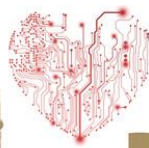




Differential effects of fingolimod and other transient receptor potential melastatin 7 (TRPM7) channel modulators on calcium paradox-induced myocardial injury in rat hearts

Matthew AMONI



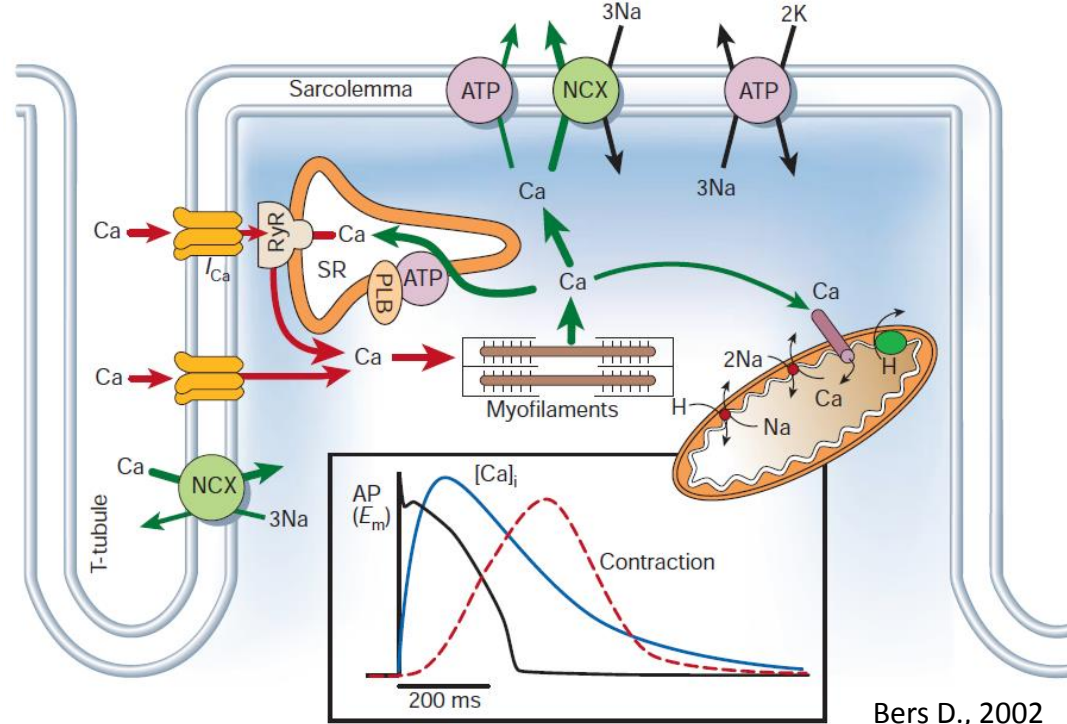
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BACKGROUND

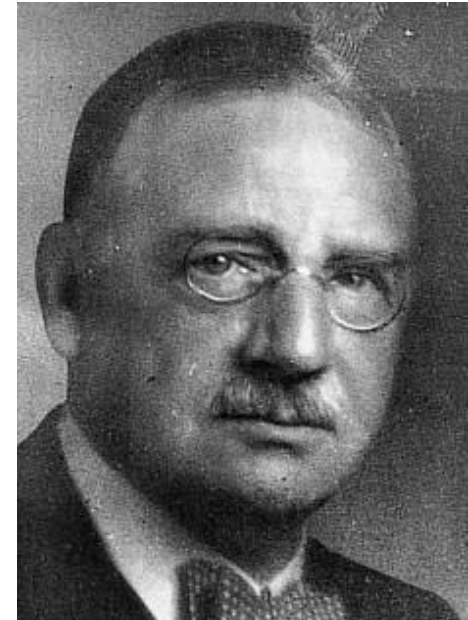
- **Calcium is drives cardiac cellular function.**
- Abnormalities of calcium (Ca^{2+}) homeostasis underlie the pathophysiology of several cardiovascular conditions.
- **Calcium homeostasis is critical for signalling.**



- Non-selective cation channels such as transient receptor potential (TRP) channels, specifically TRPM7 are implicated in abnormal Ca^{2+} homeostasis (Gwanyanya et al., 2004)
- However, the contribution of such non-selective channels to cardiac injury at organ level is unknown.
- We present preliminary work interrogating background contributors to Ca^{2+} homeostasis.

