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Combination Therapy with Sodium Nitrite and Hydralazine Attenuates Oxidative Stress in Heart Failure with Preserved Ejection Fraction

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"COMBINATION THERAPY WITH SODIUM NITRITE AND HYDRALAZINE ATTENUATES OXIDATIVE STRESS IN HEART FAILURE WITH PRESERVED EJECTION FRACTION"

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is responsible for over 50% of all heart failure cases and current therapeutics are limited[1,2]. HFpEF is a complex disease that is associated with comorbidities such as metabolic syndrome, hypertension, and dyslipidemia. These comorbidities lead to a pro-inflammatory state that increases oxidative stress and damages the vascular endothelium. Damage to the vascular endothelium leads to dysregulation of endothelial nitric oxide synthase (eNOS) and the loss of cardioprotective nitric oxide (NO). While NO based monotherapies do provide benefit in patients that suffer heart failure with reserved ejection fraction (HFrEF), they have failed to improve clinical outcomes in the setting of HFpEF[3].

Purpose

(1) To investigate the potential beneficial effects of sodium nitrite as an NO monotherapy in a well-established murine "two-hit" model of HFpEF.

(2) To study the effects of the combination of NO therapy (i.e., sodium nitrite) and the powerful antioxidant-vasodilator agent, hydralazine[4] in the same murine model of severe HFpEF.

Material and Methods

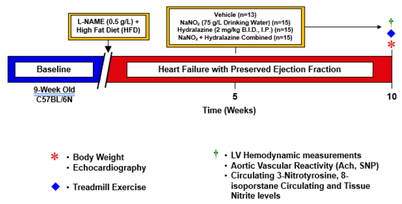


Figure 1. **Male C57/BL6N (n=15 per group) mice were fed a Western high fat diet (60% kCal from fat) and treated with L-NG-Nitro arginine methyl ester (L-NAME, 0.5 g/L/day) in the drinking water starting at 10 weeks of age. At fifteen weeks, the mice were randomly separated into four separate groups for five additional weeks: HFpEF control, sodium nitrite in drinking water (75 mg/L), hydralazine (2 mg/kg/day, i.p., b.i.d.), or the combination of sodium nitrite and hydralazine. At 20 weeks, left ventricular (LV) pressures and ex vivo hemodynamics were measured. Additionally, plasma was taken at 20 weeks to measure circulating levels of nitrite, 8-isoprostane and 3-nitrotyrosine, biomarkers for oxidative and nitrosative stress, respectively. Myocardial tissue as also collected at 20 weeks for determination of myocardial nitrite levels. Echocardiography and exercise were performed at 10 weeks, 15 weeks, and 20 weeks.**

Results

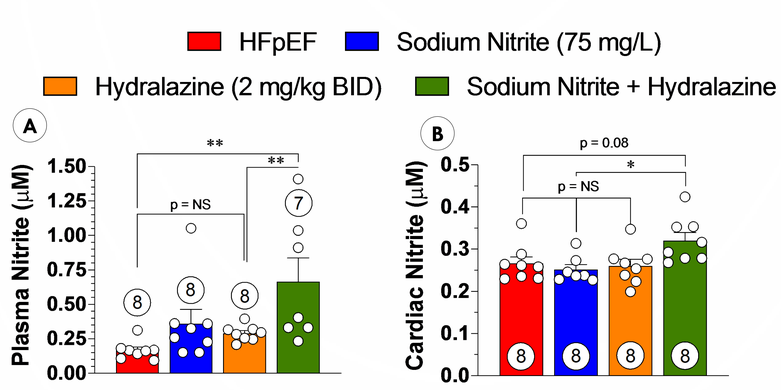
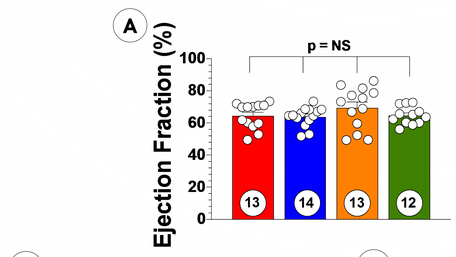


Figure 2. **High pressure liquid chromatography (HPLC) nitrite measurements in (A) plasma and (B) cardiac tissue *: p < 0.05; **: p < 0.01**



