Jake E. Doiron
L2
LSU Health Sciences Center, New Orleans, LA

Dr. David J. Lefer
Department of Pharmacology, LSU Health Sciences Center, New Orleans, LA

Effects of H_2S Therapy on the Pathogenesis of Heart Failure with Preserved Ejection Fraction

Background: Heart failure with preserved ejection fraction (HFpEF) is a complex heterogeneous disease that represents 60% of all clinical heart failure (HF) cases. With no current FDA-approved therapeutic approaches, HFpEF is widely considered one of the greatest unmet clinical needs in cardiovascular medicine. Cardiac hypertrophy and hypertension in HFpEF is partly characterized by decreased cGMP-protein kinase G (PKG) signaling in response to decreased nitric oxide (NO) bioavailability. Decreased NO bioavailability has largely been associated with systemic vascular inflammation and subsequent decrease in endothelial nitric oxide synthase (eNOS) activity. Hydrogen sulfide (H_2S), an endogenously produced signaling molecule, has shown numerous cardioprotective properties, including activation of eNOS and subsequent production of bioavailable NO.

Hypothesis: We hypothesize that administration of a novel H_2S donor (i.e. SG1002) will mitigate the pathological sequelae of HFpEF via reduced inflammation and increased NO signaling.

Methods: Male ZSF1 obese rats (n=20) were randomized to either vehicle or SG1002 (45 mg/kg/day) orally administered. Echocardiographic, metabolic, and exercise capacity assessments were conducted for 12 weeks following induction of treatment.

Results: Administration of SG1002 daily produced minimal gains in cardiac function (*E/e'*: 25.7 to 23.6; p = NS) and exercise capacity (*Distance*: 31.9% increase, p = 0.08). No significant impact on circulating *nitrite* (0.15 μM to 0.11 μM, p = NS), circulating *H_2S* (0.001 to 0.014, p = NS), and endothelium dependent vascular reactivity (*ACh*: 24.7% increase, p = NS) was observed.

Conclusion: Given the previous-success of H_2S donors in other inflammatory preclinical models, further investigation into the ZSF1 rat's genetic profile and pathologic disruption of H_2S scavenging pathways is warranted. These findings suggest diminished H_2S bioavailability as an underlying pathophysiological mechanism that contributes to HFpEF onset and progression.