INTRODUCTION

- **Calcium Paradox:** Ca^{2+} -mediated myocardial injury due to Ca^{2+} paradox (CP) has long been established experimentally in hearts temporarily perfused with Ca^{2+} -deficient solutions (Zimmerman and Hulsman, 1966).
- Clinically, varying degrees of the CP phenomenon may occur peri-operatively.
- Experimentally, cardiac tissue storage solutions and isolation of cardiomyocytes for various cellular studies.



Otto Loewi: A drug is a substance that when injected into an animal, produces
A PAPER.

Novel specific exogenous pharmacological blockers to evaluate TRPM7:

fingolimod (FTY720) (Qin et al., 2013) and nordihydroguaiaretic acid (NDGA) (Chen et al., 2010)

AIM

We therefore investigated the effects of TRPM7 channel inhibitors:

- fingolimod (FTY720)
- nordihydroguaiaretic acid (NDGA),
- as well as Mg^{2+} pre-treatment

... on Ca^{2+} Paradox-induced myocardial injury (CP).

METHODS

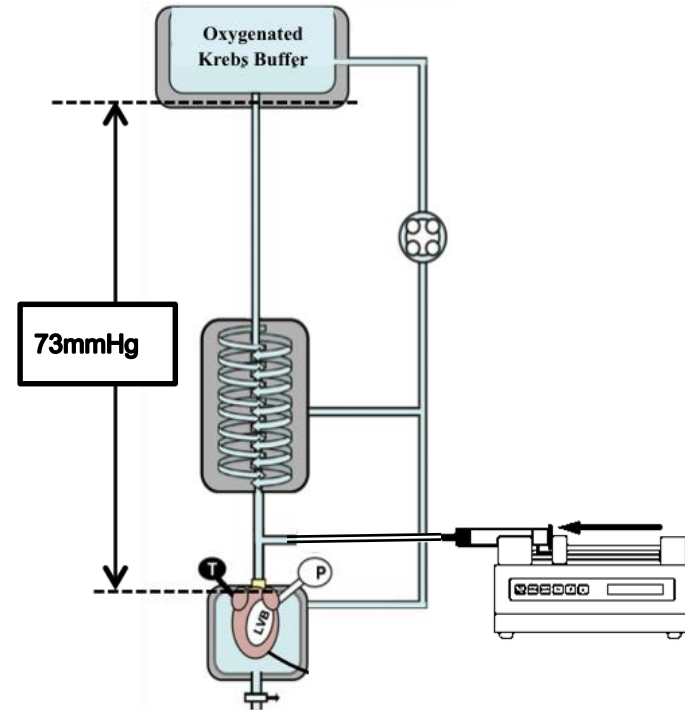
The presence of cardiac TRPM7 proteins was evaluated by immunoblotting n=5-6.

Langendorff-perfused Wistar rat hearts:

intraventricular balloon – Hemodynamics;
triphenyltetrazolium chloride stain - infarcts size.

FTY720 (1 $\mu\text{mol/L}$), NDGA (10 $\mu\text{mol/L}$), or vehicle infused prior to a CP protocol consisting of 3-min Ca^{2+} depletion, followed by 30-min Ca^{2+} repletion n=6-8.

MgSO_4 (270 mg/kg, intraperitoneally) or saline daily for 7 days were also subjected to CP n=6-9.

