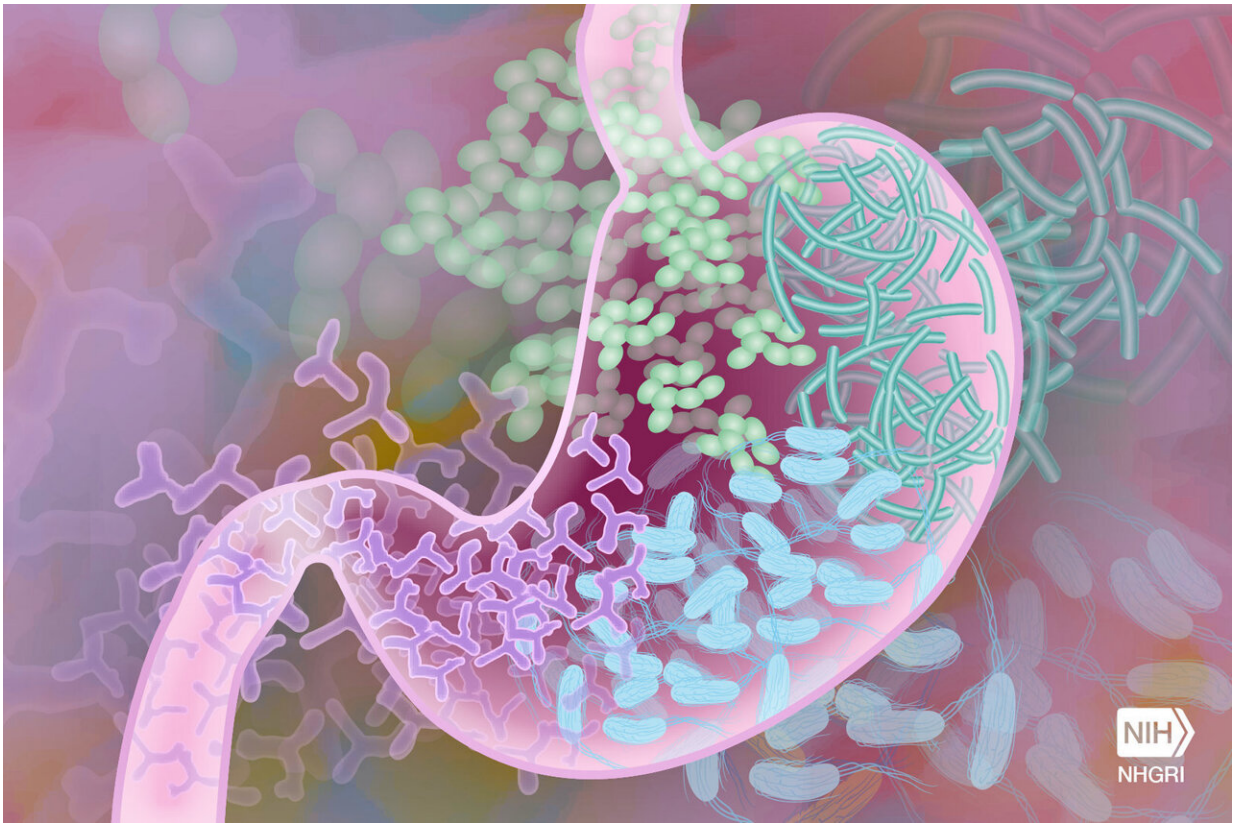

Illustration of bacteria in the human gut. Credit: Darryl Leja, National Human Genome Research Institute, National Institutes of Health

New research at Cleveland Clinic expands the link between what we eat and how the gut microbiome impacts our susceptibility to develop

different diseases—in this case, how a specific gut microbe-generated byproduct is linked to heart failure risk.

Elevated levels of phenylacetylglutamine (PAG)—a byproduct created when microbes in the gut breakdown dietary protein—can be directly linked to both increased heart failure risk and severity, according to findings published in *Circulation: Heart Failure*.

The new findings improve researchers' understanding of how the gut microbiome, through PAG levels, are linked to cardiac disease risks, and suggest potential approaches to modify PAG-associated risks through interventions such as diet and beta blocker use.

Elevated PAG levels also were shown to correspond with types of heart failure. For example, elevated blood PAG was observed in subjects with heart failure with preserved ejection fraction, a condition where the heart muscle doesn't relax enough between beats and becomes too stiff, making it less able to fill and consequently pump blood.

"Measuring blood PAG levels could provide striking value for predicting who's at risk for heart failure," says Stanley Hazen, M.D., Ph.D., department chair of Cardiovascular & Metabolic Sciences in Lerner Research Institute. "The data build a strong case that making this test available for clinicians would add to their arsenal of diagnostic tests for heart failure."

A team led by Dr. Hazen, who also serves as co-section head of Preventive Cardiology, previously discovered the link between PAG and cardiovascular diseases, including risk for heart attack, stroke and death in a 2020 study in *Cell*. In that study, PAG was shown to affect the function of adrenergic receptors on platelets, impacting functions like blood clotting risks.

This new study dug deeper into other potential functions of PAG with focus on heart failure. The team of investigators found that PAG levels were linked to heart failure risks through patient data from thousands of patients in two independent study cohorts, one from Europe and another the U.S. In other studies, introducing PAG into cardiac cells in the lab allowed researchers to better understand the mechanism behind PAG's association with heart failure—and a foundation for countering its effects.

"This study substantially expands the breadth of possible links between our diet and how our gut microbiome serves as a filter of our diet, impacting our susceptibility to develop different diseases," Dr. Hazen says. "In this case, gut microbes form a metabolite from the amino acid phenylalanine in dietary protein, adversely impacting the function of a beating cardiac muscle cell."

Targeting PAG to solve a critical health condition

About 6.2 million American adults have heart failure, a condition where the heart can't pump enough blood and oxygen to meet the needs of the body. Existing treatments include lifestyle changes, like reducing sodium or medications.

"Despite the latest advances in drug and device therapies, heart failure continues to be one of the leading causes of death and hospital admissions in the United States and worldwide," says W. H. Wilson Tang, M.D., research director for Heart Failure and Transplantation in the Department of Cardiovascular Medicine, and a co-author of the paper. "These studies suggest a better understanding on how we can modify PAG levels and lower heart failure risk is worth exploring."

In the initial studies on PAG in 2020, Drs. Hazen, Tang and colleagues showed how PAG affects multiple adrenergic receptors in

cells—including the beta-adrenergic receptor that beta-blockers target. Those studies included evidence for using drugs like carvedilol to counteract PAG effects.

One of the next steps Dr. Hazen's team is focusing on is to identify the bacteria and their enzymes that help to produce PAG, and development of therapeutic approaches to reduce PAG. Dietary interventions could also potentially help reduce risk, Dr. Hazen says.

More information: Kymberleigh A. Romano et al, Gut Microbiota-Generated Phenylacetylglutamine and Heart Failure, *Circulation: Heart Failure* (2022). DOI: 10.1161/CIRCHEARTFAILURE.122.009972

Ina Nemet et al, A Cardiovascular Disease-Linked Gut Microbial Metabolite Acts via Adrenergic Receptors, *Cell* (2020). DOI: 10.1016/j.cell.2020.02.016

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