Race and poverty appear to guide heart muscle DNA methylation in heart-failure patients

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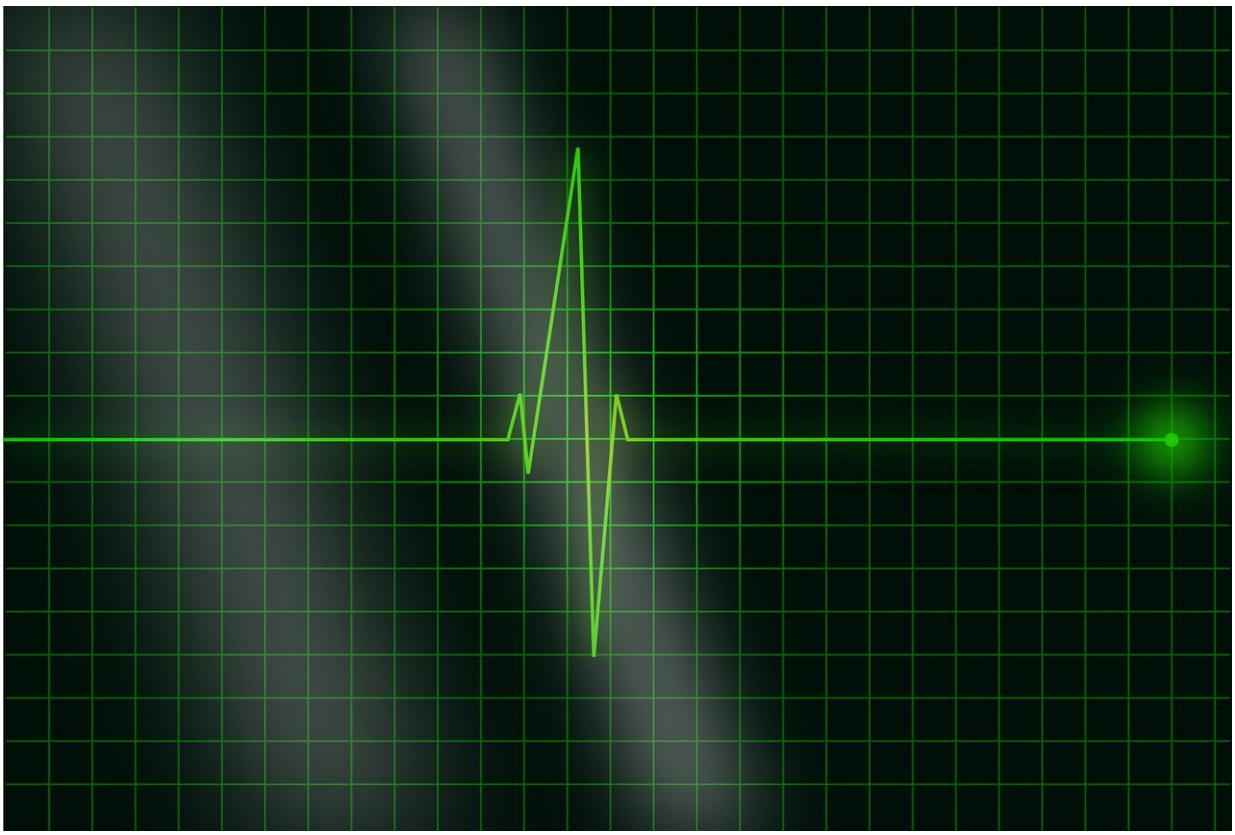

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Race associates with the risk of death from end-stage heart failure. So, identifying the molecular determinants of that risk may help the pursuit

of the novel diagnosis and prognosis of heart failure, and its therapy.

A University of Alabama at Birmingham study of end-stage heart-failure patients has found that cytosine-p-guanine, or CpG, methylation of the DNA in the heart has a bimodal distribution among the patients, and that race—African American versus Caucasian—was the sole variable in patient records that explained the difference. A subsequent look at the census tracts where the patients lived showed that the African American subjects lived in neighborhoods with more racial diversity and poverty, suggesting that the underlying variable may be a socioeconomic difference.

Methylation of DNA is a form of epigenetics, an indirect method of gene regulation that can change with gene-environment interaction. Previously the Wende laboratory has shown that these DNA modifications differentiate ischemic and non-ischemic heart failure.

The current UAB study included a pilot cohort of 11 heart-failure patients, followed by a testing cohort of 31 heart-failure patients, all of them male. The heart muscle tissue for the study was obtained when patients underwent surgery to install a left ventricular assist device, or LVAD—a small mechanical pump carried outside the body that helps a weakened heart pump blood. During the surgery, a piece of the left ventricle is excised; it is otherwise discarded but could be used for this study.

Heretofore, epigenetics has been an underexplored source of heterogeneity among patients with end-stage heart failure. The UAB researchers found differential promoter hyper-methylation of genes involved in fatty acid metabolism among African American heart muscle samples, relative to Caucasian samples, and also higher expression of lipogenesis genes. Such metabolic perturbations are a pathological hallmark of end-stage heart failure, as the heart gets more of its energy

from glycolysis—that is from glucose sugar—as it fails.

This finding generated two hypotheses, says Adam R. Wende, Ph.D., the associate professor in the UAB Department of Pathology who led the study: 1) that the epigenetic remodeling of cardiac gene regulation determines the therapeutic potential of LVADs, and 2) that epigenetic reprogramming of cardiac gene regulation constitutes a mechanism that may influence responsiveness to LVAD-induced cardiac unloading, meaning possible improvement of the heart as the pump takes over part of the work.

In contrast to the hyper-methylated promoters, the genes that had differentially hypo-methylated promoters, or lower levels of methylation, in African American hearts disproportionately represented inflammatory signaling cascades.

Additionally, the UAB researchers did a retrospective analysis of deaths from any cause in the 31 testing cohort patients two years after heart pump implantation. African Americans had a significantly higher rate of death, eight of 15 patients, versus Caucasians, two of 14.

The need for better treatment of heart failure is great. Only half of heart-failure patients respond to medical management, and African Americans experience worse clinical outcomes than any United States race or ethnicity.

"African Americans with heart failure are hospitalized at a rate 2.5-times higher than other races or ethnicities," Wende said. "Furthermore, despite a threefold higher mortality from heart-failure complications, the prevalence of heart failure among African Americans continues to increase."

"It is estimated that 3.6 percent of this community will live with heart

failure by 2030, exceeding the predicted prevalence of any other race or ethnicity in America," Wende said. "Therefore, it is paramount to identify and address the issues that underly these disturbing racial differences in heart-failure morbidity and mortality."

The UAB researchers noted the limitation that this was a single-center study; but Wende said, "Nevertheless, we provide preliminary evidence that socioeconomic factors are likely associated with racial differences in cardiac DNA methylation among men with end-stage heart failure."

The study, "Racial and socioeconomic disparity associates with differences in cardiac DNA methylation among men with end-stage heart failure," was published in the *American Journal of Physiology: Heart and Circulatory Physiology.*

More information: Mark E. Pepin et al, Racial and Socioeconomic Disparity Associates with Differences in Cardiac DNA Methylation among Men with End-Stage Heart Failure, *American Journal of Physiology-Heart and Circulatory Physiology* (2021). DOI: 10.1152/ajpheart.00036.2021

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