Protecting the Heart with Exercise

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Preconditioning in Biology and Medicine: Mechanisms and Translational Research

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EMORY UNIVERSITY

Cardiovascular Disease

- Cardiovascular disease continues to be a leading source of mortality and morbidity in the world despite advances in health care practices.
- Economically, it is estimated that about $500 billion is spent each year.
- As such, the development and implementation of therapeutic strategies to combat CVD remains a need.

Risk Factor

- Age, gender, and genetics are important risk factors associated with the development of CVD.
- However, the modern lifestyle has become an apparent risk factor.
- This sedentary lifestyle includes a high incidence of smoking and consists of a diet comprised mainly of saturated fats and sugar and devoid of fruits and vegetables.
  - As a result, hypertension, hyperlipidemia, insulin resistance, obesity, and diabetes are major risk factors for the development of CVD.

Exercise and Cardioprotection

- Numerous studies have linked a reduction in the rate of initial coronary artery disease events in physically active individuals
- Chronic exercise training has been shown to reduce many risk factors related to cardiovascular disease, including:
  - High blood pressure
  - High cholesterol
  - Obesity and Insulin resistance
- Protective effects are not confined to the period of exercise

Mechanisms of Exercise-Mediated Cardioprotection

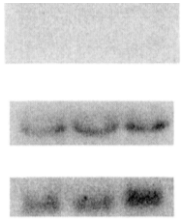
- The cardioprotection afforded by exercise has been attributed to its ability to increase:
  - Endogenous antioxidant defenses (SOD and catalase)
  - Heat-shock proteins
  - Endothelial nitric oxide synthase (eNOS)
  - Activate K_{ATP} channels
- Recent studies have reported that many of these classic PC signals may not be essential for the observed cardioprotection

Brown et al, *J Physiol* 2005

Nitric Oxide and Exercise

- The expression and activity of eNOS is increased in response to shear stress during exercise

Aorta from Dogs

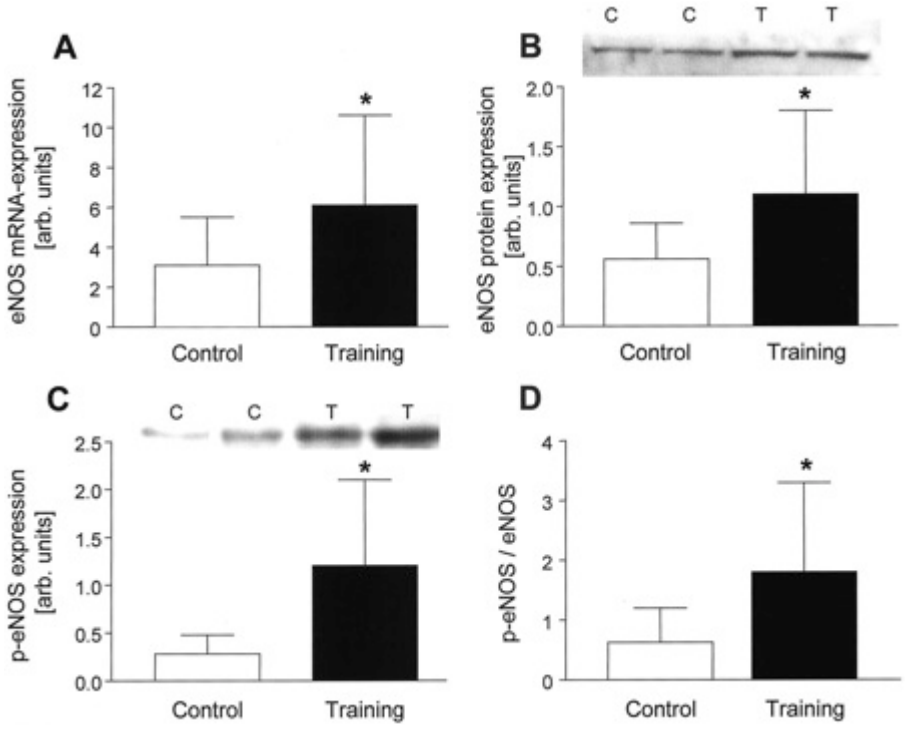


Northern blot showing that exercise induces en
tric oxide synthase (ECNOS) gene expression
ts. Total RNA (10 μg) from two exercised (Ex) do
l (C) dog was hybridized with full-length cD
S, von Willebrand's factor (vWF), or glyceralde
hate dehydrogenase (GAPDH) and washed unc
ency conditions as described.

it from 2.89±0.50 to 6.20±0.42 L/min (n=5
ating that the proximal aorta was clearly
ed to high-flow velocity. Because of difficu
solation of adequate amounts and high-
from large coronary arteries and corona
ssels, we isolated aortic endothelial cell RN
ws Northern blot analysis of total RNA i
aortic endothelial cell scrapings from cor
ised dogs probed (under high-stringency

Sessa et al. *Circulation Research* 1994

LIMA from patients with stable CAD



Hambrecht et al. *Circulation* 2003

Importance of Nitric Oxide during Exercise

- Match tissue oxygen and substrate supply to demand
  - Inducing vasodilatation of arteries in both the skeletal muscle and the heart
  - Altering carbohydrate metabolism in skeletal muscle through an enhancement of glucose uptake and inhibition of glyceraldehyde-3-phosphate dehydrogenase
- Animals deficient in eNOS do not exercise to the same extent as wild-type controls

Kingwell et al., *Pharmacol Physiol*, 2000
Momken et al., *AJPHCP*, 2004

Nitric Oxide Metabolites and Exercise

- Plasma nitrite and nitrosothiol levels are increased during exercise in both rodents and humans
  - Classically viewed as indirect markers of NO bioavailability

- Nitrite
  - Endogenous storage form of NO
  - Reduced to NO during ischemia/hypoxia

- Nitrosothiols
  - Formed by reaction of NO or nitrite with a cysteine residue
  - Reversible protective shield to prevent the irreversible oxidation of proteins
  - Redox sensitive NO donor

Table 2. Changes in plasma NO_2^- before and after exercise

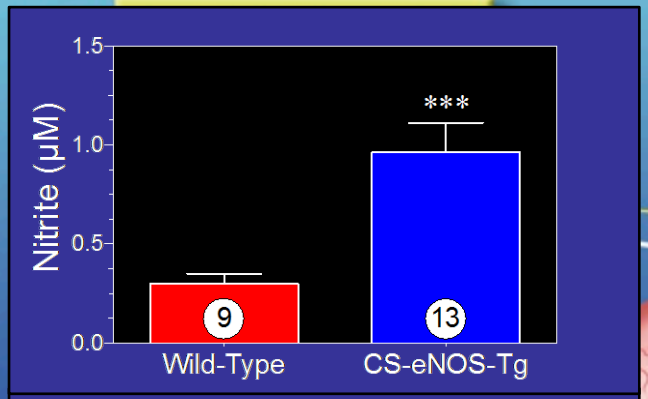
Groups	NO_2^-, µmol/l	
	before exercise	after exercise
Athletes	41.40 ± 6.06 (n = 8)*	56.00 ± 9.90 (n = 8)[a]
Sedentary subjects		
Younger	23.78 ± 5.74 (n = 12)	44.73 ± 6.48 (n = 12)[a]
Older	22.17 ± 6.14 (n = 12)	45.88 ± 9.84 (n = 12)[a]

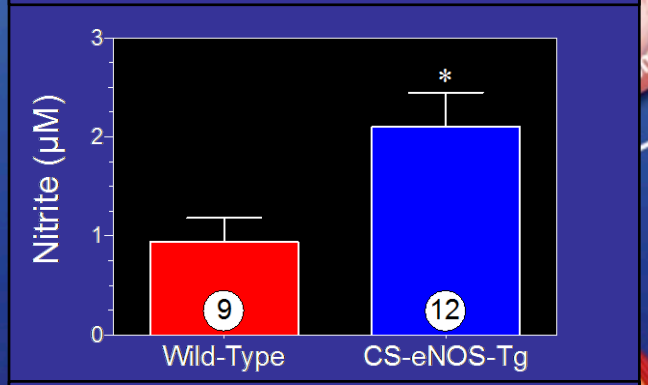
All values expressed as mean ± SD of the number of subjects shown in parentheses. Data were analysed by one-way analysis of variance followed by the Bonferroni t test.