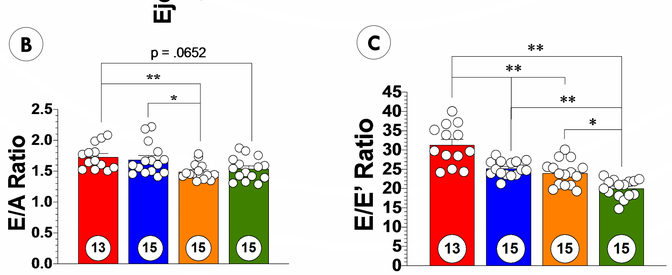


Figure 3. **Clinically relevant measures of left ventricular function. A: left ventricular ejection fraction. B: E/A ratio of peak velocity during early diastole (E wave) and during late diastole (A wave). C: E/E' ratio of peak velocity during E wave and left ventricular tissue displacement (E' wave) *: p < 0.05; **: p < 0.01**

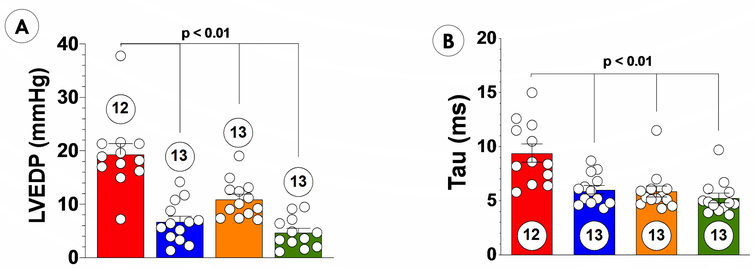


Figure 4. **Left ventricular hemodynamics: (A) left ventricular end diastolic pressure (LVEDP) and (B) relaxation constant Tau *: p < 0.05; **: p < 0.01**

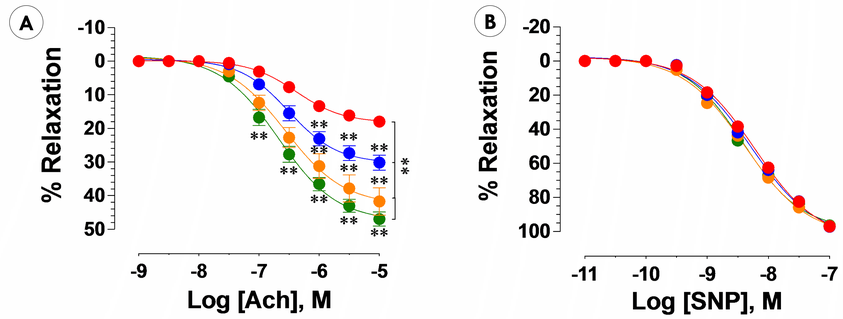


Figure 3. **Aortic vascular ring percent relaxation in response to (A) acetylcholine and (B) sodium nitroprusside (SNP) *: p < 0.05; **: p < 0.01**

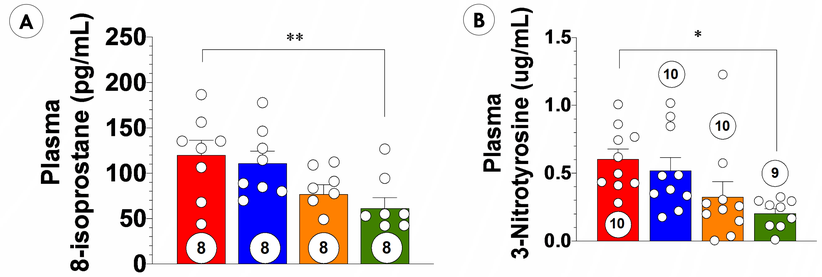


Figure 5. **Circulating plasma levels of (A) 8-isoprostane and (B) 3-nitrotyrosine. *: p < 0.05; **: p < 0.01**

Conclusions

Treatment with the combination of sodium nitrite (NO donor) and hydralazine significantly improved left ventricular and vascular function in this "two-hit" murine HFpEF model. These improvements in cardiovascular function were driven by decreases in oxidative and nitrosative stress and by increases in vascular nitric oxide bioavailability. Decreased oxidative and nitrosative stress resulted in improved vascular function and improved left ventricular diastolic function to improve overall cardiovascular health.

In future studies, we would like to perform these experiments in the ZSF1 rat. ZSF1 rats represent a clinically relevant genetic HFpEF model that features both hypertension and obesity and is considered to be superior to the mouse "two-hit" HFpEF Model.

References

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