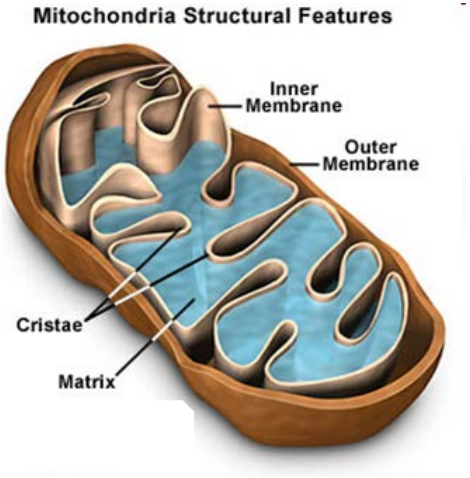
The Mitochondria in Ischemic Disease



Lilach O. Lerman, MD, PhD
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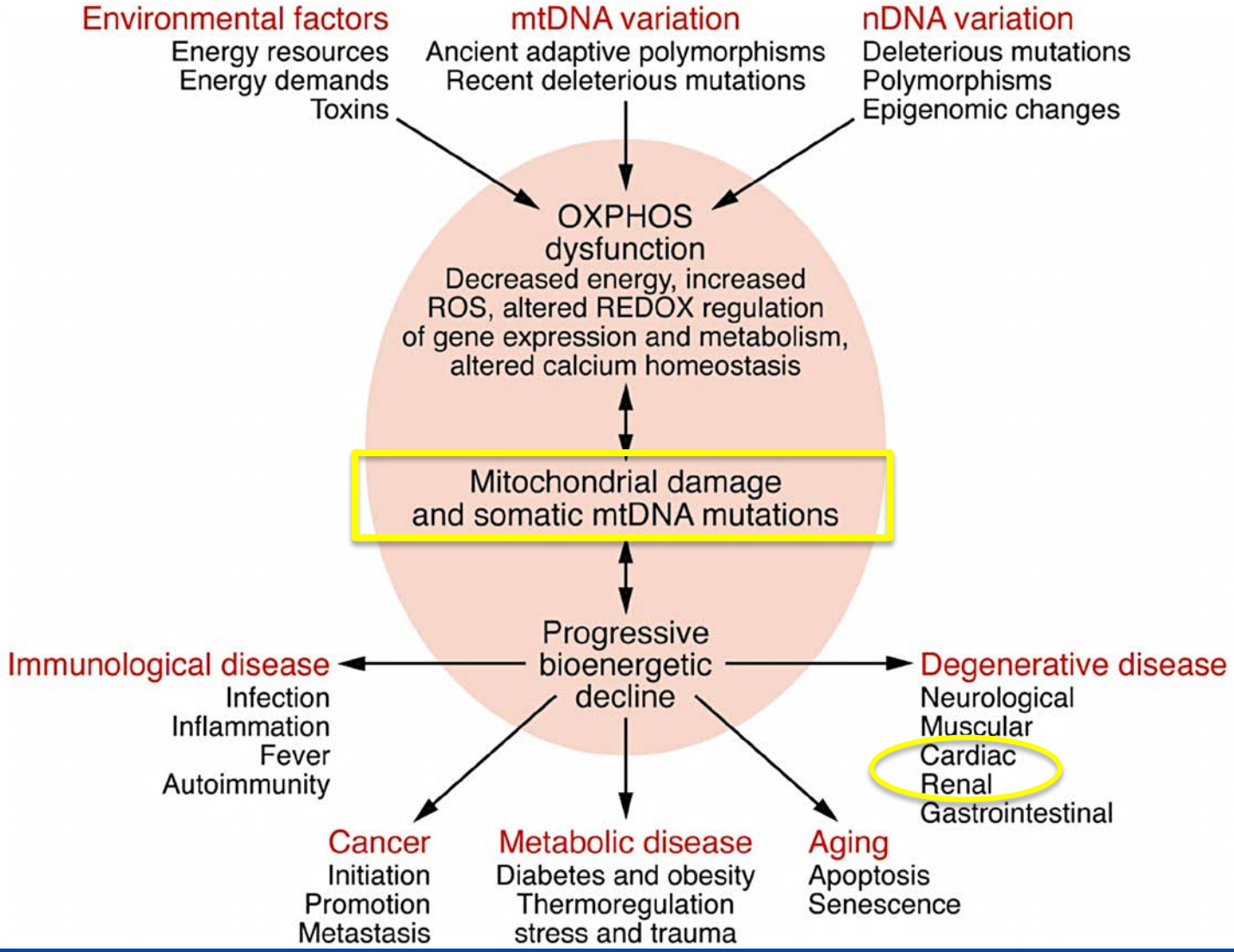
Advances In Cardiac Arrhythmias and Great Innovations In Cardiology,
Turin, Italy, 23-25 October, 2014

Bio-energetic paradigm for metabolic and degenerative diseases, cancer, and aging

