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

Introduction: Nitric oxide (NO) based therapeutics are powerful cardioprotective agents in the treatment of heart failure with reduced ejection fraction (HFrEF). However, NO therapy has failed to exert beneficial effects clinical studies of heart failure with preserved ejection fraction (HFpEF),

We investigated (1) the effects of the NO donor, sodium nitrite, as a monotherapy, (2) hydralazine monotherapy, a known vasodilator and antioxidant, and (3) combination therapy with both drugs in a murine model of HFpEF assessed of left ventricular (LV) function, exercise tolerance, vascular function and oxidative stress.

Methods: Male, C57/BL6N (n=15 per group) were placed on a Western high fat diet (60% kCal from fat) and treated with L-N^G-Nitro arginine methyl ester (L-NAME, 0.5 g/L/day) in the drinking water beginning at 10 weeks of age. At 15 weeks of age, mice were randomly assigned to 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 of age plasma was collected to measure circulating 8-isoprostane levels, a biomarker of oxidative stress. In addition, left ventricular (LV) pressures and *ex vivo* aortic ring vascular reactivity studies were measured. Echocardiography and exercise tolerance testing was performed at 10, 15, and 20 weeks of age.

Results: Plasma 8-isoprostane levels were significantly ($p < 0.05$) decreased in the sodium nitrite + hydralazine group compared to the HFpEF control group, indicating the treatment was effective at reducing oxidative stress. Sodium nitrite + hydralazine group significantly ($p < 0.05$) improved aortic ring vascular reactivity compared to the HFpEF control group. Left ventricular end-diastolic pressure (LVEDP) was significantly reduced in all treatment groups, and LVEDP was reduced to the greatest extent in the nitrite + hydralazine group vs. HFpEF control. Furthermore, we observed a significant ($p < 0.01$) improvement in LV diastolic function (i.e., E/e') in the sodium nitrite and hydralazine group that was superior to either of the treatments alone.

Conclusion: These data demonstrate that the combination of a powerful antioxidant with NO donor therapy significantly enhances the beneficial effects NO therapy in the setting of severe HFpEF.