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Meeting abstract

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2091 Manganese enhanced mri demonstrates a predominant role for nNOS, not eNOS, in modulating L-Type calcium channel flux in the heart

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Introduction

Modulation of L-Type Calcium Channel (LTCC) flux plays an important role in calcium cycling and contractility. Based upon localization within the cardiomyocyte, prevailing opinion is that neuronal nitric oxide synthase (nNOS) modulates sarcoplasmic reticular calcium release, while endothelial NOS (eNOS) modulates LTCC flux. Counter to this hypothesis, a recent *in vitro* study suggests that nNOS modulates LTCC flux. Since Mn^{2+} enters the myocyte through the LTCC in proportion to Ca^{2+} flux and shortens T1, Mn-enhanced MRI may be used to probe *in vivo* LTCC flux.

Methods

Eleven wild type (WT), 8 $eNOS^{-/-}$ and 8 $nNOS^{-/-}$ mice aged 3 months were studied by Mn-enhanced MRI on a 4.7 T MRI system (Varian, CA). Two mid-ventricular short axis slices were acquired using a saturation recovery sequence with a constant repetition time of 200 ms. Images were acquired every 2 to 3 minutes for 20 minutes prior to and 45 minutes following a 30 minute infusion of $MnCl_2$ at a dose of 0.42 ηg/kg · min. Signal-to-noise ratio (SNR) was measured from the entire myocardium for each slice and plotted against time (Figure 1). The portion of the SNR vs. time curve corresponding to $MnCl_2$ infusion was isolated and the slope of the linear fit to that data was used as the LTCC index (LTCCI). Additionally, systolic blood pressure (BP) was measured using a tail cuff system.

Results

Higher BP was found in $eNOS^{-/-}$ mice compared to $nNOS^{-/-}$ (106 ± 4 WT, 111 ± 4 $eNOS^{-/-}$, 94 ± 3 $nNOS^{-/-}$ p = 0.01 vs. $eNOS^{-/-}$). Heart rate was similar between all groups (481 ± 18 WT, 470 ± 16 $eNOS^{-/-}$, 490 ± 29 $nNOS^{-/-}$, P = NS). LTCCI trended higher in $eNOS^{-/-}$ compared to WT (P = 0.1), but was nearly twice the WT rate in $nNOS^{-/-}$ mice (P < 0.001) (Figure 1). Additionally, LTTCI was significantly greater in $nNOS^{-/-}$ compared to $eNOS^{-/-}$ mice (P < 0.05).

Conclusion

The significantly increased rate of Mn^{2+} enhancement in $nNOS^{-/-}$ mice represents the first *in vivo* evidence of modulation of LTCC flux by nNOS. Although $eNOS^{-/-}$ mice showed a trend towards a higher rate of LTCC flux compared to WT, this increase is likely a response to heightened afterload. The absence of heightened BP in $nNOS^{-/-}$ mice paired with an increased LTCCI demonstrates that nNOS, not eNOS, plays a dominant role in modulating LTCC flux.

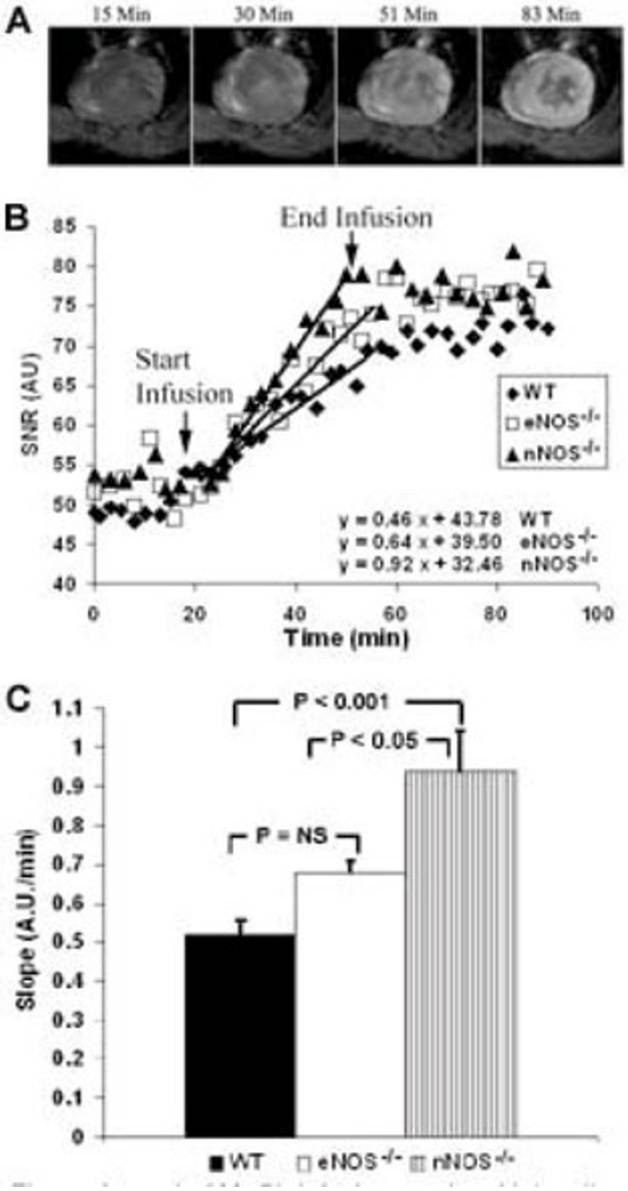

Figure 1
Impact of $MnCl_2$ infusion on signal intensity within the myocardium (A). Example SNR vs. time curves for each group. Slopes of linear fits represents measures of flux rate (B). LTTCI shown to be significantly greater in $nNOS^{-/-}$ mice vs. WT (C).