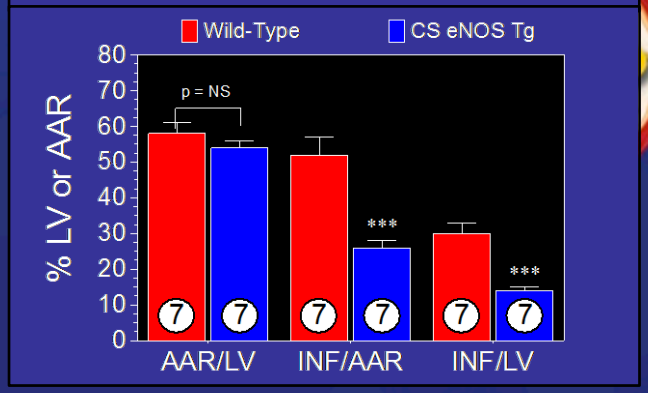
* $p < 0.001$ when compared with inactive younger and older subjects; [a] $p < 0.05$ when compared before exercise.

Franco et al 2001, *Med Principals Pract*

PHYSIOLOGICAL NITRITE (NO_2^-) HOMEOSTASIS







Nitric Oxide Synthases

→ $NO^{\cdot} + O_2^{\cdot}$

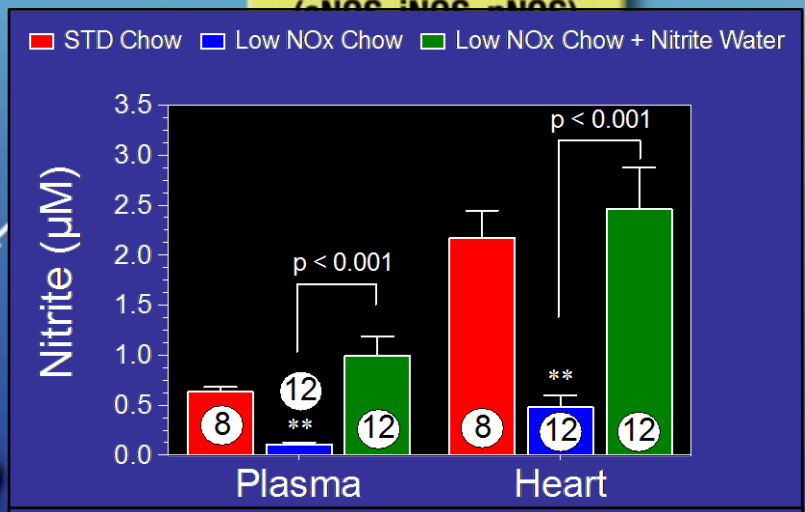
Systemic NO_2^-

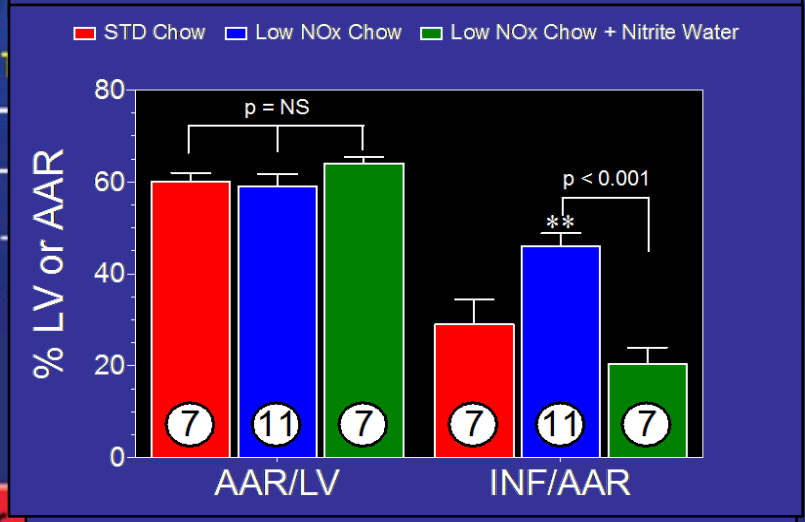
Plasma NO_2^-

HIGH

LOW

NO_2^-





Cardiovascular Health Status

$NO^{\bullet}$

Purpose

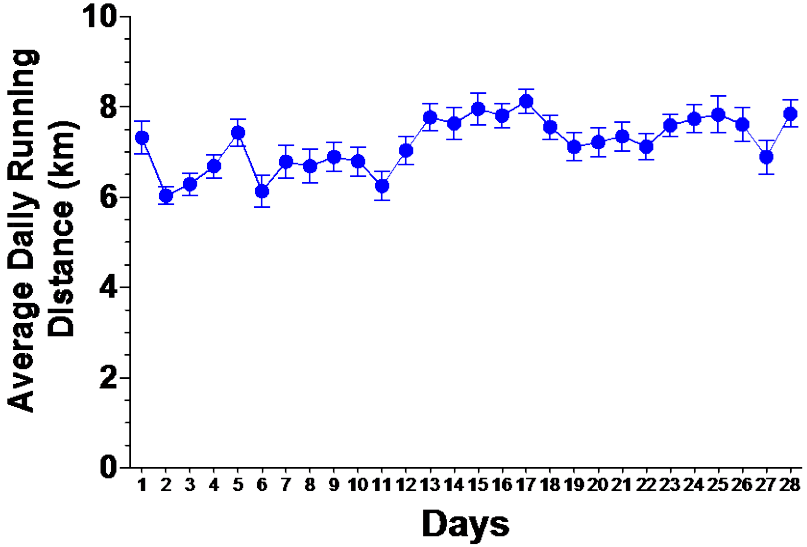
Investigate if Nitrite and Nitrosothiols formed during exercise could be stored in the heart and if they could contribute to the sustained cardioprotective effects of exercise

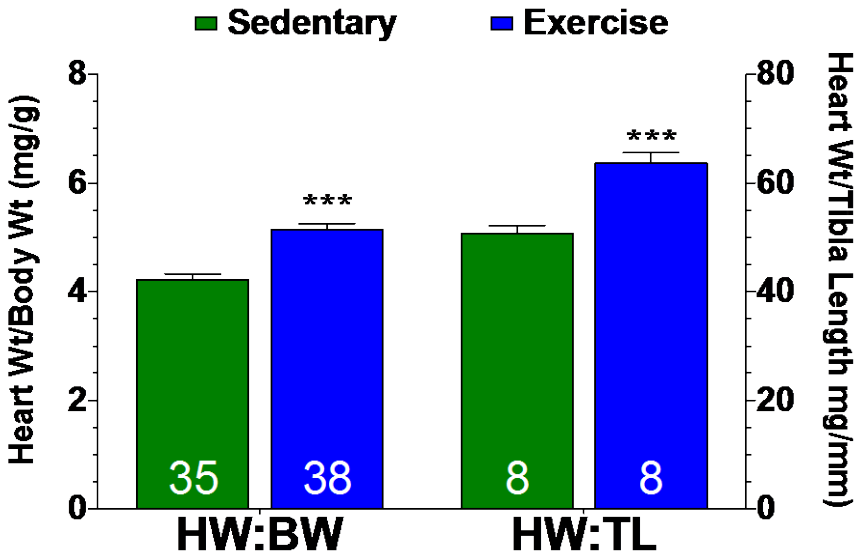
Voluntary Exercise Model

Sedentary

VE 4 wks

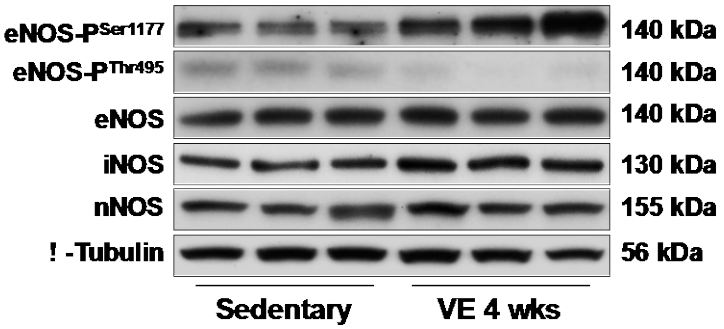
Daily Running Distances and Heart Weights

