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

Jake E. Doiron[1], Kyle B. LaPenna[1], Hunter A. Hidalgo[1], and David J. Lefer[1]
[1]Cardiovascular Center of Excellence, LSU Health Sciences Center, New Orleans, LA

LSU Health NEW ORLEANS School of Medicine

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a complex heterogeneous disease that represents 60% of all clinical heart failure (HF) cases.[1] With no approved therapies, HFpEF is widely considered the greatest unmet clinical needs in cardiovascular medicine.[2] The cardiac hypertrophy and hypertension witnessed 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.[3]

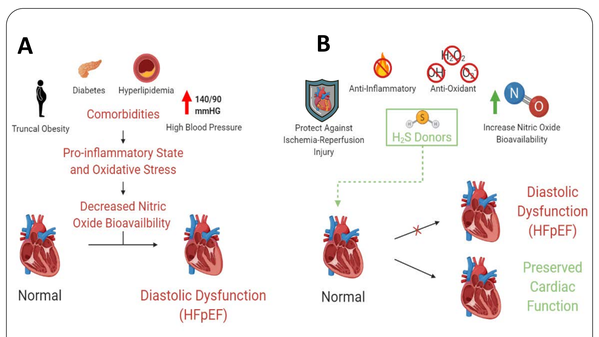
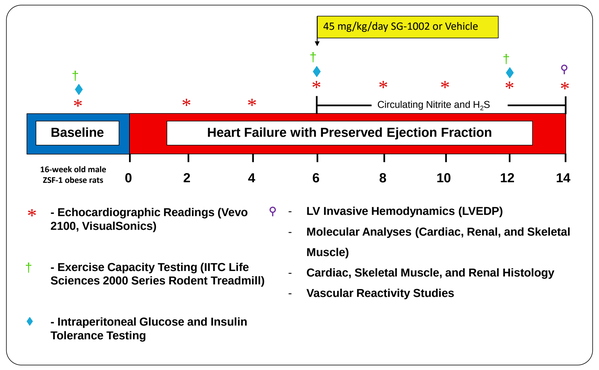


Figure 1. Normal HFpEF pathophysiology and mechanism of amelioration with H_2S therapy. (A) Normal pathophysiology of HFpEF, (B) Effects of H_2S on HFpEF pathophysiology

Hydrogen sulfide (H_2S), an endogenously produced signaling molecule, has shown numerous cardioprotective properties through eNOS activation and subsequent NO production. Given this, we believe administration of a novel H_2S donor could attenuate the pathological sequelae of HFpEF.[4]

Methods

In this study, 16-week old male ZSF-1 obese rats (n=14) were allowed to age and develop HFpEF. At 22 weeks of age, rats were randomized to either vehicle (n=6) or H_2S donor SG-1002 (45 mg/kg/day, n = 8) orally administered. Echocardiographic, metabolic, and exercise capacity assessments were taken throughout a 14-week study protocol.



Results

Body and Organ Weights

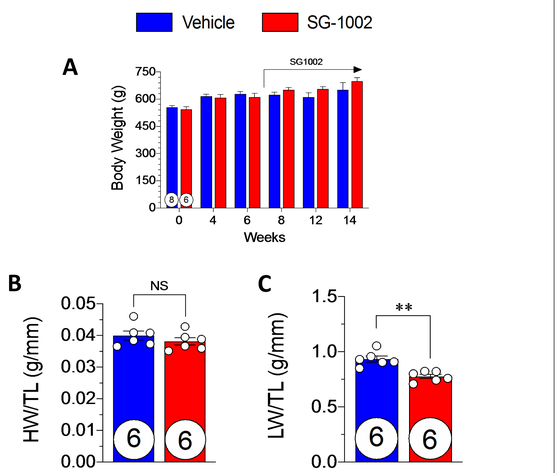


Figure 2. Body weight and organ weight measurements normalized to respective tibia length. (A) Body weight, (B) Heart weight normalized to tibia length at 14 weeks, (C) Liver weight normalized to tibia length at 14 weeks

Left Ventricular Ejection Fraction

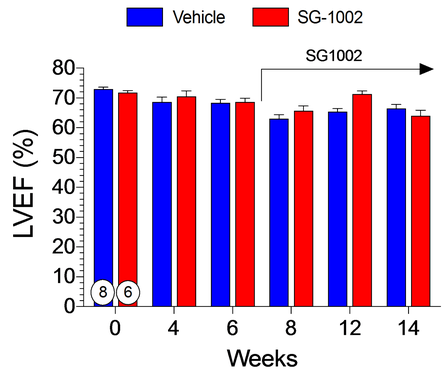


Figure 4. Left ventricular ejection fraction for confirmation of HFpEF.

Treadmill Exercise Capacity Testing

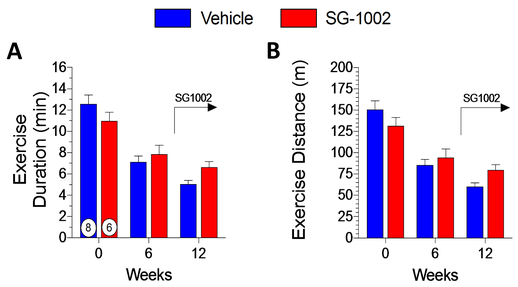


Figure 6. Treadmill exercise capacity testing. (A) Exercise capacity duration, (B) Exercise capacity distance