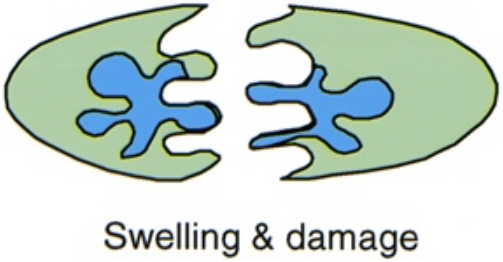


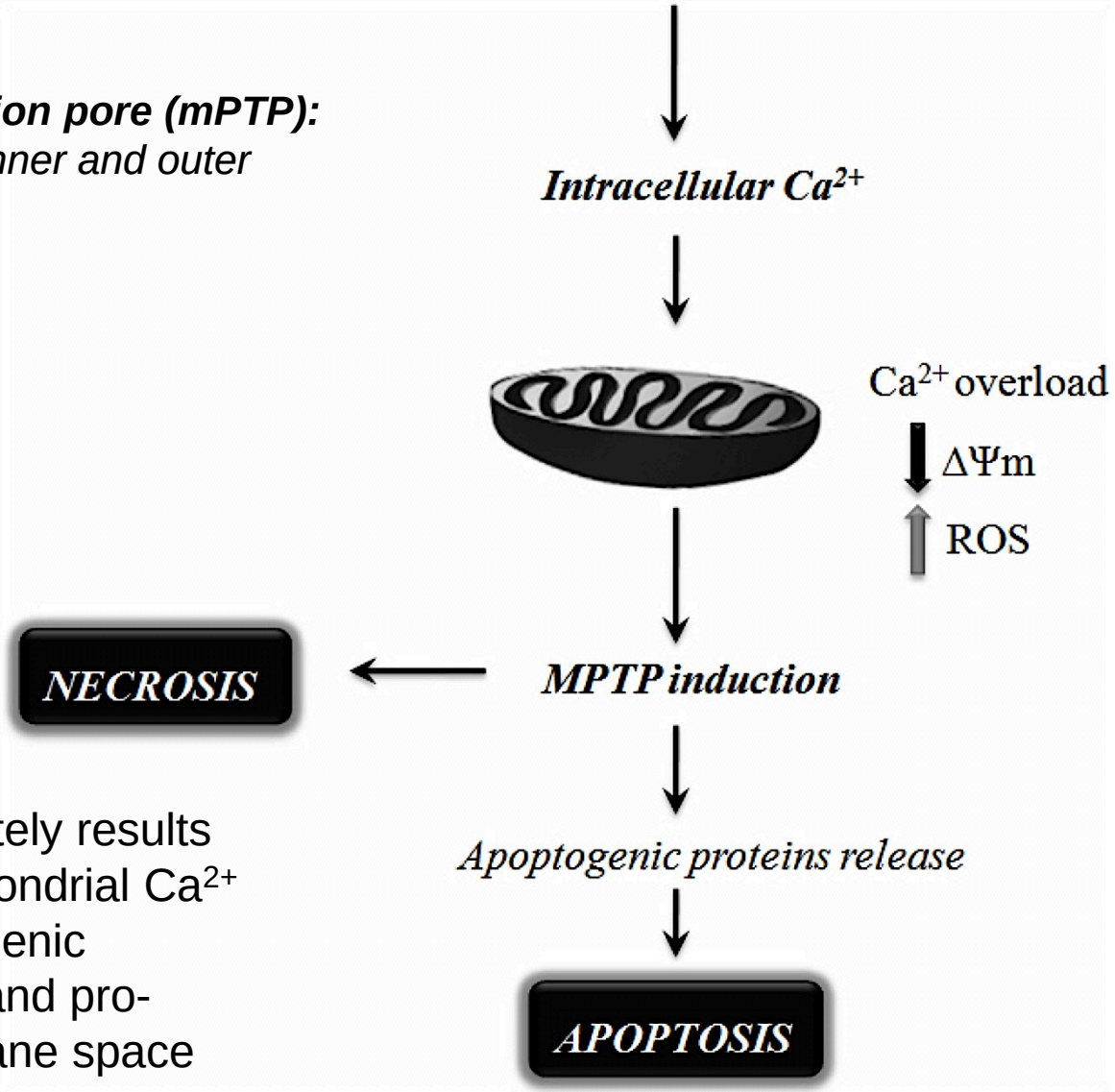
Wallace, JCI 2013

OXPHOS, oxidative Phosphorylation

Mitochondrial Injury in Ischemia

Mitochondrial permeability transition pore (mPTP):
A conductance pore that spans the inner and outer mitochondrial membranes

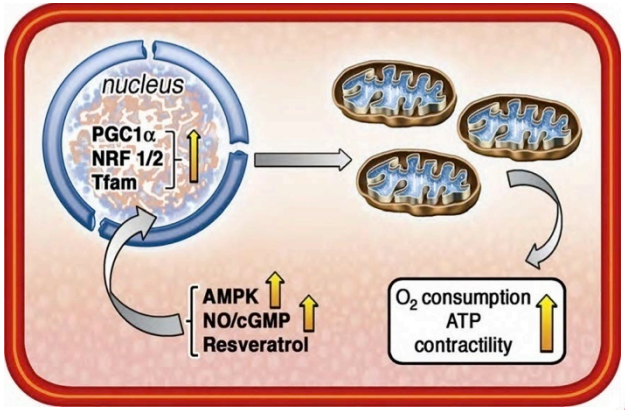




The opening of the mPTP ultimately results in mitochondrial swelling, mitochondrial Ca^{2+} efflux and the release of apoptogenic proteins, such as cytochrome *c* and pro-caspases, from the inter-membrane space

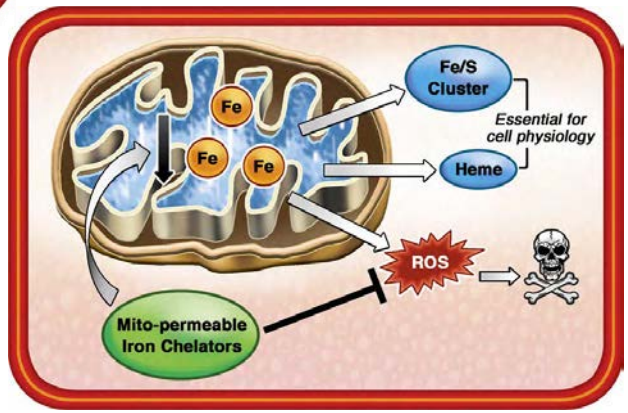
http://www.frontiersin.org/aging_neuroscience/10.3389/fnagi.2010.00138/full

Mitochondria as a Therapeutic Target



Mitochondrial Biogenesis

Adenosine monophosphate kinase (AMPK) agonists, stimulants of NO/cGMP pathway, or resveratrol can stimulate nuclear-encoded proteins peroxisome proliferator–activated receptor gamma coactivator 1 (PGC1), nuclear respiratory factor (NRF)1/2, and transcription factor A (Tfam), which, in turn, ***facilitate production of new mitochondria in the heart***.

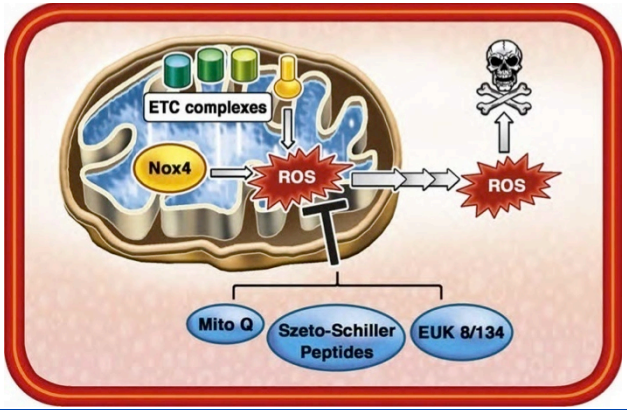


Mitochondrial Iron

Mitochondria regulate cellular iron balance. However, accumulation of iron can catalyze generation of ROS. ***Reducing mitochondrial iron*** through mitochondria-permeable iron chelators can potentially protect failing hearts.

