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EDITORIAL COMMENT

Smells Like Therapy

Targeting Sulfur Signaling in Cardiometabolic HFpEF

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Heart failure with preserved ejection fraction (HFpEF) has emerged as one of the most therapeutically challenging conditions in cardiovascular medicine. Accounting for over one-half of heart failure cases worldwide, HFpEF is not only highly prevalent, but also pathophysiologically elusive, with heterogeneity in both its clinical presentation and underlying mechanisms. Among its phenotypes, the cardiometabolic subtype—defined by obesity, hypertension, insulin resistance, and often hepatic dysfunction—has become the most common and the least tractable.[1,2] Despite recent progress in trial design and pharmacologic development, no single therapy has substantially reduced mortality in this population.[3]

HYDROGEN SULFIDE AS A MULTISYSTEM MODULATOR IN THE TREATMENT OF HFpEF

Against this backdrop, the work of Doiron et al,[4] presented in this issue of *JACC: Basic to Translational Science*, represents a stride forward. The authors provide an elegant and comprehensive investigation into the role of hydrogen sulfide (H_2S), an endogenously produced gaseous signaling molecule, in the pathogenesis and treatment of cardiometabolic HFpEF. Through a combination of clinical data and 2 robust preclinical models—the "2-hit" high-fat diet and L-NAME mouse model,[5] and the ZSF1 obese rat—they convincingly show that H_2S bioavailability is markedly reduced in HFpEF. Mechanistically, this deficiency is driven by a decrease in cystathionine γ-lyase (CSE) expression and activity, along with an increase in sulfide quinone oxidoreductase, the principal enzyme responsible for H_2S degradation. These systemic alterations are not confined to the heart, but extend to the liver and kidneys, highlighting the multisystem nature of the disorder. This reduction in circulating H_2S, which reached nearly 80% in human patients and up to 90% in ZSF1 rats, positions H_2S deficiency not as a secondary byproduct but as a central metabolic hallmark of the disease. Moving forward, the authors demonstrate that restoration of H_2S levels through pharmacological donors leads to improvements in diastolic function, vascular reactivity, cardiac fibrosis, and exercise capacity. Genetic models further support the vascular relevance of this pathway, with endothelial-specific CSE deletion worsening, and overexpression improving, the HFpEF phenotype. Notably, endothelial CSE knockout mice also exhibited increased mortality, underscoring the fundamental role of this enzyme in cardiovascular homeostasis. Building upon these observations, the study takes an additional step by investigating the therapeutic synergy between H_2S and Survodutide, a dual GLP-1/glucagon receptor agonist currently under clinical evaluation for obesity and metabolic liver disease. The combination therapy yields additive benefits, attenuating hepatic steatosis, improving metabolic indexes, reducing fibrosis, and enhancing physical performance. These results not only validate H_2S as a therapeutic axis in HFpEF, but also suggest that its integration with incretin-based therapies may unlock

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broader systemic benefits in patients with cardiometabolic disease.

WHAT COMES NEXT?

As with all impactful studies, this work opens several avenues for further exploration. A key question is whether the benefits of H_2S therapy extend to later stages of HFpEF, given that treatment here was initiated early in disease progression when endogenous H_2S levels were not yet fully depleted. Determining the efficacy of H_2S supplementation in more advanced stages could inform its translational potential. Another area that warrants deeper investigation is the role of hepatic H_2S signaling. Although the authors focused on endothelial CSE, this enzyme is also prominently expressed in the liver—a central organ in systemic metabolism and increasingly recognized as a contributor to HFpEF through interorgan crosstalk.[6,7] The observed down-regulation of hepatic CSE and up-regulation of sulfide quinone oxidoreductase in the current models suggest a potentially important hepatic contribution, which could be more directly tested using liver-specific genetic approaches. Additionally, while CSE is a major H_2S-producing enzyme, the role of 3-mercaptopyruvate sulfurtransferase—the most abundantly expressed H_2S-generating enzyme in the murine heart—remains unclear.[8] Whether 3-mercaptopyruvate sulfurtransferase can compensate for CSE deficiency or plays a distinct role in HFpEF pathophysiology remains to be elucidated. The study's inclusion of single-nucleus RNA sequencing revealed dynamic changes in the expression of multiple sulfur-metabolism enzymes in cardiomyocytes during HFpEF progression, a valuable foundation for future cell-type-specific analyses. In addition, the observation that combination therapy improves multiple metabolic and inflammatory parameters—including reductions in oxidative stress markers such as 3-nitrotyrosine and 8-isoprostane—emphasizes the potential of H_2S to restore redox balance and mitigate systemic inflammation, both of which are recognized contributors to HFpEF. The impact on exercise capacity, often considered a clinically meaningful endpoint in HFpEF, also supports the translational relevance of the findings. Moreover, the use of Survodutide—an emerging agent with dual GLP-1/glucagon receptor activity that has recently shown promise in improving both glycemic control and hepatic steatosis in clinical trials—positions this study within the context of ongoing developments in metabolic therapeutics.

Taken together, this study contributes meaningfully to the evolving view of HFpEF as a systemic syndrome rooted in inflammatory, metabolic, and vascular dysfunction.[3] It aligns with recent clinical findings from trials such as STEP-HFpEF (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity) and SUMMIT (A Study of Tirzepatide (LY3298176) in Participants With Heart Failure With Preserved Ejection Fraction (HFpEF) and Obesity), suggesting that metabolic cotargeting—including incretin-based agents—may be particularly effective in the obese phenotype of HFpEF. What distinguishes the current work is its clear mechanistic framing and the preclinical demonstration of a synergistic, interorgan therapeutic strategy that modulates redox and metabolic tone across heart, liver, and vasculature. As the field moves toward a more holistic model of HFpEF, therapies that act beyond the myocardium—like H_2S donors—deserve close attention.

CONCLUSIONS

The study by Doiron et al[4] lays important groundwork for a new class of translational strategies in HFpEF. By demonstrating that H_2S deficiency is both a hallmark and a modifiable driver of cardiometabolic HFpEF, and by revealing synergy with GLP-1/glucagon agonism, the authors present a compelling case for further investigation of H_2S-based combination therapies. The path to clinical application will require careful attention to timing, dosing, target tissue specificity, sex differences, and long-term safety, but the conceptual leap this study offers is significant. HFpEF is a disease of many systems, and effective treatments may need to be equally multidimensional.

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