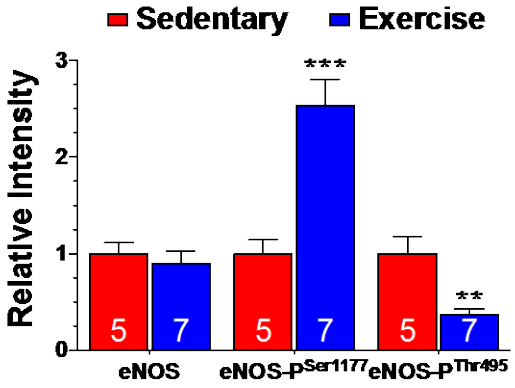


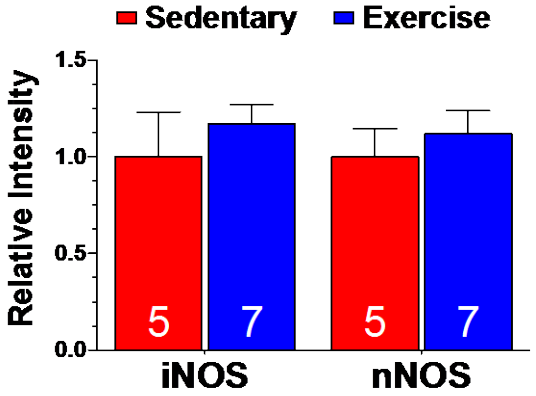


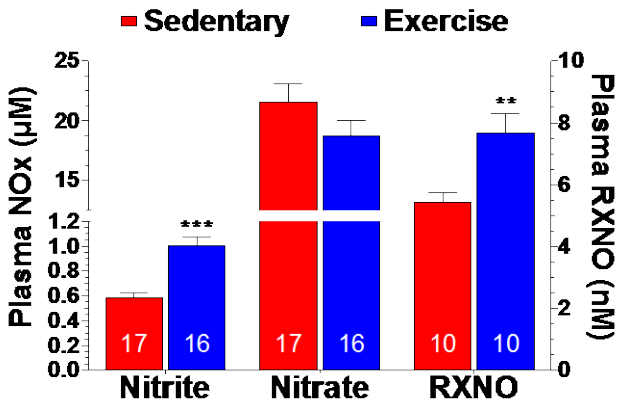
*** p<0.001 vs. Sedentary

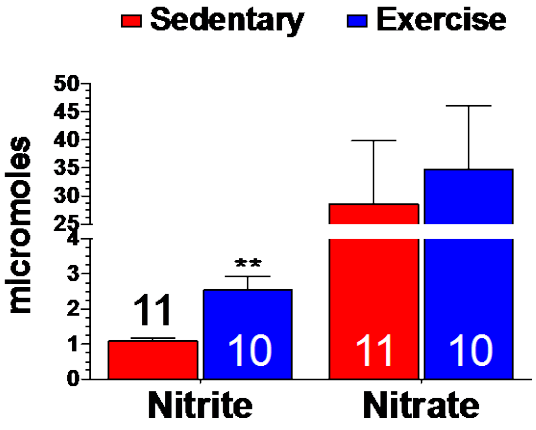
Cardiac NOS Expression and NO Levels following Exercise

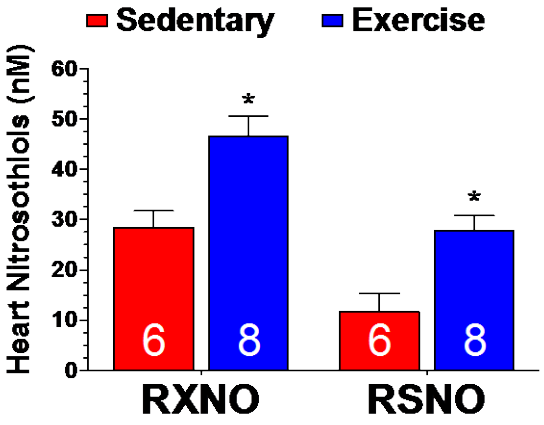








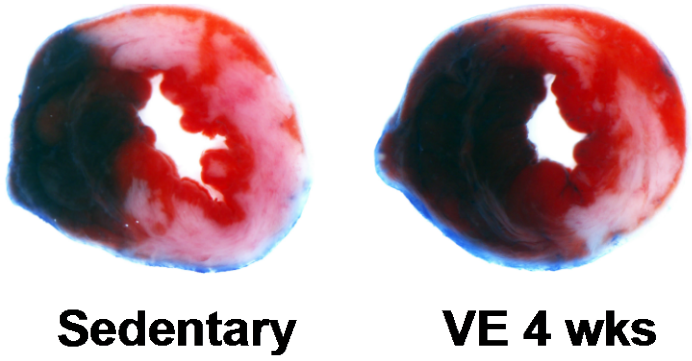


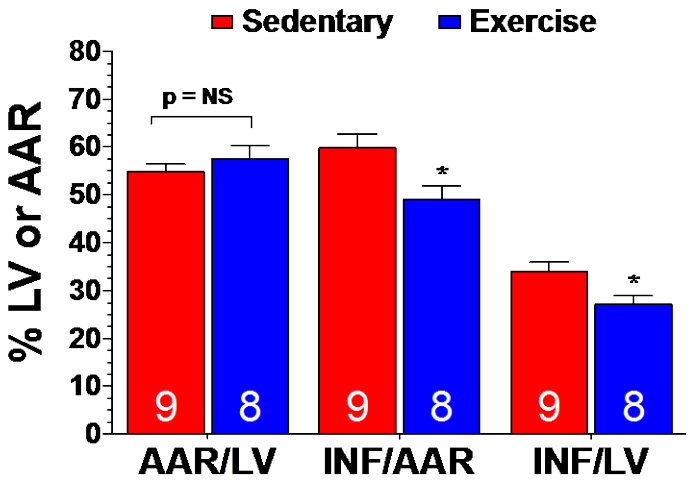


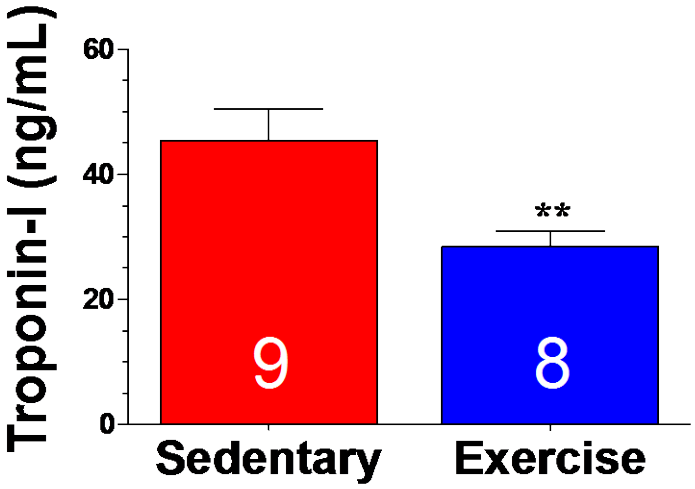
*p<0.05, **p<0.01, ***p<0.001 vs. Sedentary