Mitochondrial production of reactive oxygen species

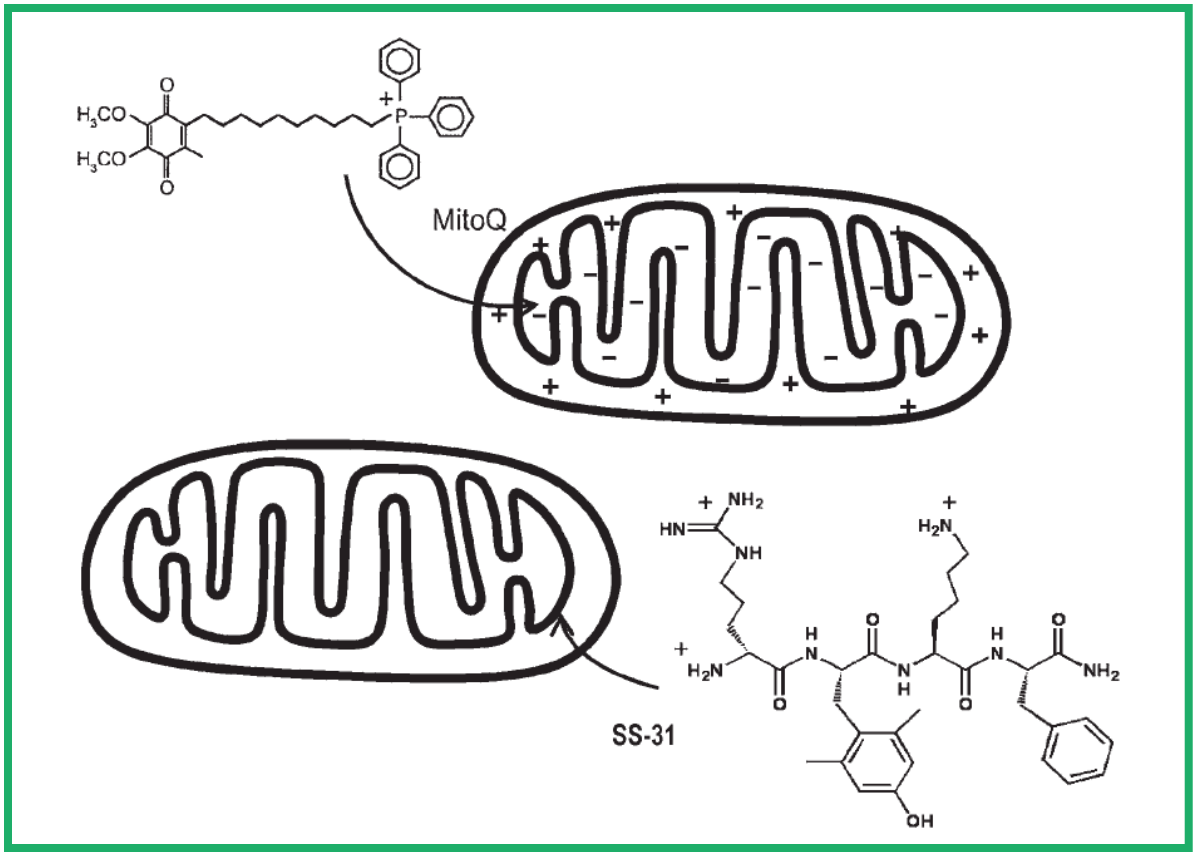
Mitochondrial electron transport chain (ETC) complexes and NAD(P)H oxidase 4 (Nox4) might generate excessive ROS, and mitochondria are sensitive to oxidative stress. Various approaches have been applied for **targeting antioxidants to mitochondria, including MitoQ, MnSOD/catalase mimetics, and Szeto-Schiller peptides (Bendavia).**



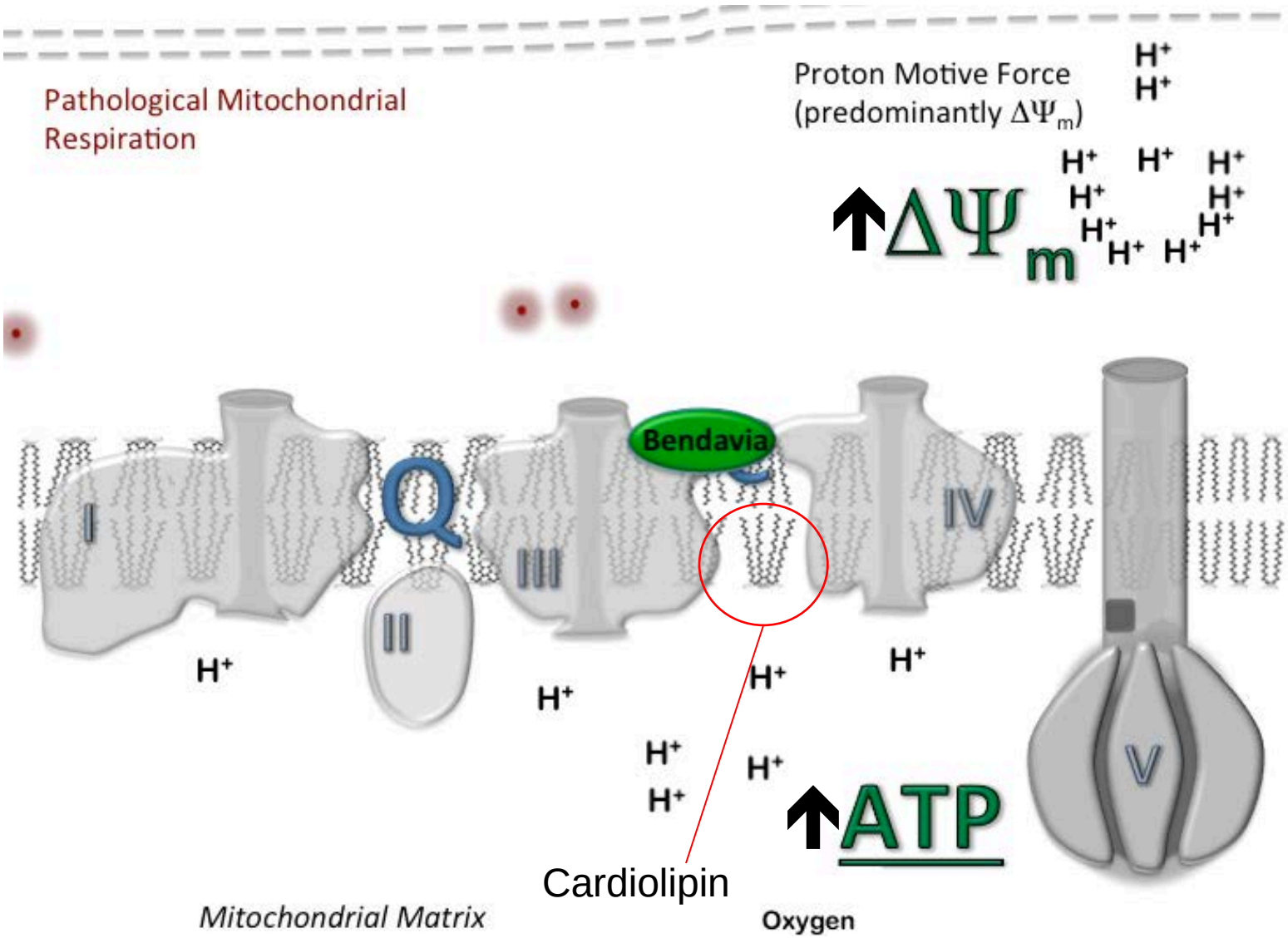
Bayeva M, Gheorghiade M, Ardehali H. J Am Coll Cardiol 61: 599-610, 2013.

