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LETTER TO THE EDITOR

Transformative Cardiometabolic Advancements

Metabolic inflexibility and mitochondrial dysfunction in HFpEF: a cardiometabolic perspective

Gianluca Pagnoni,[1] Aurora Vicenzi,[2] and Francesca Coppi[3]

[1]*Cardiology Unit of Emergency Department, Guglielmo da Saliceto Hospital, Piacenza, Italy;* [2]*National Institute for Cardiovascular Research (INRC), Bologna, Italy; and* [3]*Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena, Italy*

TO THE EDITOR: We read with great interest the study demonstrating that cardiac metabolic remodeling promotes mitochondrial dysfunction through dicarbonyl and glycative stress in heart failure with preserved ejection fraction (HFpEF). The identification of mitochondrial protein glycation as a mechanistic link between altered substrate utilization and impaired oxidative phosphorylation provides important insight into HFpEF pathophysiology (1).

The reported accumulation of mitochondrial advanced glycation end products and its association with diastolic dysfunction supports the concept that metabolic stress directly contributes to myocardial dysfunction rather than representing a secondary phenomenon (1). Impaired glyoxalase activity despite increased enzyme expression further suggests that endogenous detoxification pathways are insufficient under conditions of oxidative stress.

These findings align with evidence that HFpEF is characterized by metabolic inflexibility, including impaired glucose oxidation alongside alterations in fatty acid metabolism (2). Although several studies have reported preserved or increased reliance on fatty acid utilization, emerging evidence suggests that fatty acid oxidation may itself become inefficient or impaired during HFpEF progression, indicating that increased lipid dependence does not necessarily translate into effective energy production (2). Maintenance of a balanced interplay between substrates appears essential for optimal myocardial performance, whereas disruption of metabolic flexibility may contribute to energetic inefficiency, mitochondrial dysfunction, and contractile impairment (3).

From a clinical perspective, these metabolic alterations are highly relevant, as functional capacity and outcomes in cardiovascular disease are strongly influenced by adherence to therapeutic strategies, such as exercise-based rehabilitation, which remains suboptimal despite proven benefits (4). In parallel, accurate and reproducible phenotyping is crucial; advances in echocardiographic assessment, particularly tissue Doppler-derived indices, may improve reliability in longitudinal evaluation (5).

Importantly, the translational relevance of experimental findings depends on the ability of preclinical models to reflect the complexity of human HFpEF. Models incorporating cardiometabolic stressors have highlighted the systemic nature of the disease. For instance, combined dietary and diabetogenic interventions reproduce an HFpEF phenotype characterized by preserved ejection fraction, diastolic dysfunction, and profound alterations in myocardial substrate metabolism, including increased fatty acid oxidation and impaired ketone utilization (6). These observations reinforce the concept of HFpEF as a cardiometabolic syndrome.

Despite the strength of the reported associations, causality between dicarbonyl stress and mitochondrial dysfunction remains to be established. Targeted interventions aimed at reducing glycative stress will be essential to determine whether these mechanisms represent viable therapeutic targets.

In conclusion, these findings provide important mechanistic insight into the metabolic-mitochondrial axis in HFpEF and support a more integrated framework linking substrate metabolism, mitochondrial function, and clinical phenotyping.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

G.P. drafted manuscript; G.P. and A.V. edited and revised manuscript; F.C. approved final version of manuscript.

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Correspondence: A. Vicenzi (aurora.vicenzi@gmail.com).
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