

# Cellular stress response – researchers discover potential therapeutic target for heart failure

**Researchers at the German Centre for Cardiovascular Research (DZHK) have identified a key molecule involved in a form of heart failure that has so far been difficult to treat.**

Heart failure with preserved ejection fraction (HFpEF) – a condition in which the heart pumps normally but still fails to meet the body's needs – is affecting an increasing number of people, particularly those with obesity or hypertension. While effective treatments exist for other types of heart failure, targeted therapies for HFpEF remain elusive.

Now, a research team led by Prof. Johannes Backs at Heidelberg University Hospital and at the Medical Faculty Heidelberg has identified a critical mechanism that contributes to HFpEF development: the enzyme NNT (nicotinamide nucleotide transhydrogenase), located in the mitochondria – the cell's energy powerhouses. NNT regulates the balance between energy production and protection against harmful oxidative stress caused by excess free radicals.

Lead author Dr Mark Pepin, from the Institute for Experimental Cardiology at Heidelberg University Hospital, says: "Our study is the first to show that cardiometabolic HFpEF is not solely a consequence of systemic diseases like obesity and high blood pressure, but also results from interactions between genetic and environmental factors."

## A Central Role in Pathological Cardiac Remodeling

Using a mouse model, the researchers demonstrated that animals lacking functional NNT were significantly protected from developing HFpEF – despite exhibiting obesity, hypertension, and glucose intolerance, just like their counterparts. This is the first study to provide direct evidence that NNT plays a central role in the pathological remodeling of the heart muscle.

"Our findings show that it's not just the metabolic diseases themselves that matter – it's also how the heart responds to the resulting stress," says Pepin. Of particular interest was the role of the growth factor FGF1, which is activated by NNT and is associated with stiffening of the heart muscle.

## New Prospects for a Previously Treatment-Resistant Condition

These insights open up new possibilities for targeted HFpEF therapies – for example, by inhibiting NNT. "This represents a promising strategy to better understand and treat one of the most common and hardest-to-manage cardiovascular diseases," says Backs.

### Publication:

Pepin ME, Konrad PJM, Nazir S, et al. Mitochondrial NNT Promotes Diastolic Dysfunction in Cardiometabolic HFpEF. *Circulation Research*, Mai 2025  
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### Press release

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### Further information

- German Centre for Cardiovascular Research (DZHK)