Left Ventricular Structure and Function

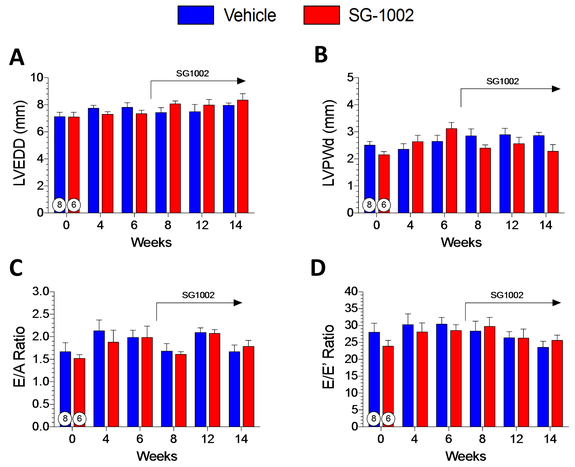


Figure 3. Left ventricular structure and functional parameters. (A) Left Ventricle End Diastolic Dimension, (B) Left Ventricle Wall Diastolic Thickness, (C) Ratio (E/A) of peak velocity blood flow during early diastole (E wave) to late diastole (A wave), (D) Ratio (E/E') of peak velocity blood flow during early diastole (E wave) to early diastolic mitral annulus velocity (E' wave)

Diabetic Assessment Testing

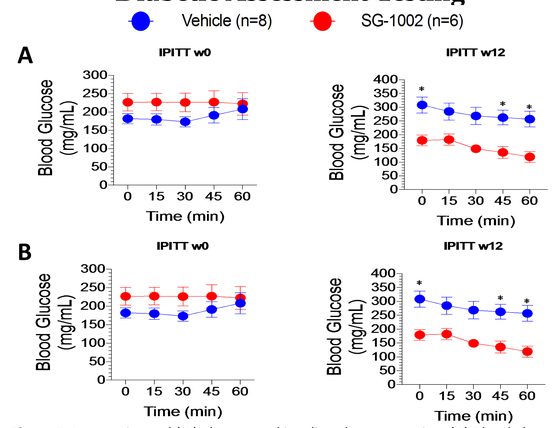


Figure 5. Intraperitoneal (IP) glucose and insulin tolerance testing. (A) Blood glucose post-IP 40% w/v glucose injection, (B) Blood glucose post-IP 0.15U insulin/mL (0.75U insulin/kg) insulin injection

Aortic Ring Relaxation

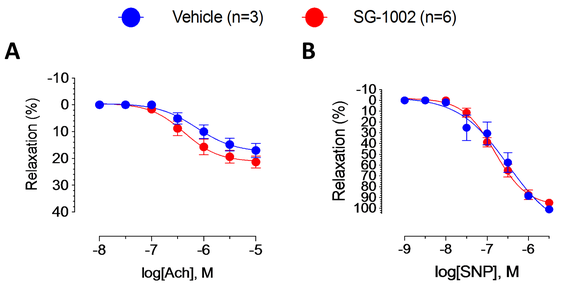


Figure 7. Aortic ring relaxation. (A) Percentage relaxation upon Acetylcholine (ACh) administration, (B) Percentage relaxation upon Sodium Nitroprusside (SNP) administration

Results

Circulating H_2S and Nitrite

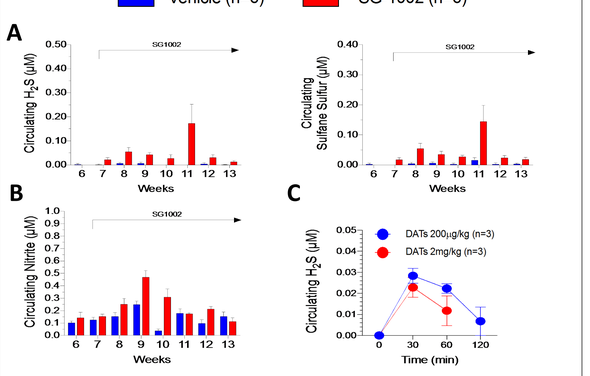
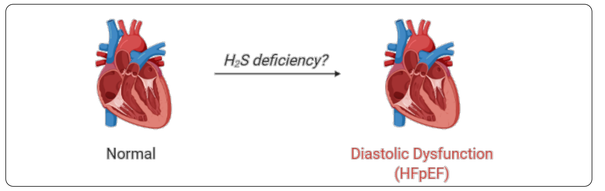


Figure 8. Circulating Nitrite and H_2S of both orally administered (SG-1002) and IP injection (DATs) H_2S donors. (A) Circulating H_2S and Sulfane Sulfur of orally administered H_2S donor (SG-1002), (B) Circulating Nitrite of orally administered H_2S donor (SG-1002), (C) Circulating H_2S of intraperitoneal injection low and high-dose DATs

Conclusions and Implications

No significant improvements in cardiac function, vascular reactivity or exercise capacity were noted upon administration of low-dose SG-1002. Interestingly, circulating nitrite and H_2S levels did not show significant increases with low-dose oral SG-1002, high-dose oral SG-1002, or IP injection of the robust H_2S donor DATs.

Given the previous—success of H_2S donors in other inflammatory preclinical models, further investigation into the ZSF-1 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.



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3. Shah, S. J.; Borlaug, B. A.; Kitzman, D. W.; McCulloch, A. D.; Blaxall, B. C.; Agarwal, R.; Chirinos, J. A.; Collins, S.; Deo, R. C.; Gladwin, M. T.; Granzier, H.; Hummel, S. L.; Kass, D. A.; Redfield, M. M.; Sam, F.; Wang, T. J.; Desvigne-Nickens, P.; Adhikari, B. B. *Circulation* **2020**, *141* (12), 1001–1026.
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