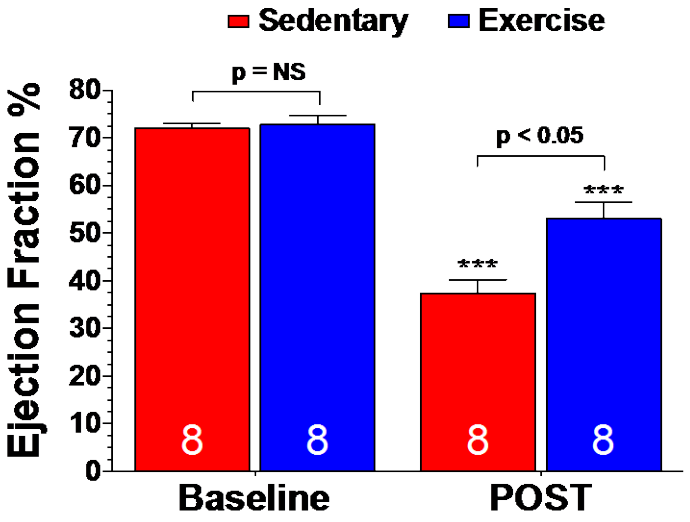
Myocardial Injury

45 min Ischemia and 24 hr or 1 wk Reperfusion





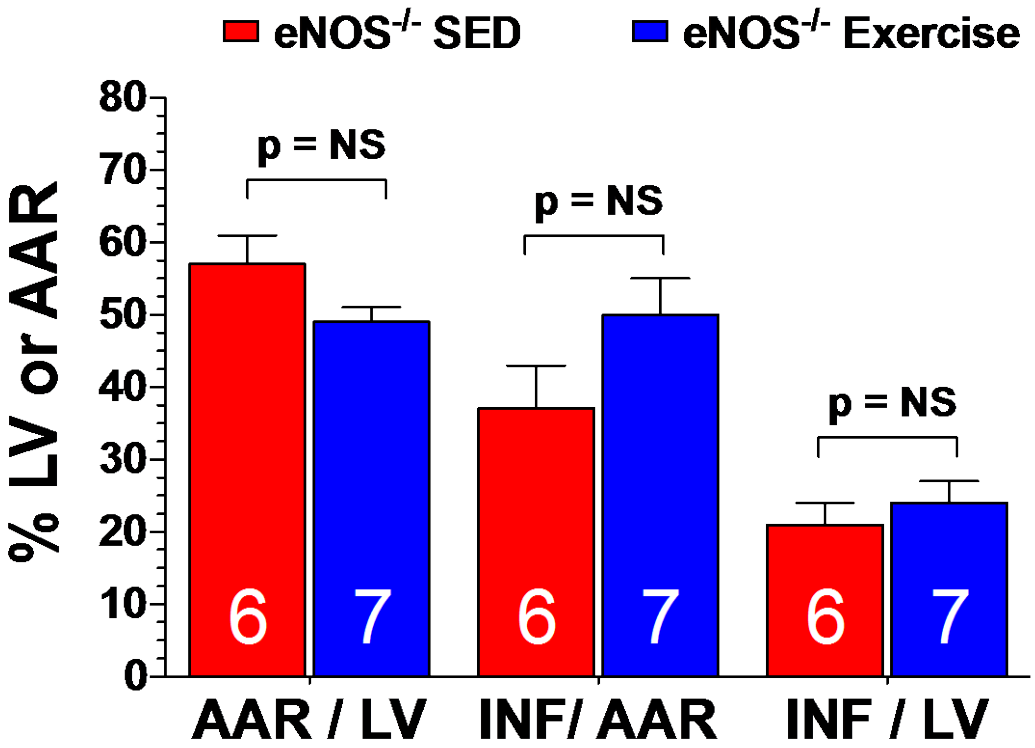




*p<0.05 and *p<0.01 vs. Sedentary; *p<0.001 vs. Baseline

Myocardial Infarct Size

45 min Ischemia and 24 hr Reperfusion



Are the sustained cardioprotective effects of exercise mediated by NO metabolites?