Mitochondrial Targeted Peptides

- Small synthetic peptides (<10 amino acids)
- Stable in aqueous solution, resist peptidase degradation
- Passive diffusion into a variety of cell types
- Mitochondrial uptake ~x1,000-5,000

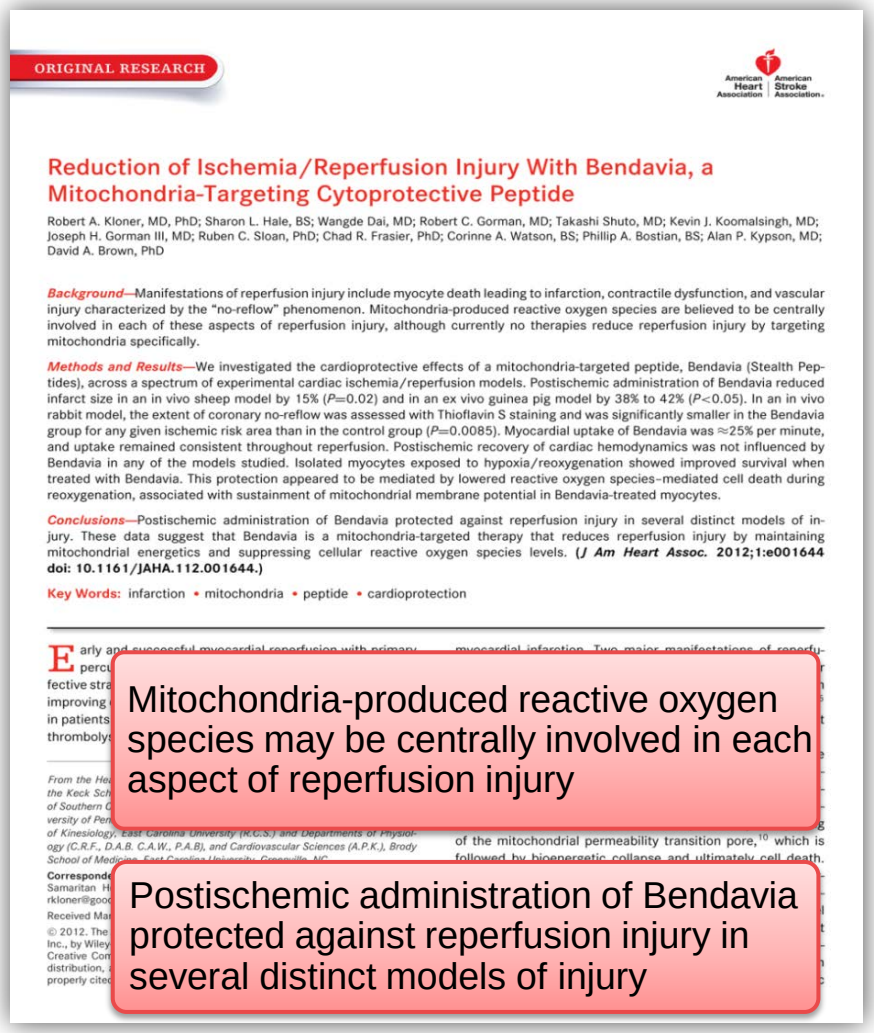


Bendavia (SS-31) stabilizes cardiolipin



Courtesy of Stealth Biopharmaceuticals, Inc.

Reduction of Ischemia/Reperfusion Injury with Bendavia, a Mitochondria-Targeting Cytoprotective Peptide



ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Reduction of Ischemia/Reperfusion Injury With Bendavia, a Mitochondria-Targeting Cytoprotective Peptide

Robert A. Kloner, MD, PhD; Sharon L. Hale, BS; Wangde Dai, MD; Robert C. Gorman, MD; Takashi Shuto, MD; Kevin J. Koomalsingh, MD; Joseph H. Gorman III, MD; Ruben C. Sloan, PhD; Chad R. Frasier, PhD; Corinne A. Watson, BS; Phillip A. Bostian, BS; Alan P. Kypson, MD; David A. Brown, PhD

Background—Manifestations of reperfusion injury include myocyte death leading to infarction, contractile dysfunction, and vascular injury characterized by the "no-reflow" phenomenon. Mitochondria-produced reactive oxygen species are believed to be centrally involved in each of these aspects of reperfusion injury, although currently no therapies reduce reperfusion injury by targeting mitochondria specifically.

Methods and Results—We investigated the cardioprotective effects of a mitochondria-targeted peptide, Bendavia (Stealth Peptides), across a spectrum of experimental cardiac ischemia/reperfusion models. Postischemic administration of Bendavia reduced infarct size in an in vivo sheep model by 15% (P=0.02) and in an ex vivo guinea pig model by 38% to 42% (P<0.05). In an in vivo rabbit model, the extent of coronary no-reflow was assessed with Thioflavin S staining and was significantly smaller in the Bendavia group for any given ischemic risk area than in the control group (P=0.0085). Myocardial uptake of Bendavia was ≈25% per minute, and uptake remained consistent throughout reperfusion. Postischemic recovery of cardiac hemodynamics was not influenced by Bendavia in any of the models studied. Isolated myocytes exposed to hypoxia/reoxygenation showed improved survival when treated with Bendavia. This protection appeared to be mediated by lowered reactive oxygen species–mediated cell death during reoxygenation, associated with sustainment of mitochondrial membrane potential in Bendavia-treated myocytes.

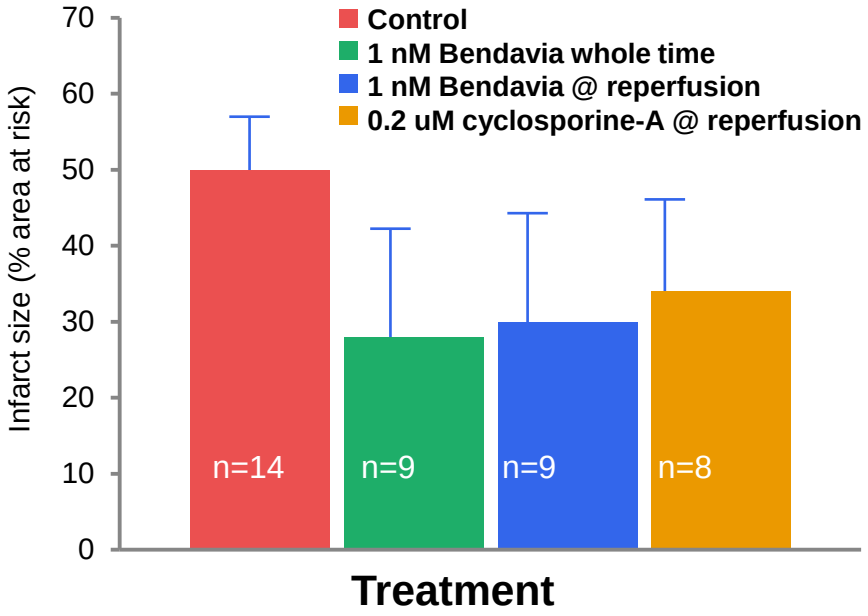
Conclusions—Postischemic administration of Bendavia protected against reperfusion injury in several distinct models of injury. These data suggest that Bendavia is a mitochondria-targeted therapy that reduces reperfusion injury by maintaining mitochondrial energetics and suppressing cellular reactive oxygen species levels. (***J Am Heart Assoc.*** **2012;1:e001644 doi: 10.1161/JAHA.112.001644.)**

