

 **CARDIAC FUNCTION AND HEART FAILURE**

HYDRALAZINE-NITROGLYCERIN COMBINATION REDUCES DIASTOLIC CALCIUM LEAK IN ADULT CARDIOMYOCYTES FROM NITRIC OXIDE SYNTHASE-1-DEFICIENT MICE

ACC Poster Contributions

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Background: Diastolic calcium (Ca) leak is observed in heart failure. Cardiomyocytes from Nitric Oxide Synthase-1-deficient (NOS1 KO) mice exhibit increased sarcoplasmic reticulum (SR) Ca leak. On the other hand, nitrates in combination with hydralazine are currently used in heart failure treatment in African-American patients. Although their action as vasodilators of both nitric oxide and hydralazine are well known, their complementary effects on the myocardium remain obscure. We hypothesize that hydralazine-nitroglycerin combination is able to modulate the sarcoplasmic calcium channel ryanodine receptor (RyR2).

Methods: Adult cardiomyocytes were isolated from NOS1 KO mice (n=20) and their wild type control (WT, n=14). Myocytes were stimulated at 0.5, 1, 2, 3 and 4 Hz and treated with or without nitroglycerin+hydralazine, nitroglycerin alone or hydralazine alone. Cytosolic Ca was measured with fura-2. The observed decrease in the fura-2 fluorescence ratio in presence of tetracaine (after stop pacing) was considered as the SR Ca leak. Ca content was estimated by superfusing with caffeine. S-nitrosylation of RyR2 was assessed by immunohistochemical staining against Cys-NO.

Results: The combination hydralazine-nitroglycerin significantly reduced the SR Ca leak in NOS1 KO myocytes in a concentration-dependent manner to similar levels of those in WT controls. On the other hand, hydralazine alone had the same effect as the combination. Also both the combination and hydralazine alone increased SR Ca content at different frequencies. On the contrary, only at the highest concentration of hydralazine or the combination were able to increase the Ca re-uptake rate. Cys-NO staining was weaker in WT than NOS1 KO and no treatment restored S-nitrosylation in NOS1 KO myocytes.

Conclusions: Our data suggest that hydralazine would be responsible for the beneficial effects observed at pharmacologically relevant concentrations of the nitroglycerin-hydralazine combination, by preventing the diastolic SR Ca leak. The observed improvement in heart failure patients under nitrates-hydralazine treatment may be in part due to the prevention of Ca leakage, thereby optimizing the Ca handling.