Voluntary Exercise Model

Sedentary

VE 4 wks

VE 4 wks

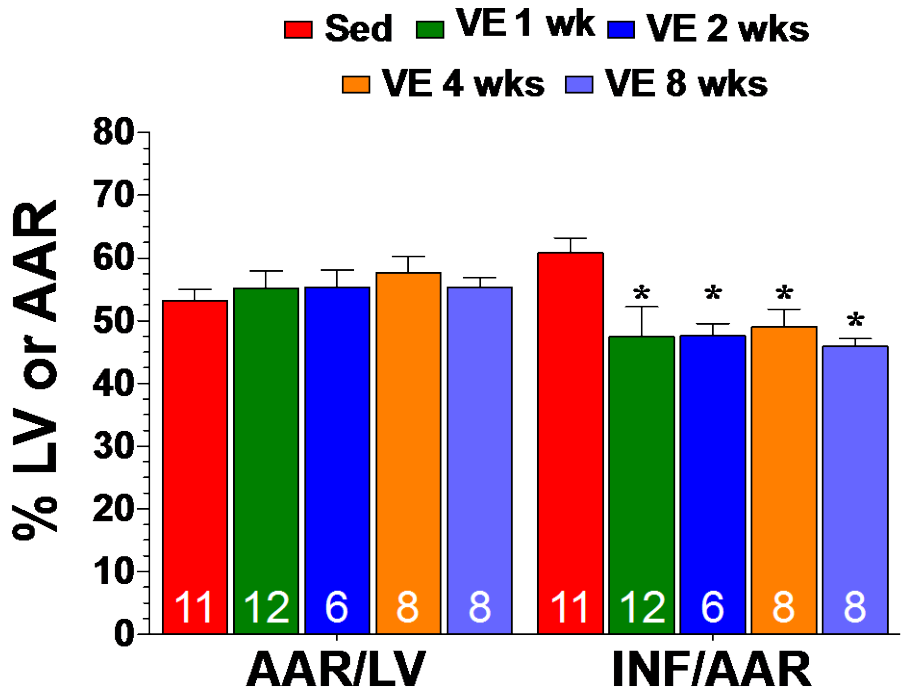
VE 4 wks

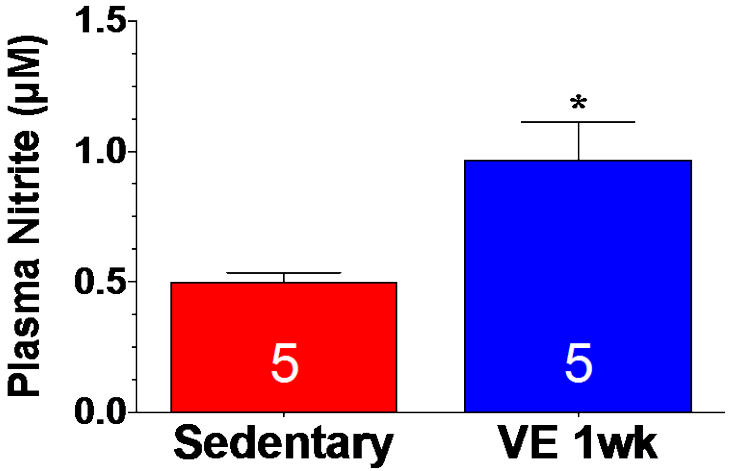
Sedentary
1 wk

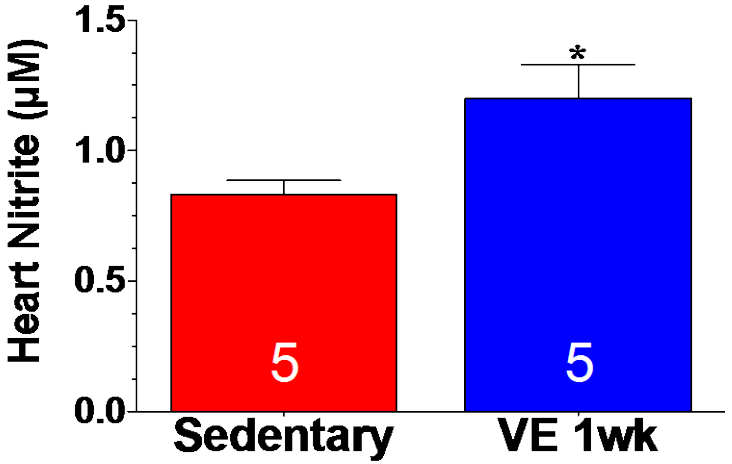
Sedentary
4 wks

Myocardial Injury

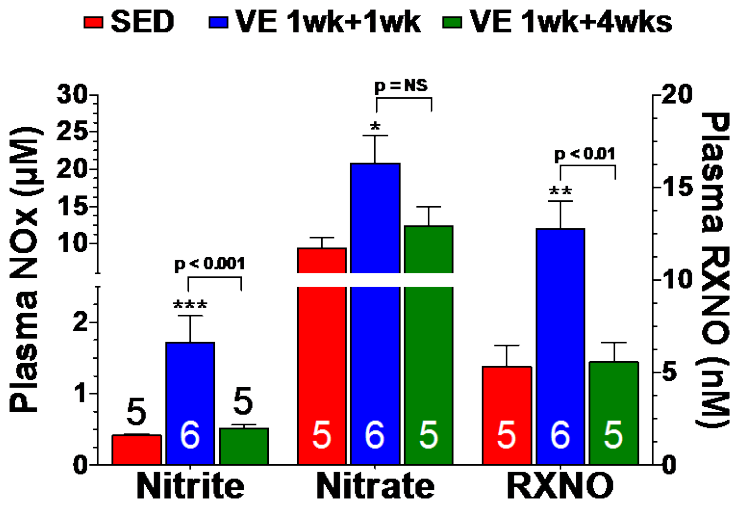
45 min Ischemia and 24 hr Reperfusion

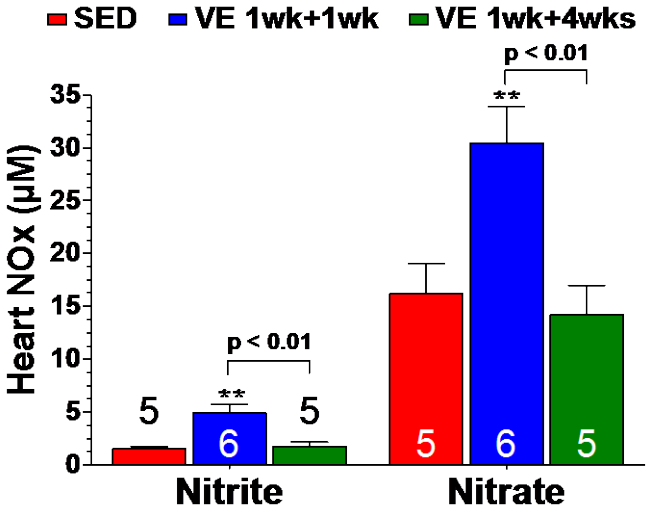


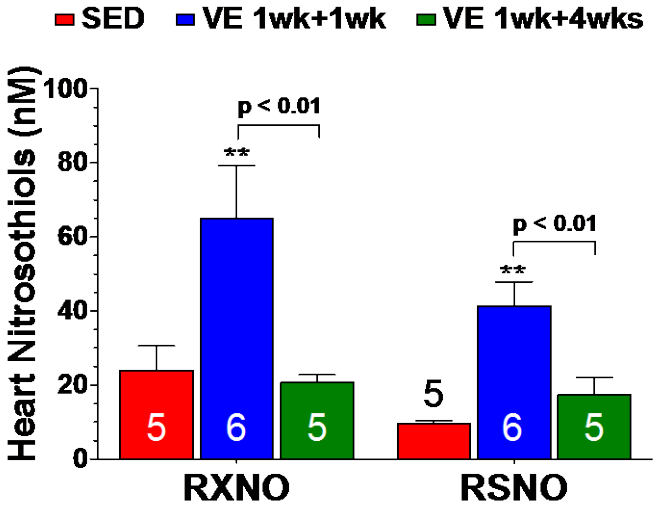


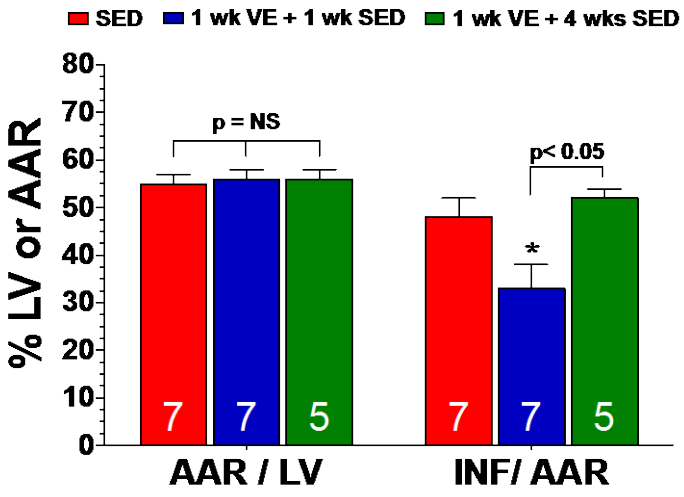


NO Levels and Infarct Size





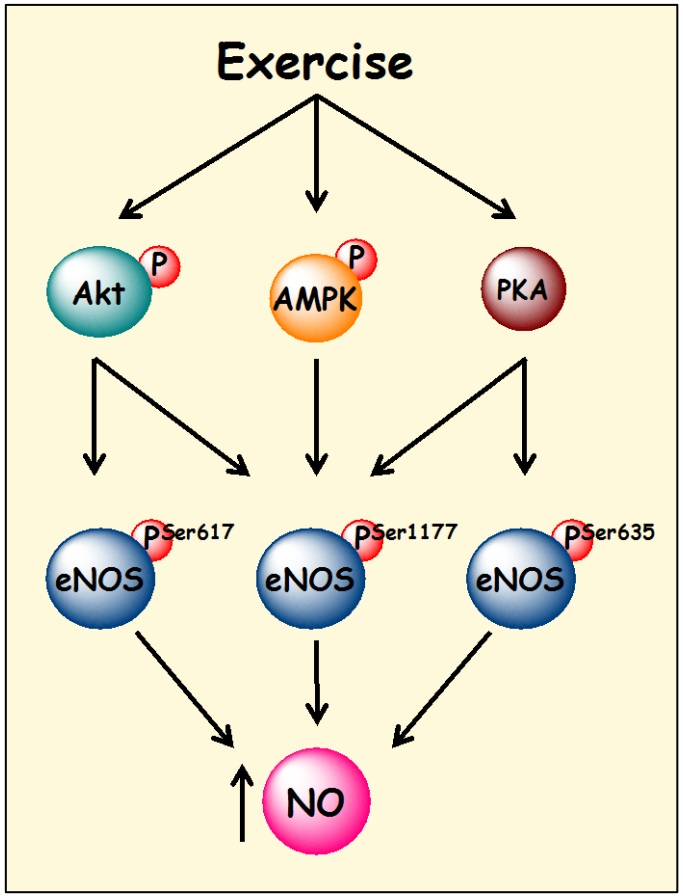




*p<0.05, **p<0.01, ***p<0.001 vs. Sedentary

What leads to the activation of eNOS during exercise?