Key Words: infarction • mitochondria • peptide • cardioprotection

Mitochondria-produced reactive oxygen species may be centrally involved in each aspect of reperfusion injury

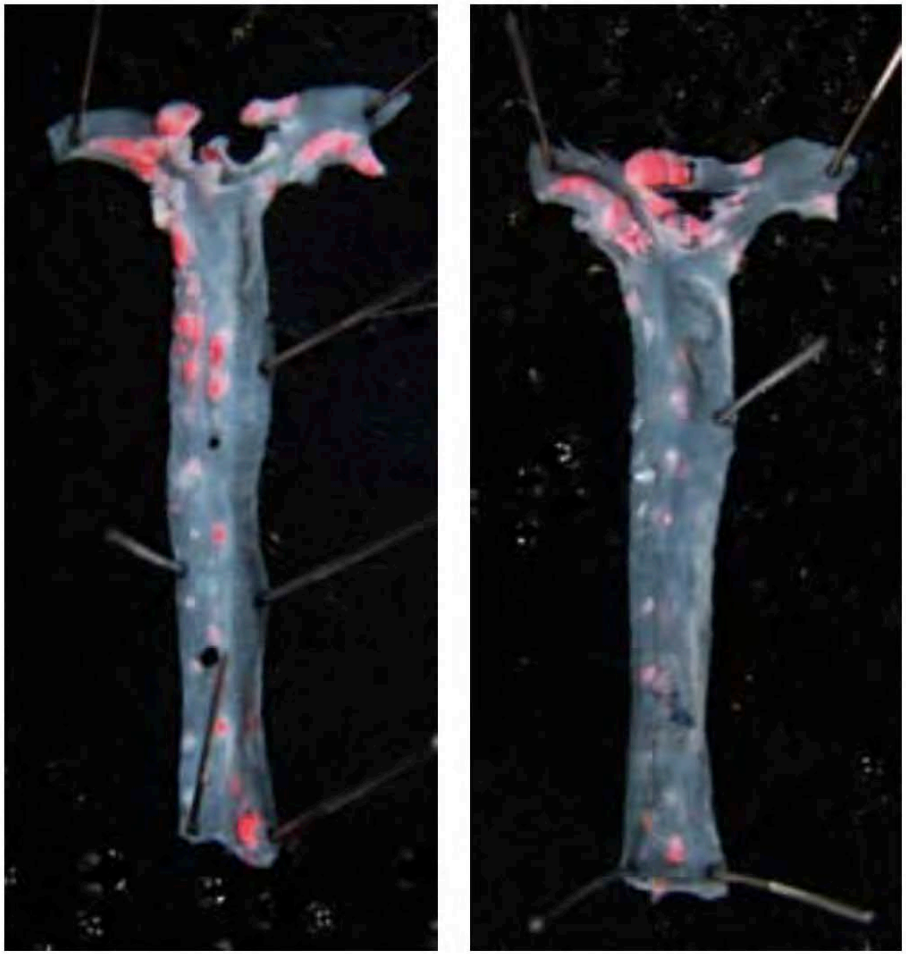
Postischemic administration of Bendavia protected against reperfusion injury in several distinct models of injury

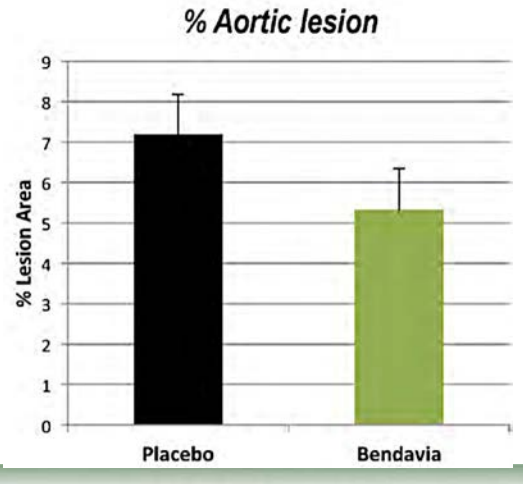
Infarct Size in Isolated Guinea Pig Hearts Exposed to Ischemia/Reperfusion (20 min/2h)



Kloner et al: J Am Heart Assoc 1, 2012

Bendavia reduces atherosclerotic plaques in ApoE K/O Mice





Atherosclerosis

Bendavia Does Not Change Plasma Lipids

Plasma lipid levels at 12 weeks

	Placebo	Bendavia
Total cholesterol	1103 ± 84	1003 ± 90
VLDL cholesterol	53 ± 6	44 ± 5
LDL cholesterol	1020 ± 79	939 ± 88
HDL cholesterol	30 ± 4	21 ± 4
Triglycerides	40± 7	55 ± 11
Phospholipid	473 ± 28	434 ± 31

Rader et al 2012

Mitochondrial injury in Experimental Ischemic Renal Disease in Pigs

1. ***Revascularization (acute reversal of ischemia and hypertension)***
2. ***Chronic atherosclerotic renal artery stenosis (chronic ischemia & renovascular hypertension)***

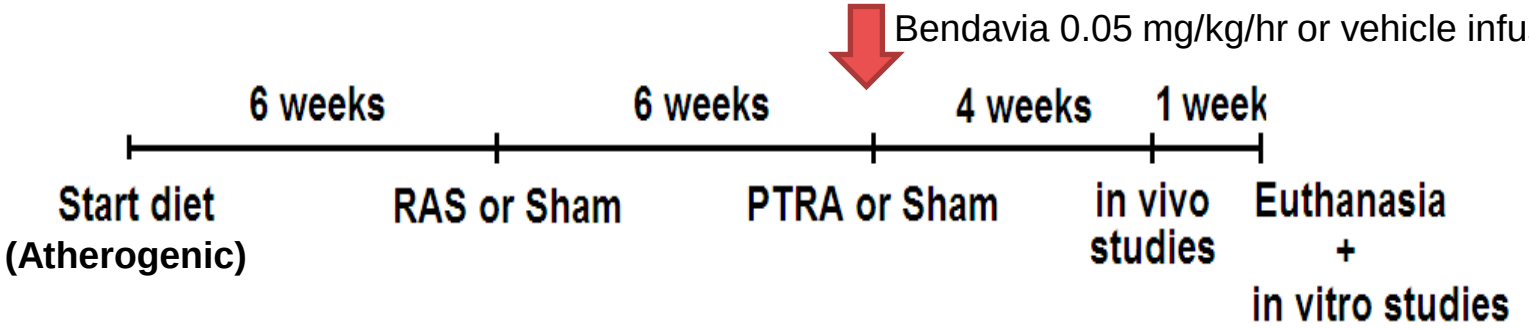
Hypertension
Journal of the American Heart Association

