JACC: BASIC TO TRANSLATIONAL SCIENCE
PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION.

VOL. 9, NO. 6, 2024

EDITORIAL COMMENT

Coordinate Targeting of Mitochondrial Energetics, Antioxidant Defenses, and Inflammation

Is NAD^+ Boosting an HFpEF Elixir?*

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Heart failure with preserved ejection fraction (HFpEF) is associated with female sex, obesity, metabolic syndrome, hypertension, inflammation, and aging. Furthermore, cardinal HFpEF biochemical features include perturbations in mitochondrial energy metabolism and flexibility, in concordance with reduced levels of oxidized nicotinamide adenine dinucleotide (NAD^+) and of nicotinamide phosphoribosyltransferase (NAMP), an enzyme controlling NAD^+ recycling through the NAD^+ salvage pathway.[1,2] These biochemical signatures may be foundational to HFpEF pathophysiology as NAD^+ levels control redox enzyme reactions and sirtuin enzyme activity, and function as a substrate for multiple cellular homeostasis pathways.[3]

In this context, it is not unexpected that NAD^+ precursors nicotinamide and nicotinamide riboside (NR) improve diastolic function and aspects of myocardial mitochondrial bioenergetics in HFpEF models.[1,2] In addition to exploring underlying mechanisms of action, an important question is whether NAD^+ boosting exclusively improves myocardial biology or modifies additional risk factors or comorbidities associated with the pathophysiology of HFpEF. To begin exploring some of these questions, in this issue of *JACC: Basic to Translational Science*, Koay et al[4] assessed sex-specific effects of preventive vs therapeutic NR in a high-fat diet (HFD) and nitric oxide inhibition (L-NAME, to evoke hypertension)-induced HFpEF model. Furthermore, they evaluated the effect of HFD and L-NAME reversal on these same HFpEF parameters. Interestingly in this study, NR supplementation, in the presence of HFD/L-NAME, had more pronounced ameliorative effects in male mice on blood pressure and cardiac hypertrophy, and on maintaining cardiac relaxation and global longitudinal strain. In contrast, when NR was introduced 5 weeks after HFD/L-NAME, NAD^+ boosting had similar beneficial effects in male and female mice. In contrast, cessation of HFD/L-NAME reversed body weight, fat mass, and insulin sensitivity, effects that were not evident in response to NR supplementation in the presence of HFD/L-NAME. Concomitantly, reversal of HFD/L-NAME similarly restored blood pressure and certain aspects of diastolic function in both sexes.

Together, these data support the potential for the use of NR in the treatment of HFpEF, although potential sex difference in efficacy were identified. Furthermore, this study highlighted that reversal of comorbidities (obesity and hypertension) had broader systemic effects compared with NR. At the mechanistic level, cardiac proteomics analysis implicated that NR supplementation with HFpEF increased tricarboxylic acid cycle activity, mitochondrial oxidative metabolism, and branched chain amino acid metabolism. These data were supported by NR-augmented mitochondrial basal and energized metabolism in cardiac tissue homogenates. At

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2024.02.013

the same time, distinctions in the systemic effects of NR vs HFD/L-NAME reversal were also operational at the level of cardiac metabolism with indirect markers of improved insulin sensitivity and reduced ketone utilization evident following caloric and hypertensive risk factor reversal, but not with NR supplementation. In addition to fuel metabolism pathway alterations, NAD^+ boosting resulted in elevation of NADPH levels and reduced glutathione, pointing to enhanced antioxidant defense capacities, an essential component in maintenance of redox homeostasis.