- Activation of eNOS during exercise can be caused by shear stress
- Shear induced signaling can be mediated by:
  - Akt
  - PKA
  - AMPK



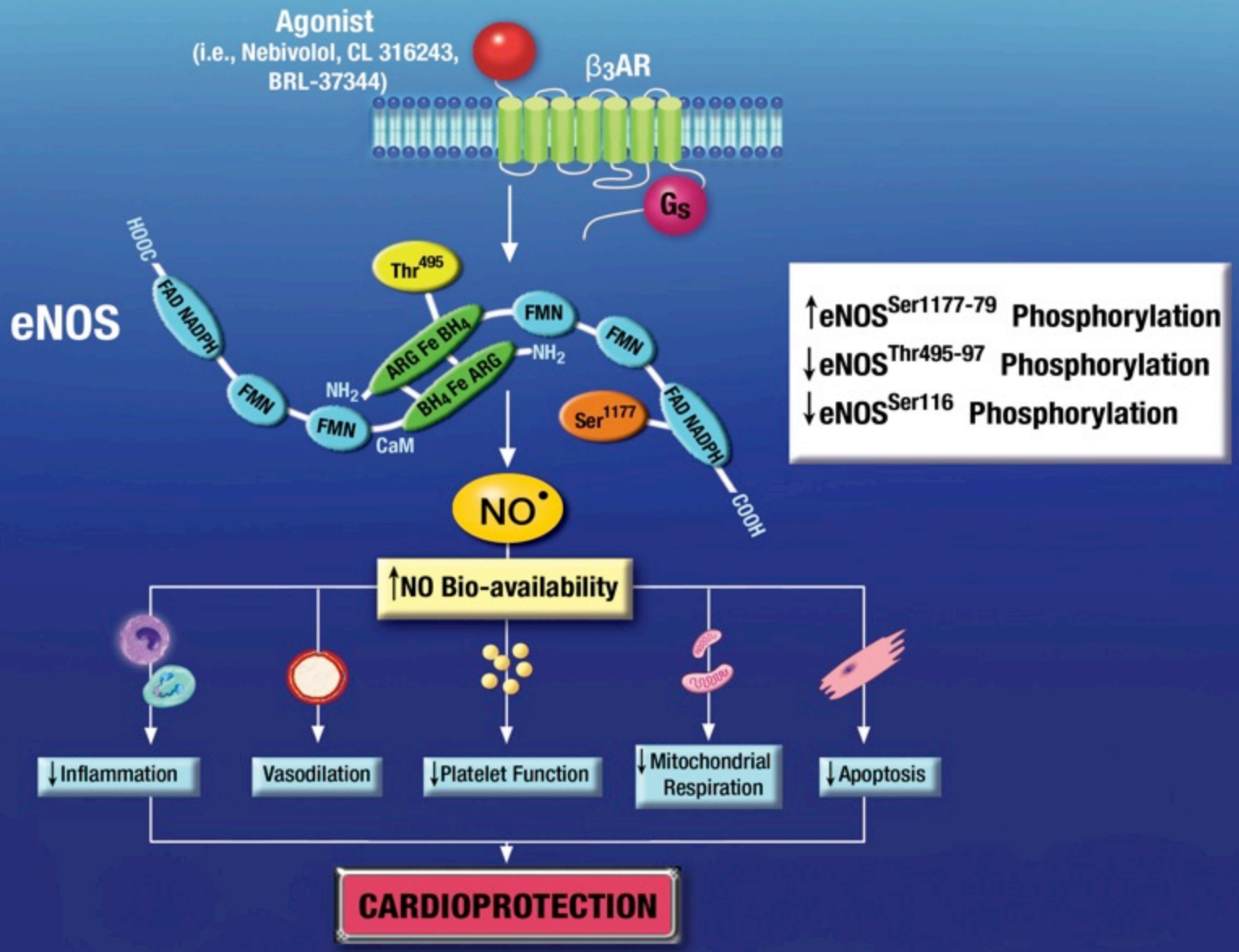
Dimmeler et al., *Nature*, 1999
Zhang et al., *J Physiol*, 2009

β_3-Adrenergic Receptors in the Heart

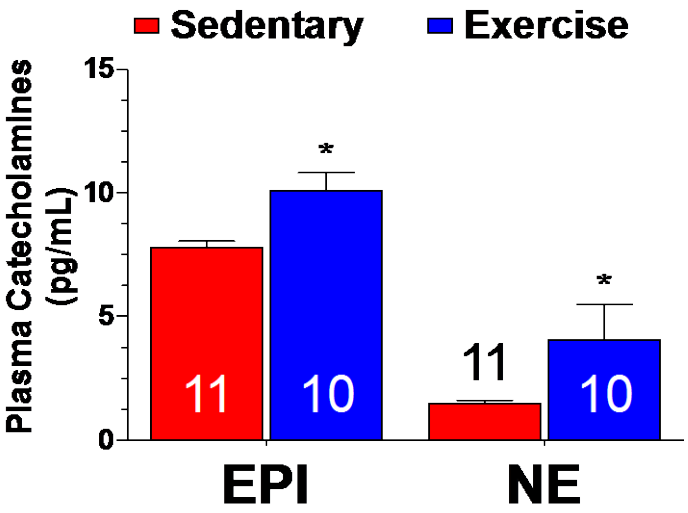
- Three populations of β-adrenergic receptors (β-ARs) potentially modulate cardiac function (β_1-, β_2-, and β_3-ARs)
- G protein-coupled receptor superfamily and modulate cardiac function after stimulation by catecholamines
- β_3-ARs have recently emerged as potential targets for the treatment of cardiovascular diseases
  - Hypertension
  - Acute myocardial infarction
  - Heart failure

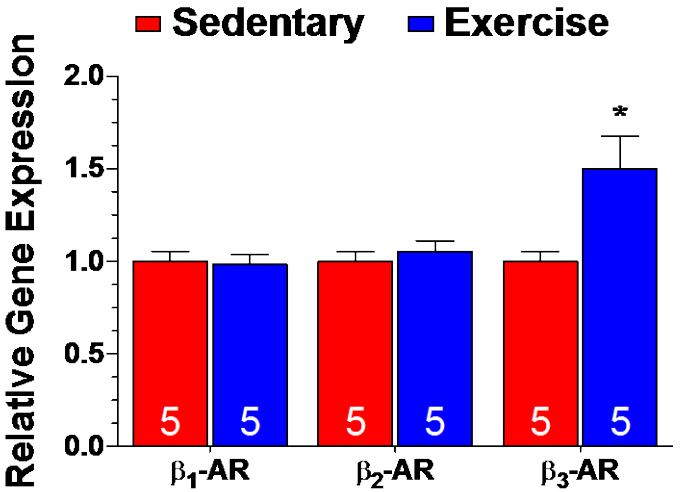
Rozec and Gauthier *Pharmacol Ther*, 2006

