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Harnessing Endogenous Vasoprotection: Novel Strategies to Target Coronary Microvascular Dysfunction in Heart Failure with Preserved Ejection Fraction

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SHORT SUMMARY:

Heart failure with preserved ejection fraction (HFpEF) is increasingly recognized as a syndrome driven, in part, by coronary microvascular dysfunction and rarefaction, which impair myocardial perfusion and contribute to left ventricular (LV) diastolic dysfunction. We hypothesize that targeted modulation of vascular signaling pathways can restore microvascular integrity and improve cardiac performance in HFpEF. Our studies demonstrate that pharmacological inhibition of adenosine kinase (ADK) and phosphodiesterase 9A (PDE9A) enhances coronary microvascular vasodilator function and ameliorates LV diastolic abnormalities, supporting a mechanistic link between nucleotide signaling and vascular health in HFpEF. Furthermore, large-scale proteomic

analyses of myocardial and vascular tissues from HFpEF models reveal dysregulation in metabolic, inflammatory, and cytoskeletal pathways that may underlie microvascular disease. We propose that these proteomic signatures can serve both as mechanistic insights and as targets for therapeutic intervention. Based on these findings, we hypothesize that spatially and temporally controlled activation of endogenous vasoprotective mechanisms—such as purinergic and cyclic nucleotide signaling—can yield sustained improvements in coronary microvascular function and overall HFpEF outcomes. This approach opens new avenues for precision therapies aimed at restoring vascular homeostasis in HFpEF.

SHORT BIO:

At the Medical College of Georgia, Augusta University, I serve as a Professor of Physiology and lead a cardiovascular research laboratory. I am a medical doctor with a Ph.D. in biomedical sciences. After earning my medical degree, I transitioned to a basic scientist in my chosen field, cardio- and cerebrovascular pathophysiology, and underwent postdoctoral research training at New York Medical College in Valhalla, United States. Subsequently, I became a senior research fellow at the University of Oxford in the United Kingdom. My laboratory has been at the forefront of applying microvascular physiology, imaging, and molecular biology technologies. Over the past 20 years, my lab has developed specialized expertise in studying human microvascular pathological complications related to degenerative disorders. Research in my laboratory has received support from NIH R01 grants, and I have led and sponsored research and training projects funded by the AHA. These research programs are fuelled by long-standing collaborative relationships with investigators both within and outside my institution, all sharing a common focus on the mechanisms of vascular pathologies.

My current research program examines how small vessel disease contributes to diastolic heart failure linked to cardiometabolic disease.

I am committed to fostering diversity, equity, and inclusion in my research and mentoring. I strive to create a supportive environment in my laboratory where individuals from all backgrounds can thrive and contribute unique perspectives to advance science. My expertise in studying the function of human and rodent cardio- and cerebrovascular function and molecular regulation of age-induced cellular processes are represented by 110 per reviewed publications, receiving more than 7,300 citations, h-index: 50. I believe my expertise is invaluable in furthering our understanding of the vascular contributions to heart and kidney diseases.

RELEVANT PUBLICATIONS:

PDE9A Inhibition Improves Coronary Microvascular Rarefaction and Left Ventricular Diastolic Dysfunction in the ZSF1 Rat Model of HFpEF. Fopiano KA, Zhazykbayeva S, El-Battrawy I, Buncha V, Pearson WM, Hardell DJ, Lang L, Hamdani N, Bagi Z.

Microcirculation. 2024 Nov;31(8):e12888. doi: 10.1111/micc.12888. Epub 2024 Sep 26. PMID: 39325678

Phosphodiesterase 9A inhibition improves aging-related increase in pulmonary vascular resistance in mice. Buncha V, Fopiano KA, Lang L, Ilatovskaya DV, Verin A, Bagi Z. Geroscience. 2024 Oct;46(5):5191-5202. doi: 10.1007/s11357-024-01270-5. Epub 2024 Jul 9. PMID: 38980632

Adenosine kinase inhibition enhances microvascular dilator function and improves left ventricle diastolic dysfunction.

Davila A, Tian Y, Czikora I, S Weissman A, Weinand N, Dong G, Xu J, Li J, Su H, Kapuku G, Huo Y, Bagi Z. Microcirculation. 2020 Aug;27(6):e12624. doi: 10.1111/micc.12624. Epub 2020 May 25. PMID: 32352607

Adenosine Kinase Inhibition Augments Conducted Vasodilation and Prevents Left Ventricle Diastolic Dysfunction in Heart Failure With Preserved Ejection Fraction. Davila A, Tian Y, Czikora I, Li J, Su H, Huo Y, Patel V, Robinson V, Kapuku G, Weintraub N, Bagi Z. Circ Heart Fail. 2019 Aug;12(8):e005762. doi: 10.1161/CIRCHEARTFAILURE.118.005762. Epub 2019 Aug 1. PMID: 31525084