

Identifying a subgroup of heart failure patients could lead to improved care

6 June 2018, by Christina Crowe



Researchers found that classifying heart failure patients based on the oxidant vs. antioxidant levels in the blood may serve as a predictive tool for guiding personalized antioxidant therapies. Credit: University of Alabama at Birmingham

For more than six decades, oxidative stress has been linked to heart failure, a progressive weakening of the heart muscle that can lead to death. While antioxidant supplements such as vitamin C, vitamin B and beta-carotene have been widely used in heart failure, they often prove ineffective.

Rajasekaran Namakkal-Soorappan, Ph.D., assistant professor of Molecular and Cellular Pathology, School of Medicine at the University of Alabama at Birmingham and colleagues at the PSG-Institute of Medical Sciences & Research, Coimbatore, India, sought to determine whether some [heart failure](#) patients might have reductive [stress](#) instead of oxidative stress, and whether that condition and its related mechanisms might help personalize treatment of heart failure patients, resulting in better outcomes.

Namakkal-Soorappan and colleagues Thiagarajan Sairam, Ph.D., and Ramalingam Sankaran, M.D., recruited patients at PSG Hospitals and found that classifying heart failure patients based on the oxidant vs. antioxidant levels in the blood, known as the circulating redox status, may serve as a predictive tool for guiding personalized antioxidant therapies.

Specifically, they found that members of a subgroup of heart failure patients have a hyper-reductive state, called reductive stress, and some have normal redox states. This raises some interesting questions about one of the most prevalent health issues facing Americans today.

"We are hypothesizing that the general treatment of antioxidants for heart failure may not be beneficial for a subset of heart failure patients," Namakkal-Soorappan said. "Patients with normal redox may not need any antioxidants. There is very solid evidence that antioxidants seem to fail in some patients, possibly because the right antioxidant was not used. The specificity of antioxidants is very important for its use."

The study, "Evidence for a hyper-reductive redox in a sub-set of heart failure patients," was published in the *Journal of Translational Medicine* on May 18. While sample size was relatively small—54 heart failure patients and 42 healthy controls—the results could impact how heart failure patients are treated and could guide personalized antioxidant therapies.

"This was the first evidence to correlate some heart patients' having too many antioxidants," Namakkal-Soorappan said.

The study used the circulatory redox state to separate the heart failure patients into normal redox, hyper-oxidative and hyper-reductive groups. A majority of patients, 42 percent, exhibited a hyper-oxidative state; nearly an equal number, 41 percent, exhibited a normal redox state; and 17

percent exhibited a hyper-reductive state.

"This finding suggests a strong implication for reductive stress in the progression of heart failure, but the mechanisms are unknown," Namakkal-Soorappan said.

Namakkal-Soorappan, along with Ivor Benjamin, M.D., and their research team at the University of Utah Department of Medicine, first discovered in 2007 that hypertrophy, or enlargement of the heart, is caused by a chaperone protein, alpha-B-crystallin, that is mutated in cardiac myocytes, the muscle cells of the heart associated with reductive stress.

"The cardiac cells respond to stress by enlarging," Namakkal-Soorappan said. "Patients who have this genetic mutation develop hypertrophy."

This enlargement normally occurs when patients are in their 40s or older, as aging usually leads to [oxidative stress](#).

"However, when we closely studied this mutated gene in animal models over their lifespans, transgenic mice developed hypertrophy in six to eight months, which is equivalent to a human being in his or her late 30s, and to our surprise, these mice had excess levels of antioxidants to create reductive stress," he said. "We thought it could be oxidative because of aging, but it's not." We decided to use the terminology of reductive stress—originally named in the 1960s and lately as seen in patients with Alzheimer's disease, but not often described in pathophysiology of other major human diseases."

What does this mean clinically?

Though the sample size is not sufficient to make definitive conclusions, it simply means that patients come in diverse forms, though their clinical diagnosis may be the same, and therefore in terms of treatment "one size does not fit all." Prescribing antioxidant treatment to all may not only not be beneficial, but could result in harm. The good news is that testing for reductive stress is accomplished easily in about two hours with a blood test, says co-senior author Ramalingam Sankaran, dean and

professor at the PSG Institute of Medical Sciences & Research, Coimbatore, Tamil Nadu, India. This medical research was generously supported in part by PSG & Sons' Charities in Coimbatore.

Future steps include a study to screen for reductive stress in several different heart diseases that lead to [heart failure](#), with a long-term goal of conducting collaborative research as part of a multi-site clinical trial, Namakkal-Soorappan says.

"We would like to study a couple thousand [patients](#) and screen them for genetic mutations, and analyze for correlations to study how human beings develop this [reductive stress](#)," Thiagarajan and Namakkal-Soorappan said.

Provided by University of Alabama at Birmingham

APA citation: Identifying a subgroup of heart failure patients could lead to improved care (2018, June 6) retrieved 25 November 2022 from <https://medicalxpress.com/news/2018-06-subgroup-heart-failure-patients.html>

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