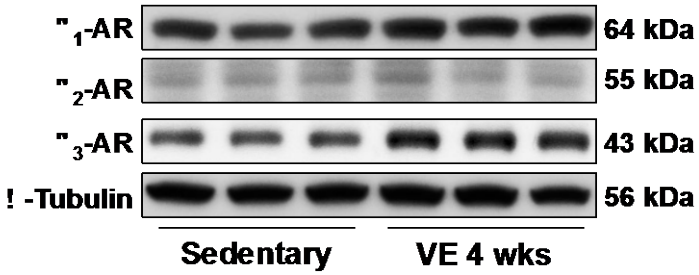
β_3 – ADRENERGIC RECEPTOR ACTIVATION AND ENDOTHELIAL NITRIC OXIDE SYNTHASE

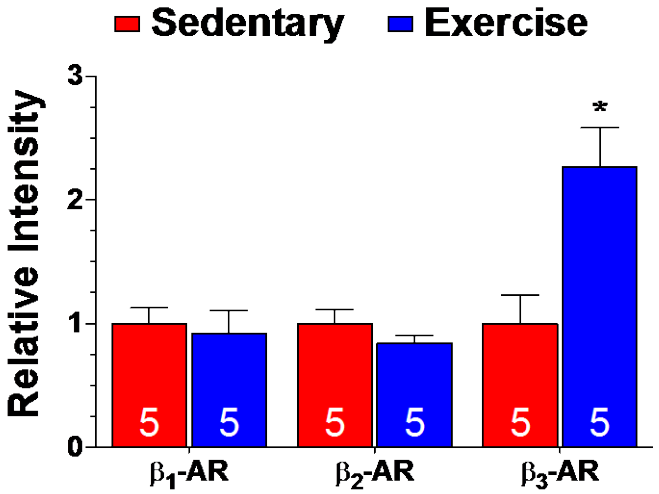


β-Adrenergic Receptor Expression following Exercise









*p<0.05, **p<0.01, ***p<0.001 vs. Sedentary

Voluntary Exercise Model

Wild-Type

β3-AR KO

Sedentary

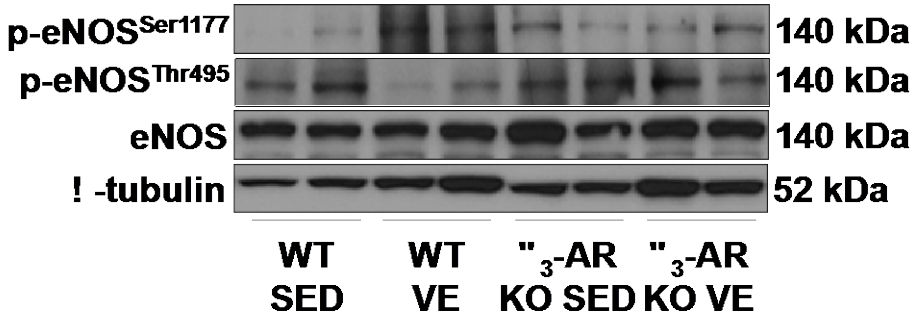
VE 4 wks

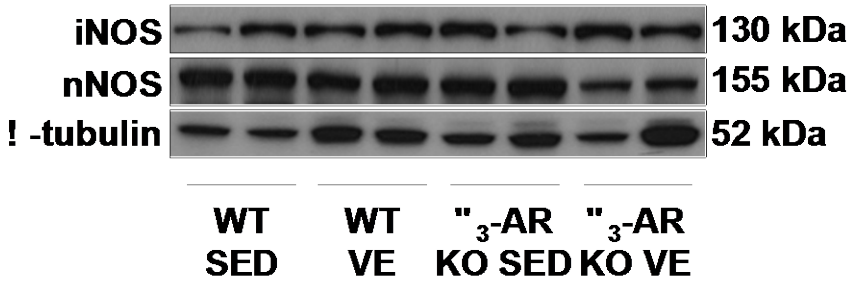
Sedentary

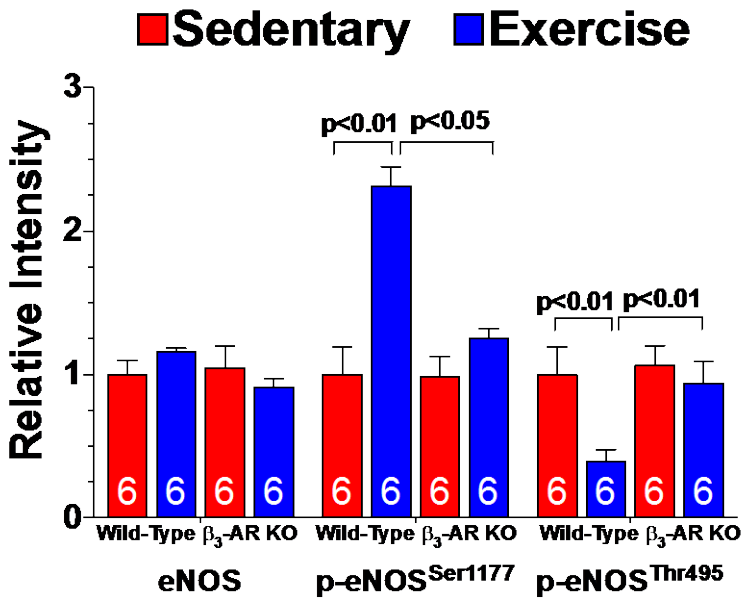
VE 4 wks

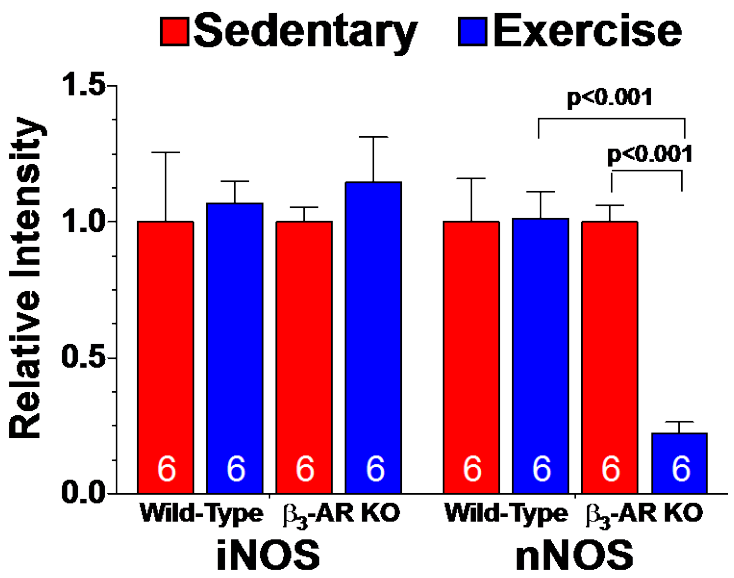
Cardiac NOS Expression

β_3-ARKO Mice



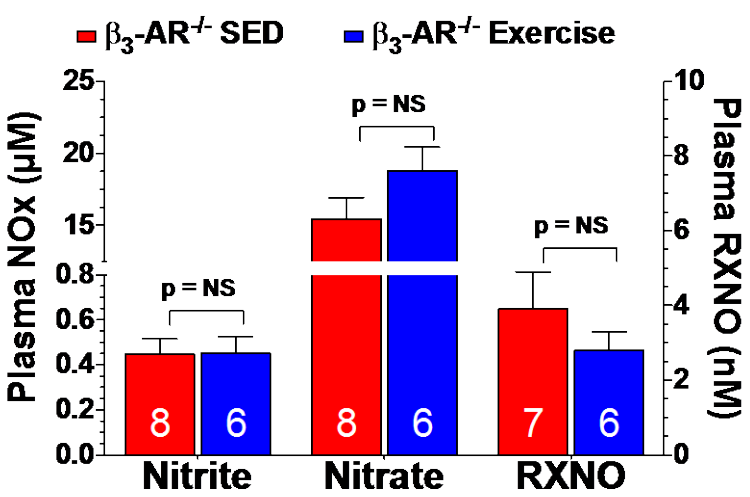


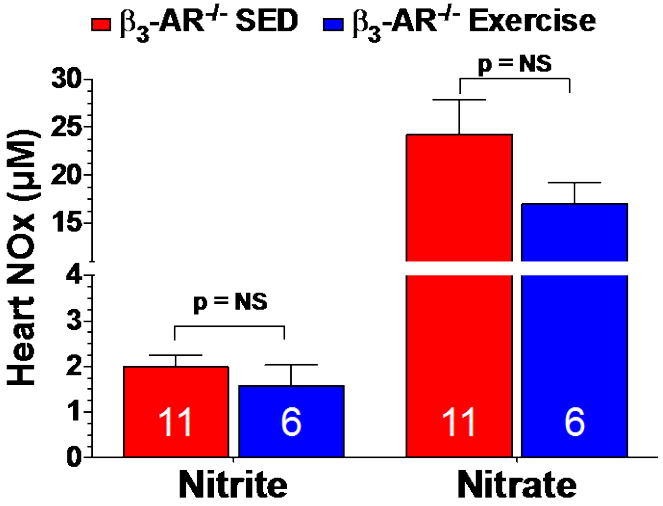


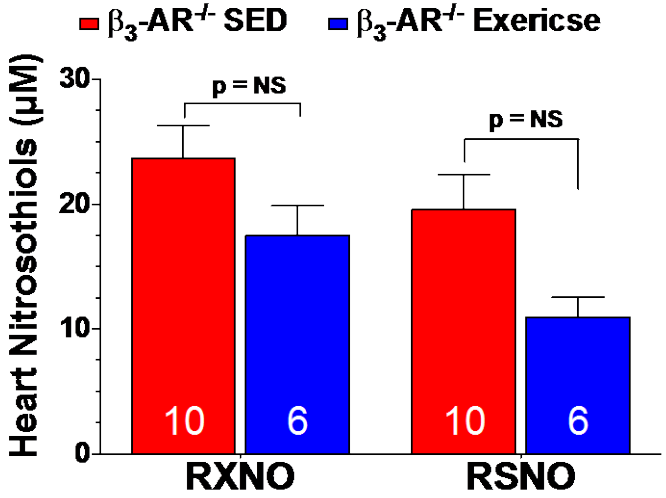


NO Levels following Exercise

β_3-ARKO Mice



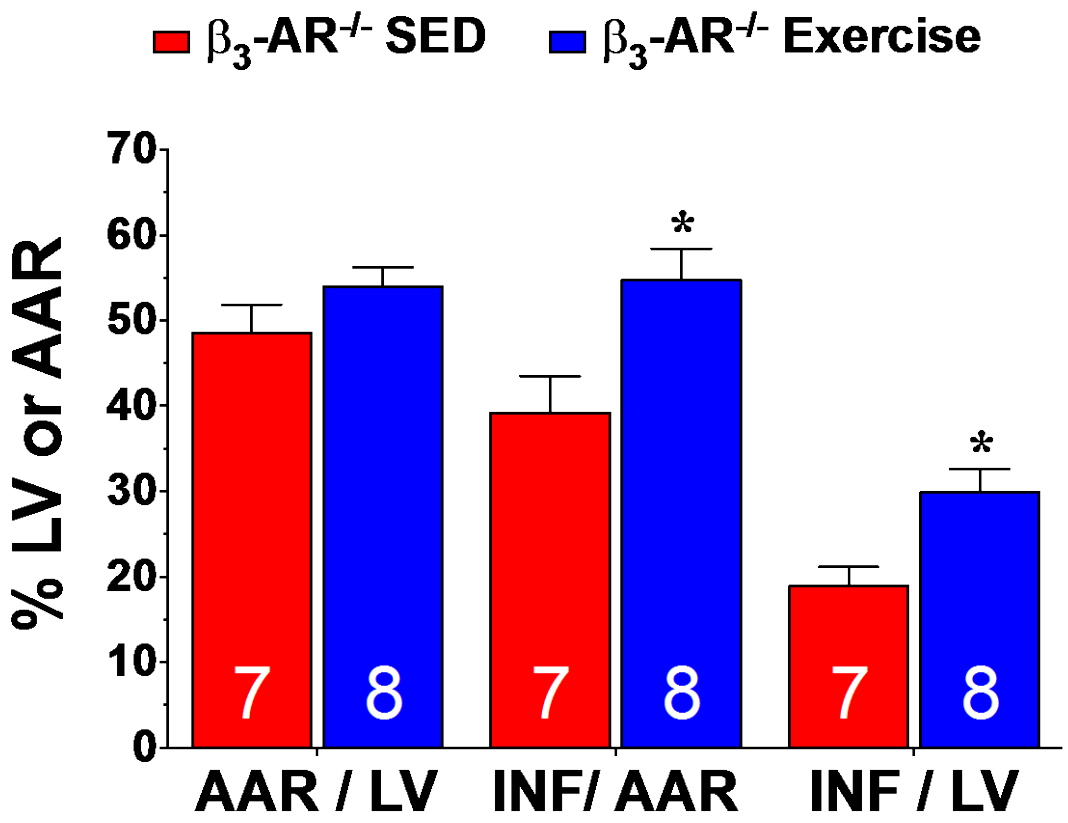