American Heart Association

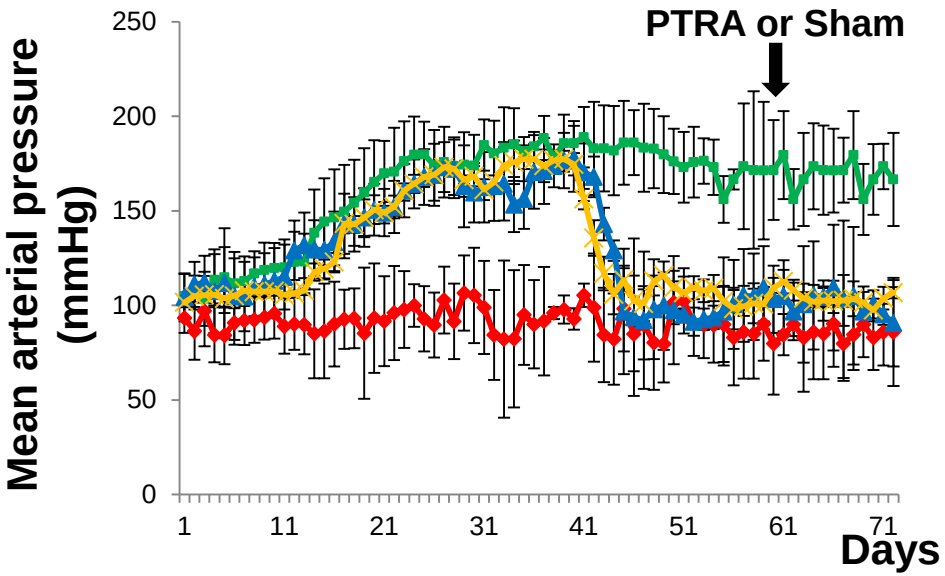
A Mitochondrial Permeability Transition Pore Inhibitor Improves Renal Outcomes After Revascularization in Experimental Atherosclerotic Renal Artery Stenosis

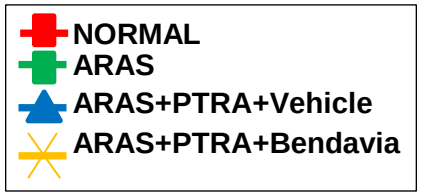
Alfonso Eirin, Zilun Li, Xin Zhang, James D. Krier, John R. Woollard, Xiang-Yang Zhu, Hui Tang, Sandra M. Herrmann, Amir Lerman, Stephen C. Textor and Lilach O. Lerman

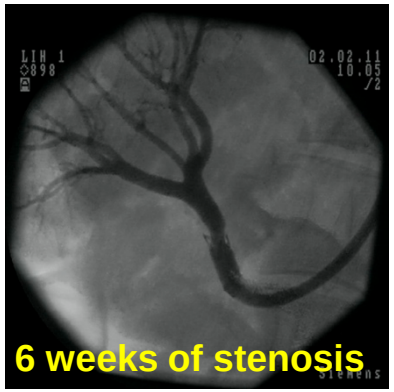
- **Bendavia given after established Atherosclerotic Renal Artery Stenosis (ARAS)**
- **One IV dose during Percutaneous Transluminal Renal Angioplasty (PTRA) & Stenting with assessments 4 weeks later**

