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Changes in how the heart produces energy may be the earliest signal of cardiac deterioration

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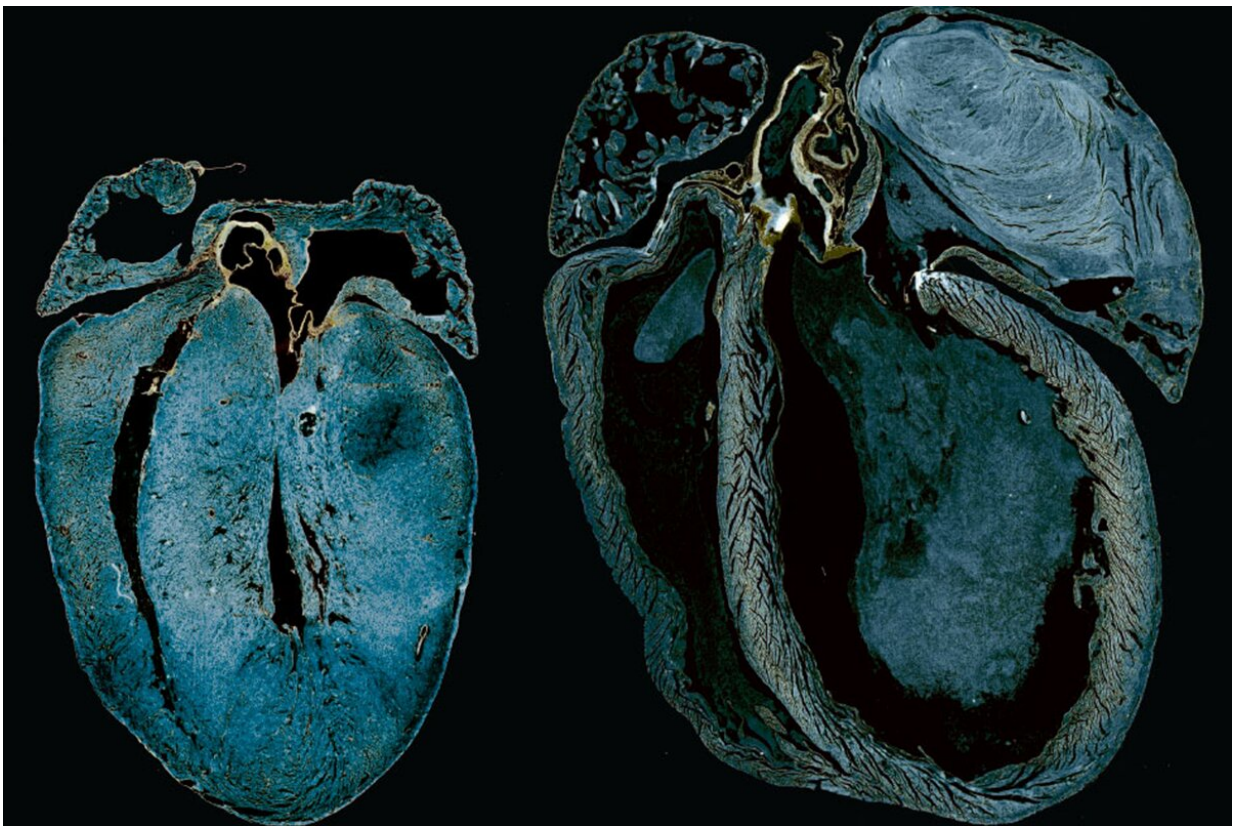

Sections of a normal heart (left) and a heart in which energy production deficiency caused dilation of the chambers (right), which is a sign of heart failure. Credit: Paul Delgado-Olguin/The Hospital for Sick Children (SickKids)

Heart failure is often identified only when the heart has already deteriorated. This is in large part because the cause is unknown for about 70% of people who experience heart failure.

Researchers at The Hospital for Sick Children (SickKids) have discovered that one of the earliest signs of heart failure is a change in how the heart produces energy, with findings offering a potential way to preempt heart failure before the heart begins to deteriorate.

Led by Dr. Paul Delgado-Olguín, a scientist in the Translational Medicine program, the research may also help to explain the diversity of causes underlying heart failure.

"We were surprised to find that dysregulation of energy production was the earliest sign of heart failure," says Delgado-Olguín. "People associate deficiency in energy production with later stage heart failure, but our findings show this could actually be the cause of heart failure, not a result."

Changes in energy production signal heart deterioration

In a healthy heart, a protein called lysine demethylase 8 (Kdm8) helps to maintain a balanced energy use, also known as metabolism, by repressing TBX15, another protein that decreases energy production.

In a study published today in *Nature Cardiovascular Research*, the research team analyzed a large dataset on gene expression, the process by which DNA is converted to proteins, in human hearts at a later stage of heart failure and found that KDM8 was less active. This allowed TBX15 to be more highly expressed, leading to changes in metabolism. Researchers also found that TBX15 was expressed at the highest levels in hearts where energy production genes were most strongly suppressed.

"There are many genes that help regulate energy production in our bodies, but we were able to identify changes in specific proteins that occur well before cardiac deterioration," says Delgado-Olguín.

After identifying change in energy production as an early sign of heart failure, the research team drilled down further to explore how metabolic pathways could be modified to prevent the failure. In doing so they found that the nicotinamide adenine dinucleotide (NAD^+) pathway, which regulates energy metabolism, was less active. The team was then able to intervene and prevent heart failure in a mouse model by providing NAD^+ injections and boosting energy production.

"This research suggests it may be possible to alter certain metabolic pathways to prevent heart failure before damage to the heart begins," says Delgado-Olguín. "Our research sets the stage to identify children and adults that may be at a higher risk of heart failure, and to improve energy balance in their hearts to prevent it."

Precision health could help predict and prevent heart failure

For the study team, this research is helping contribute to the future of Precision Child Health at SickKids, a movement to deliver individualized care for every child.

"Heart failure is so diverse," says Delgado-Olguín. "But if we could determine that an individual's particular heart is not using energy efficiently early on and is at risk of heart failure, we may be able to predict how they respond to treatment targeted to specific metabolic pathways that could prevent cardiac deterioration."

While international research on NAD^+ treatment in late-stage heart failure is underway, the team hopes that this latest research from the

Delgado-Olguín Lab will spark new research on early identification and preventative treatment.

More information: Abdalla Ahmed et al, KDM8 epigenetically controls cardiac metabolism to prevent initiation of dilated cardiomyopathy, *Nature Cardiovascular Research* (2023). DOI: 10.1038/s44161-023-00214-0

Provided by The Hospital for Sick Children