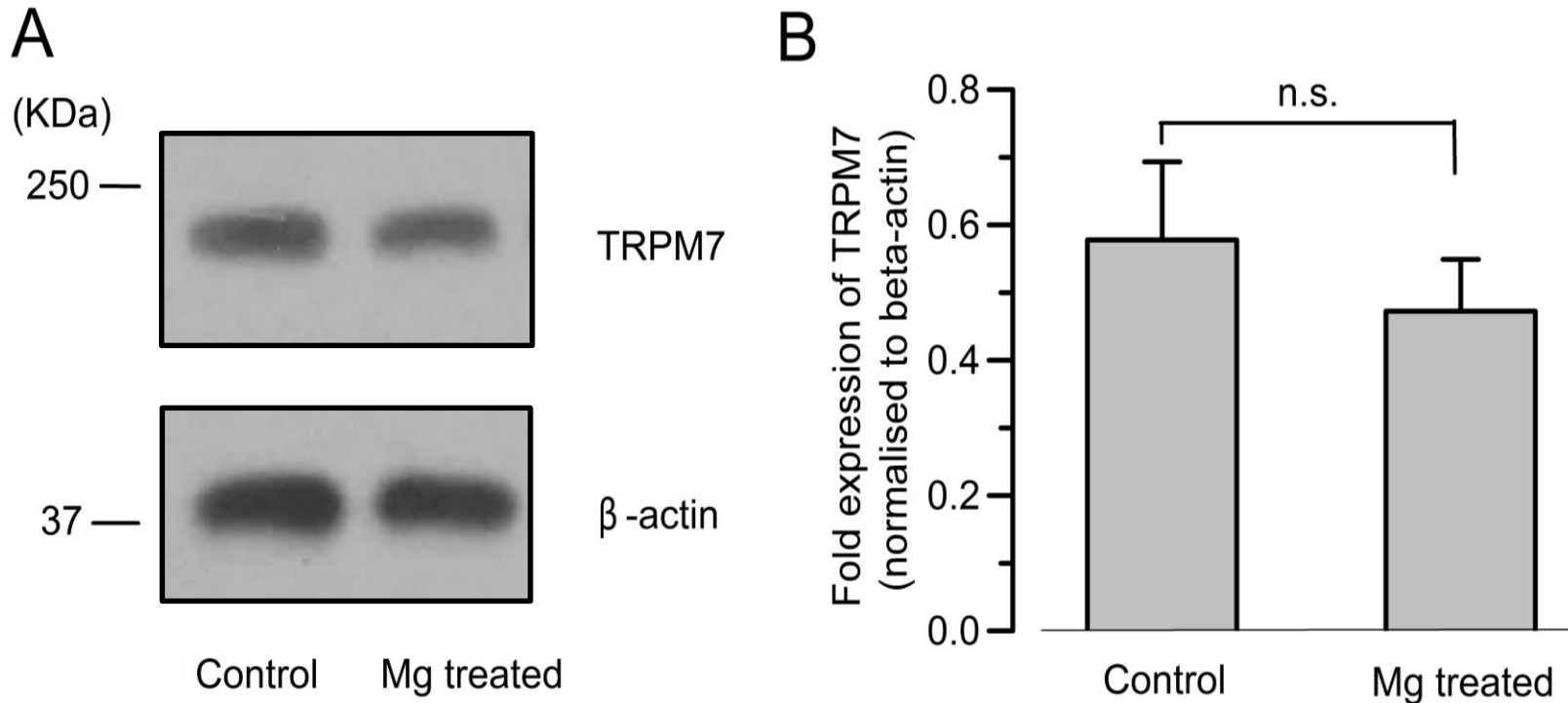


STATISTICS

GraphPad Prism 6 software package – ANOVA & t-test.
Data are presented as mean \pm SEM; $P < 0.05$ = significant.