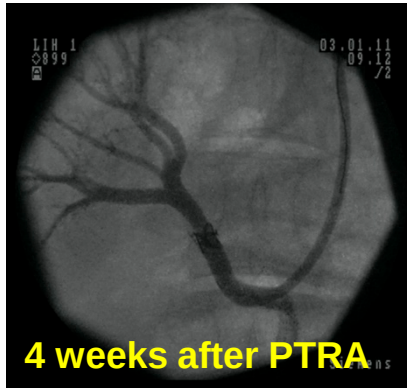


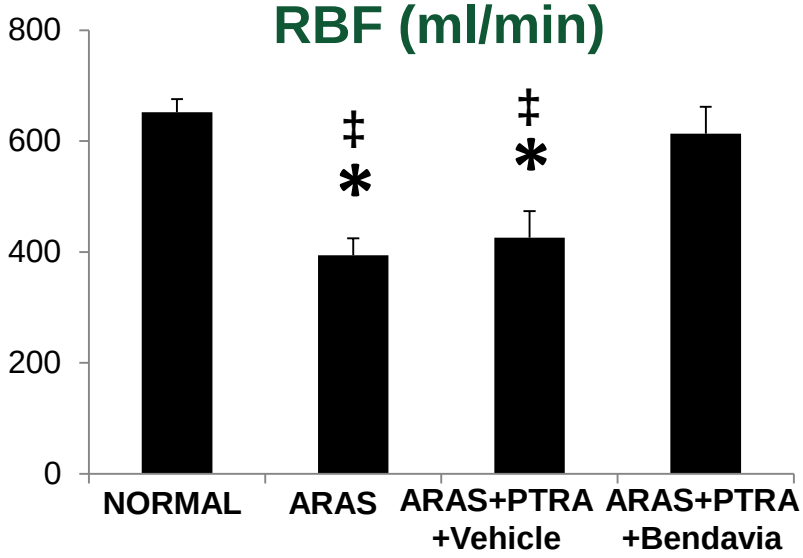
Renal outcomes 4 weeks after PTRA

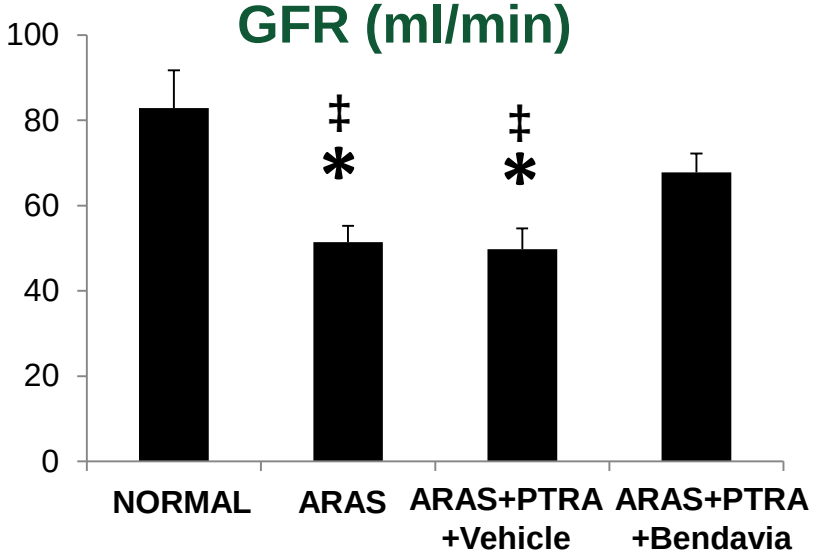








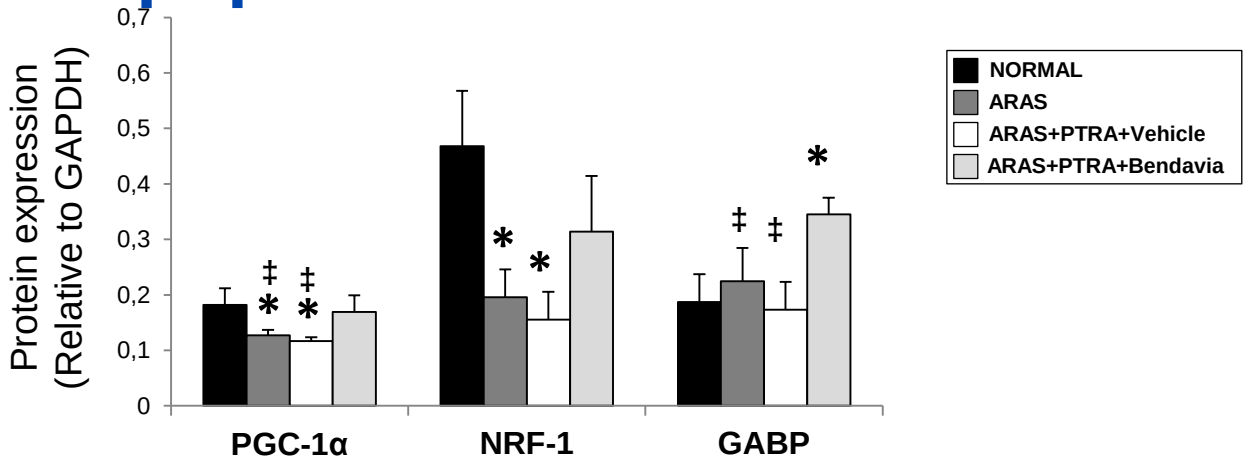




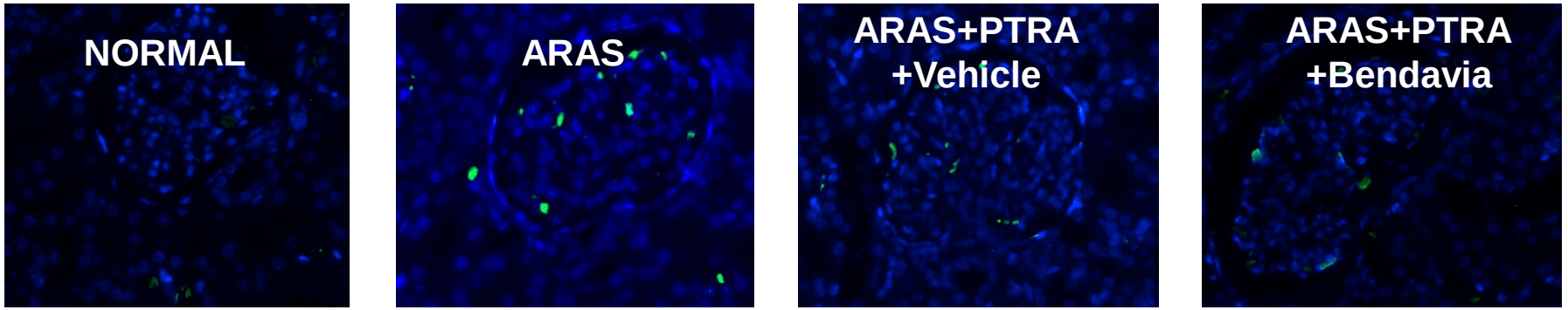
MAYO CLINIC

** p<0.05 vs. Normal, ‡p<0.05 vs. ARAS+PTRA+Bendavia*

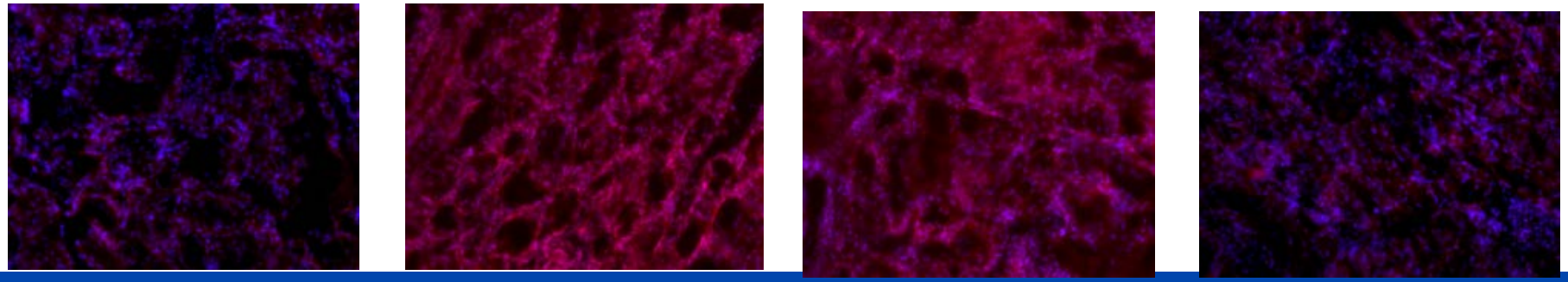
Bendavia Improves Renal Mitochondrial Biogenesis, and Decreases Apoptosis & Oxidative Stress