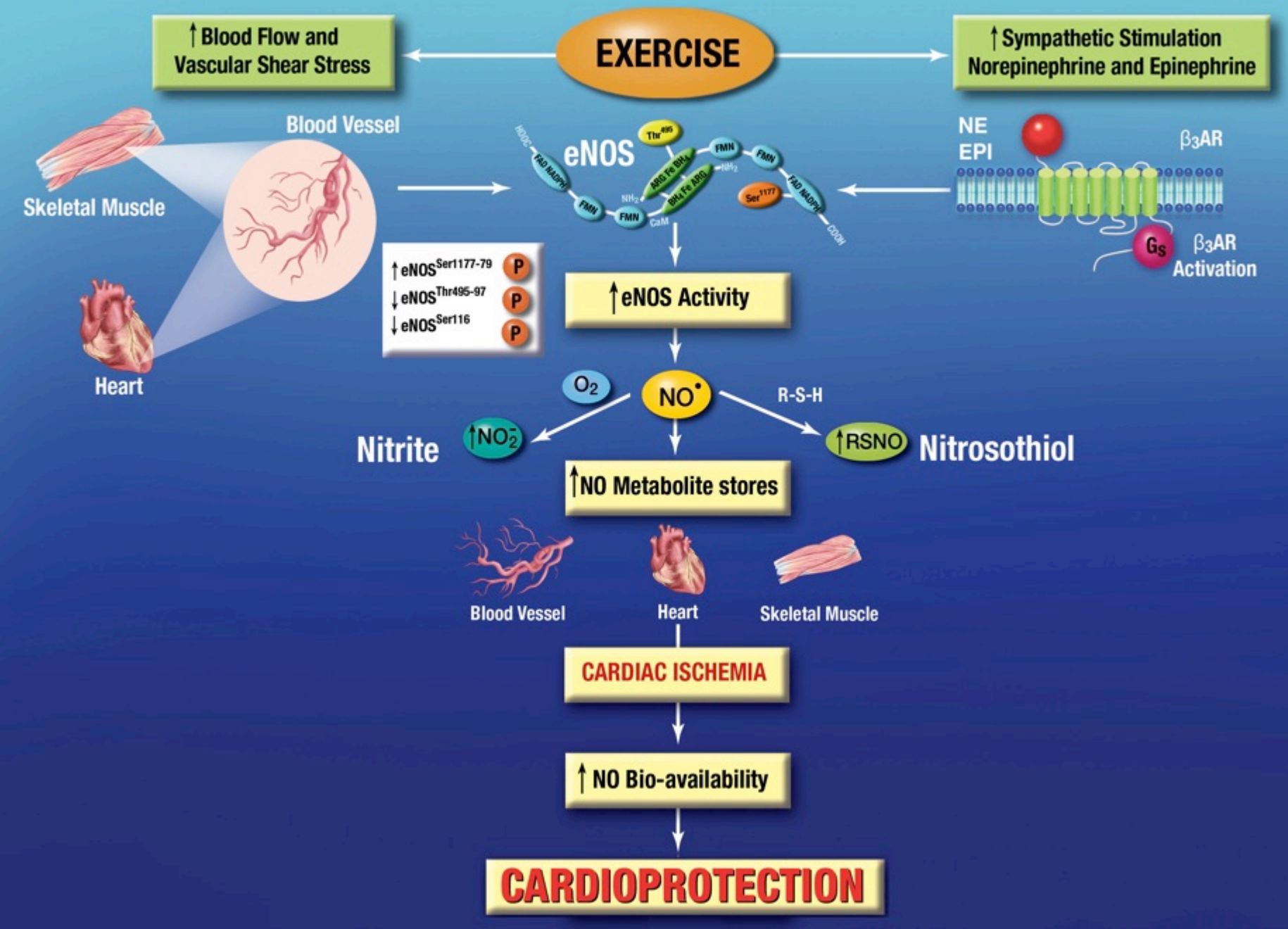
*p<0.05, **p<0.01, ***p<0.001 vs. Sedentary

Myocardial Injury

45 min Ischemia and 24 hr Reperfusion



EXERCISE AND NITRIC OXIDE HOMEOSTASIS



Summary and Conclusions

- Exercise provides sustained cardioprotection against acute myocardial ischemia-reperfusion injury by increasing NO metabolites
- β_3-ARs play a critical role in regulating:
  - the phosphorylation and coupling of eNOS
  - the generation of NO in response to exercise
- β_3-AR-eNOS-NO signaling axis is important for how the heart adapts to exercise and is essential for exercise-mediated cardioprotection

Colleagues and Collaborators

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Rui Wang, Ph.D. – Lakehead University