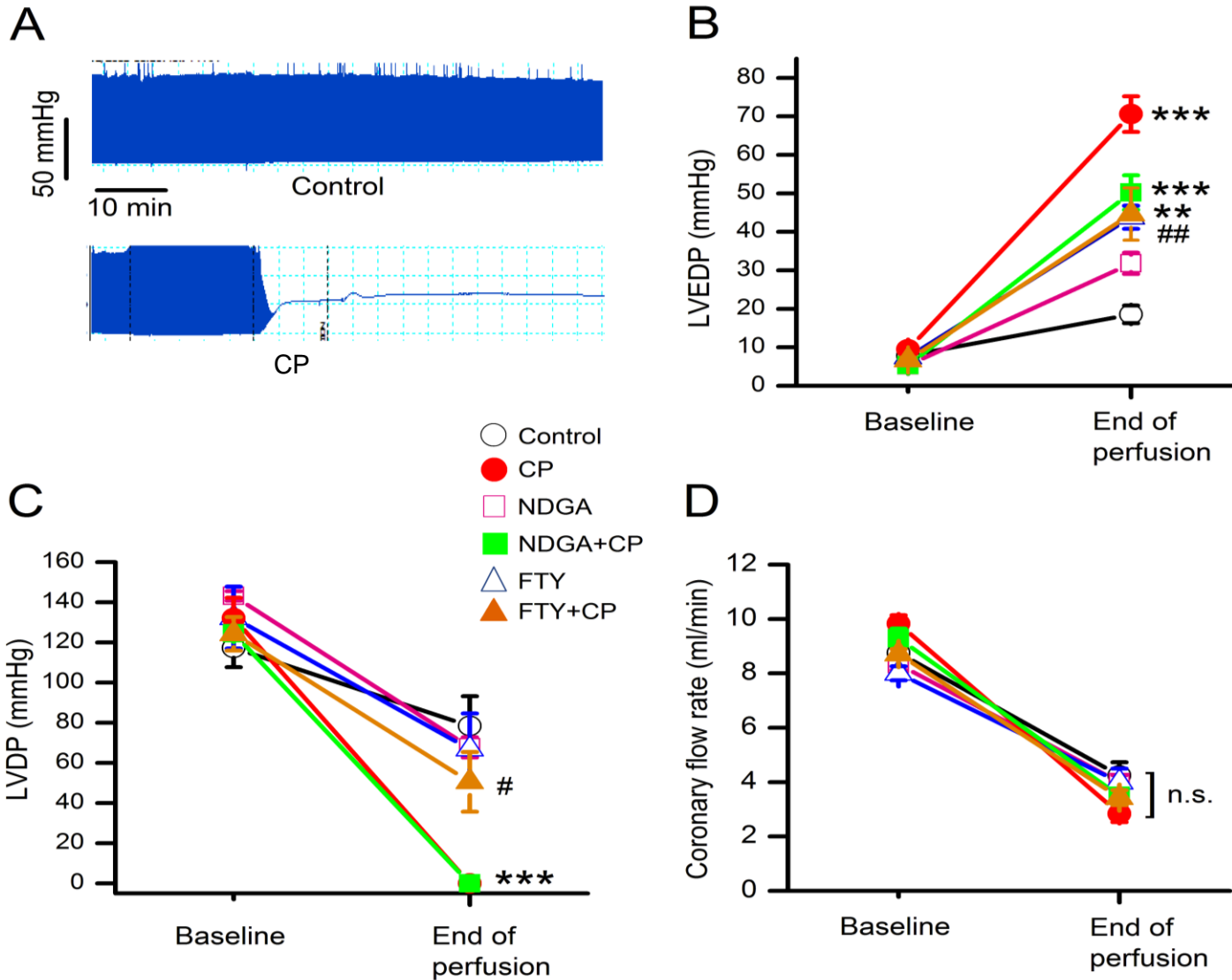
RESULTS

The expression of TRPM7 channels in cardiac ventricular tissue:



RESULTS

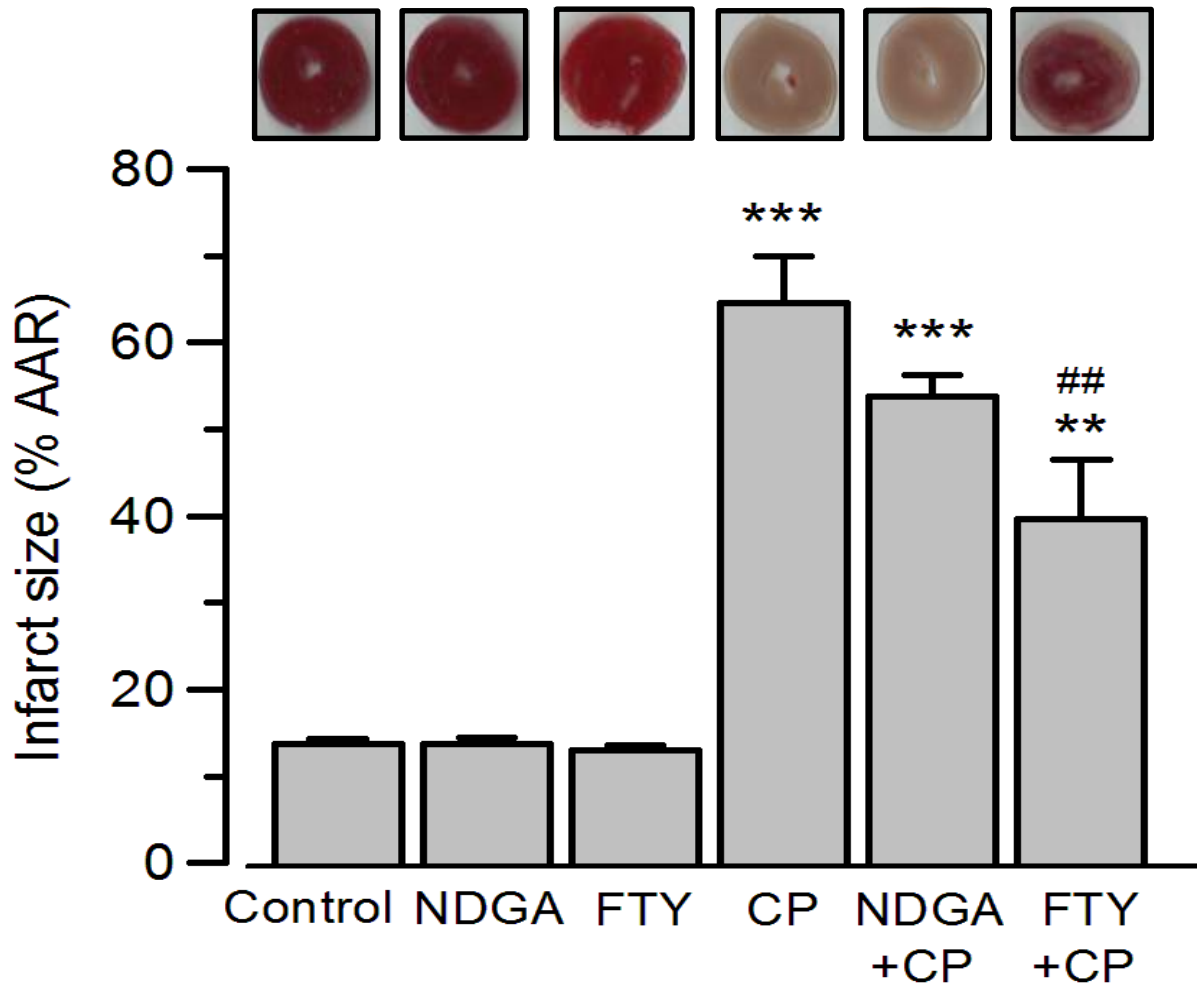
Effects of NDGA and FTY720 on CP-induced hemodynamic changes:



Although both FTY720 and NDGA minimized the CP-induced elevation of left ventricular end-diastolic pressure, only FTY720 improved LV developed pressure ($p=0.029$). Pre-treatment with Mg²⁺ affected CP-induced infarct size