Taking these results together, this study uncovered distinctions between the reversal of HFpEF comorbidities and NR at the systemic level and uncovered a potential sex difference in the efficacy of NR as a preventive supplement against the development of HFpEF. This study also reinforced the role of NR in improving mitochondrial energetics and uncovered additive benefits of NR in enhancing antioxidant defenses in the myocardium. An additional interesting feature of NR, compared with nicotinamide is that it bypasses NAMP in NAD^+ salvage, a feature of NR confirmed in human myocardial tissue in this study.[4]

Emerging pilot human studies support that NR supplementation attenuates 2 additional HFpEF risk factors: insulin resistance and inflammation.[5] The data on insulin sensitivity remain limited, although data supporting that NR blunts inflammatory signaling are emerging in both innate and adaptive immune cells, in inflammatory and autoimmune conditions, and in degenerative diseases linked to inflammation, including in heart failure with reduced ejection fraction.[5] In HFpEF, inflammation is manifest at the level of innate and adaptive inflammatory cell infiltrates into the myocardium[6] and by circulating inflammatory peptides identified by multiplex immunoassaying (Olink) analysis.[7] Interesting, these proteomic inflammatory signals correlated directly with the extent of echocardiographic features of HFpEF.[7] Collating these findings suggests that NAD^+ boosting with NR may target broader underpinnings of HFpEF including metabolic perturbations, disruptions in redox homeostasis, and dampening of inflammatory signaling.

A recent question arising is whether increased NAD^+ catabolites N1-methyl-2-pyridone-5-carboxamide (2PY) and N1-methyl-4-pyridone-3-carboxamide (4PY), which associate with excess major adverse cardiac events (MACE),[8] may be an adverse consequence of NAD^+ boosting. Although this association is important, it currently needs to be evaluated with caution, given that these metabolites are directly increased by inflammation via the leukocyte cell surface glycoprotein and NADase, CD38.[9] In addition, the direct correlation of 4PY with C-reactive protein in the MACE association study[8] questions whether the increased 2PY/4PY levels are causative of MACE in patients at risk for coronary artery disease or are reflective of the underlying inflammatory milieu. It is interesting that in the context of the heart, genetic and antibody-directed inhibition of CD38 attenuates doxorubicin-induced cardiomyopathy.[10] Here, too, the mechanisms uncovered included maintenance of mitochondrial function and the blunting of inflammatory gene expression.[10]

Integrating these findings suggests that NR, via potential ameliorative effects on mitochondrial metabolism, antioxidant defenses, and inflammation may be an intriguing adjunctive supplement for the management of HFpEF. However, at the same time, the mechanism whereby NAD^+-catabolic metabolites are associated with MACE need to be resolved. Nevertheless, despite these intriguing findings, it should be recognized that major limitations of this study include the short-term nature of the experimental model and the relative youth of the mice vs the chronic and age-associated pathophysiology of HFpEF in humans.

In addition to these limitations, the biggest challenge to incorporate NAD^+ boosting into the lexicon of HFpEF management will be the ability to validate the efficacy of NR in HFpEF in human clinical trials. The practical challenges here are illustrated by the 2023 ACC Expert Consensus Decision Pathway on Management of HFpEF. This panel advises, given the beneficial effects in mulitple clinical trials, that there is now an increasingly foundational role of sodium-glucose cotransporter 2 (SGLT2) inhibitors for the management of HFpEF. SGLT2 inhibitors similarly exhibit antioxidant and anti-inflammatory effects and improve cardiac mitochondrial oxidative function in HFpEF, albeit through different mechanisms. Furthermore, the American College of Cardiology Consensus Statement places a strong emphasis on comorbidity reduction in HFpEF, effects also shown in Koay et al's study.[4] In this context, these recommendations add an additional hurdle to validating effects of NAD^+ boosting in human disease, because the benefits of NR would need to be above and beyond the expanding therapeutic armamentarium and comorbidity management strategies targeting HFpEF: a high bar indeed, although an intriguing

concept to explore given the pleiotropic effects of NAD^+ boosting.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Sack is funded by the Division of Intramural Research of the National Heart, Lung, and Blood Institute, National Institutes of Health (ZIA-HL005102). Dr Sack's laboratory studies mechanisms of action of nicotinamide riboside (NR) on immunomodulation in human inflammatory disease. His laboratory receives no direct financial support or compensation but acquires NR and matching placebo from Chromadex through Cooperative and Development Research Agreements and Material Transfer Agreements.

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KEY WORDS diastolic heart failure, heart failure, NAD^+ repletion