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Left ventricular (LV) diastolic dysfunction is a hallmark of Heart Failure with preserved Ejection Fraction (HFpEF)

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Left ventricular (LV) diastolic dysfunction is a hallmark of Heart Failure with preserved Ejection Fraction (HFpEF), an escalating global health challenge. We demonstrated selective depletion of the oxidized form of nicotinamide adenine dinucleotide (NAD+) and the rate-limiting enzyme of the NAD+ biosynthetic salvage pathway, nicotinamide phosphoribosyl transferase (NAMPT), in human myocardium with LV diastolic dysfunction. Despite reduced expression of NAMPT protein, we showed that NAD+ can be replenished in human myocardium with diastolic impairment ex vivo and the murine HFpEF model. In a murine model of metabolic alteration-driven HFpEF [a combination exposure to high-fat diet (HFD) and L-N G -Nitro arginine methyl ester (L-NAME)], we compared the benefits of NAD+ precursor supplementation versus dietary intervention. We tested NAD+ repletion by nicotinamide riboside (NR) supplementation using two clinically-relevant strategies: 1) Prophylactic NR repletion before HFpEF onset and 2) Therapeutic NR repletion after the development of HFpEF. We found that dietary intervention restored myocardial insulin-dependent glucose uptake and glycolysis but did not rescue HFpEF. In contrast, both NAD+ repletion strategies prevented or rescued HFpEF, respectively, plausibly due to restoration of myocardial energetics, mitochondrial respiration and upregulation of antioxidant defence.

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