RESULTS

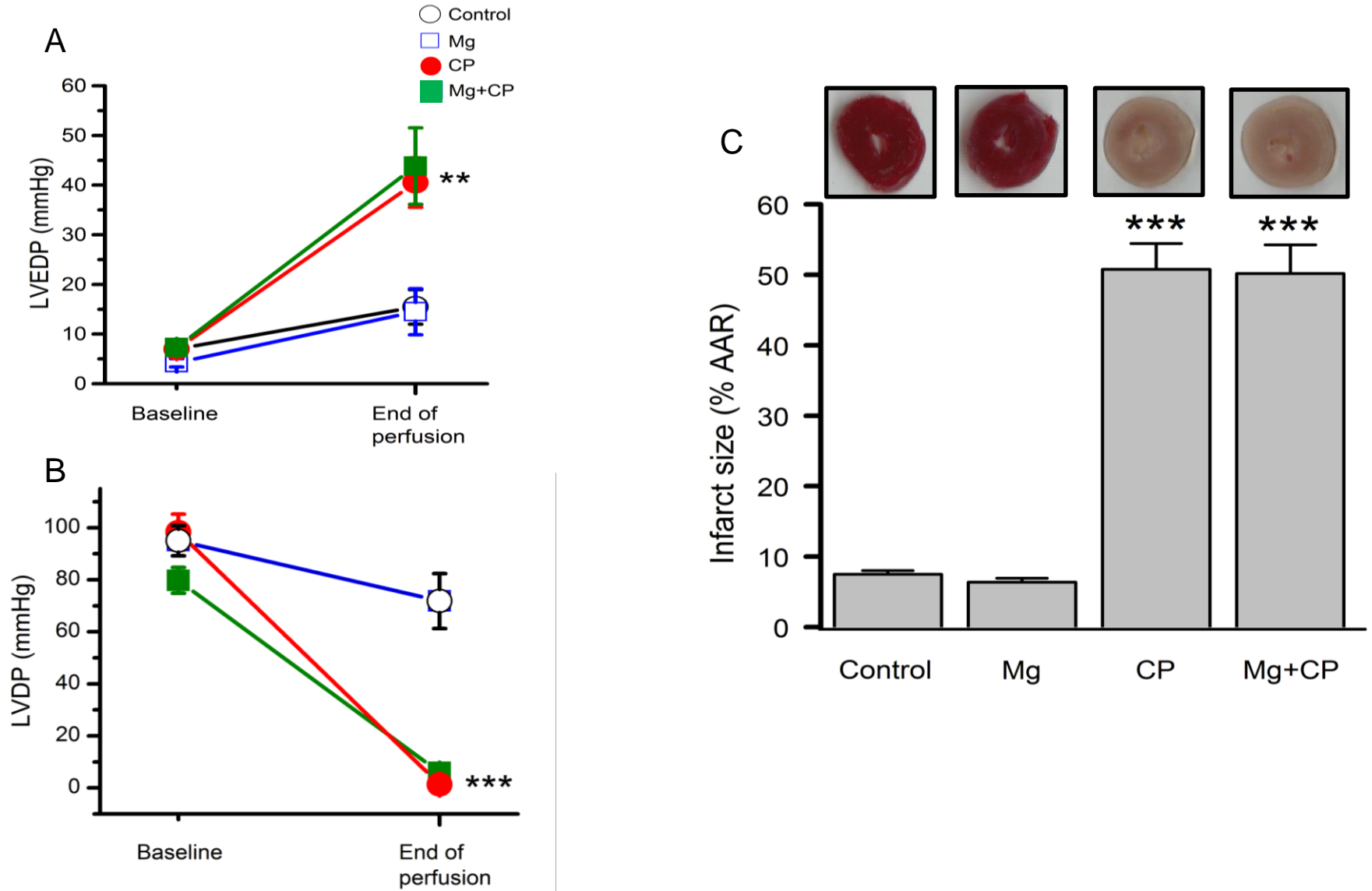
Effects of NDGA and FTY720 on Ca²⁺ paradox (CP) induced infarcts:



FTY720, but not NDGA, decreased CP-induced infarct size from $64.6 \pm 5.3\%$ to $39.0 \pm 6.8\%$ ($p=0.001$; $n=6$).

RESULTS

Effects of Mg²⁺ pretreatment on CP-induced hemodynamic changes and infarcts:



CONCLUSION

TRPM7 protein presence in cardiac ventricular tissue.

Among the TRPM7 channel modulators tested, FTY720, but not NDGA or pre treatment with Mg²⁺, reversed CP-induced myocardial damage and dysfunction
(suggesting that the action of FTY720 seems to be unrelated to the capacity of the drugs to inhibit TRPM7 channels)

FTY720 may have a potential therapeutic role during cardiac perfusion,
but future studies need to investigate the mechanisms underlying the cardioprotective effect of FTY720 in CP.

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