TUNEL

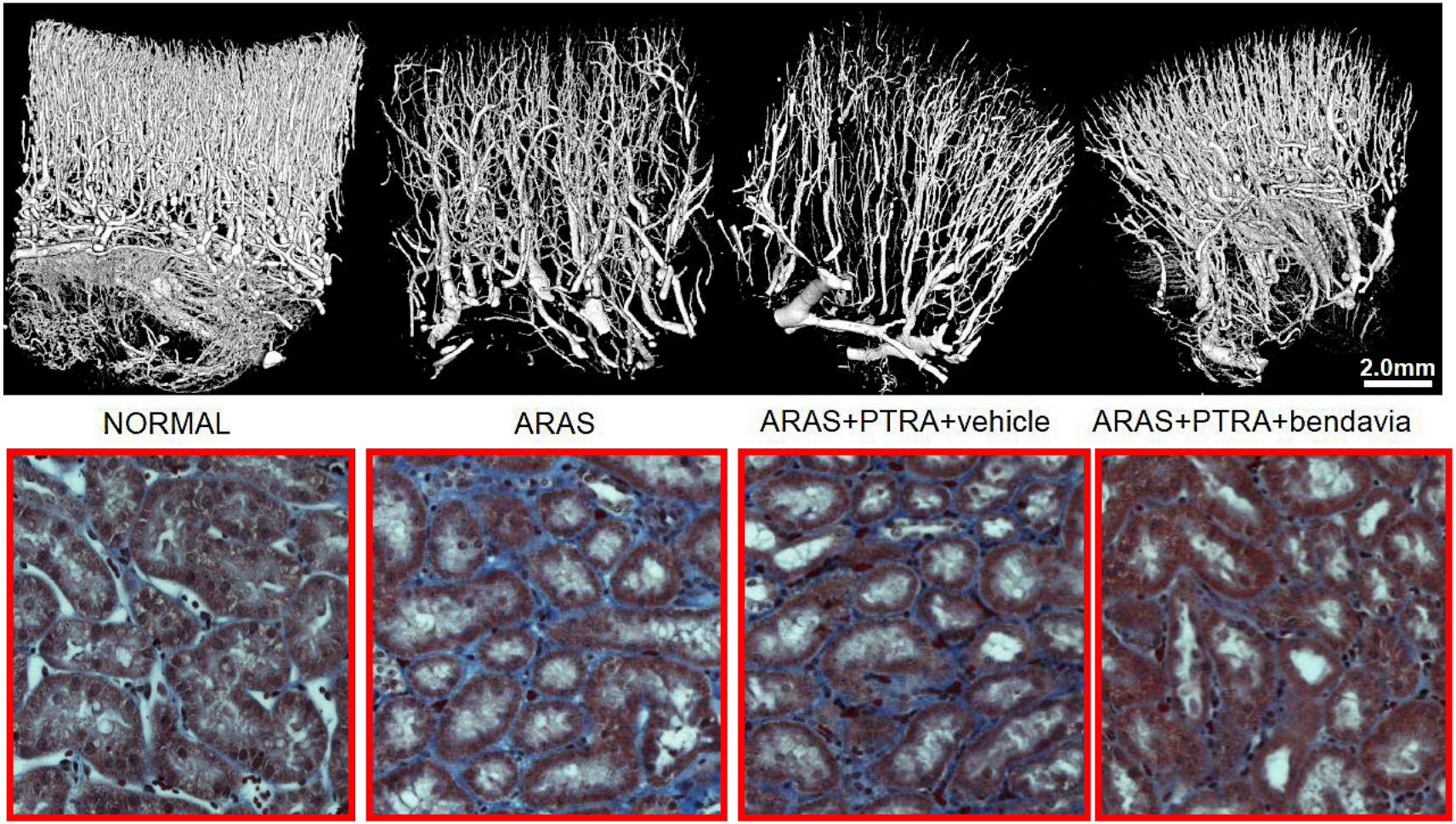


DHE



** p<0.05 vs. Normal, ‡p<0.05 vs. ARAS+PTRA+Bendavia*

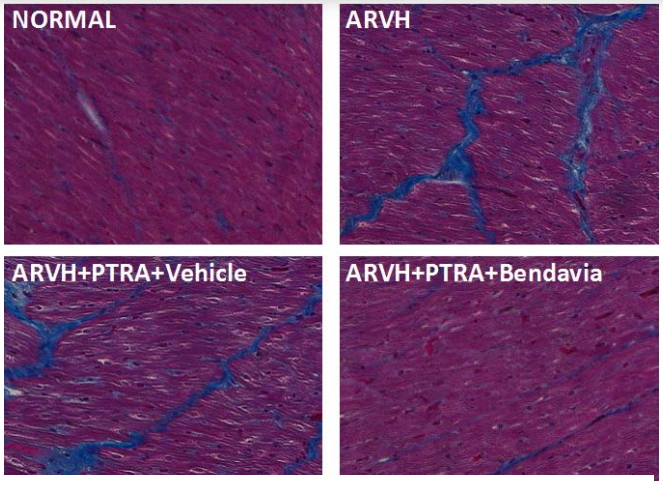
Bendavia Increases Microvascular Density and Decreases Fibrosis in the Post-Stenotic Kidney

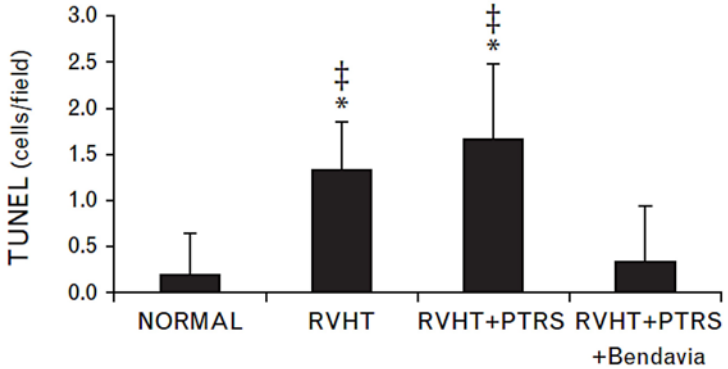


Tubulointerstitial fibrosis

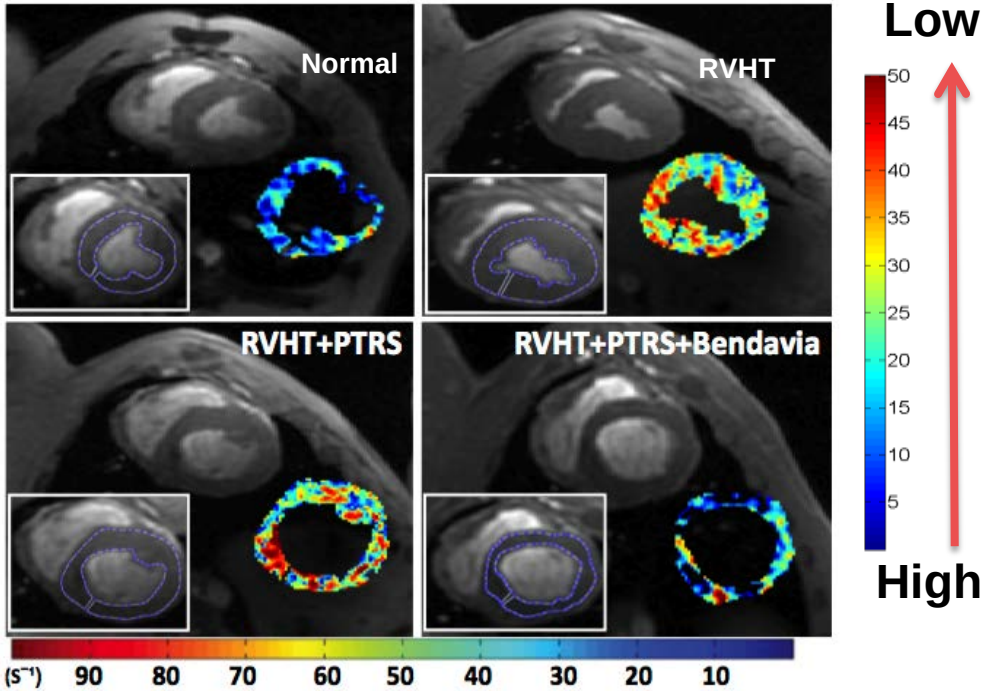
Mitochondrial targeted peptides attenuate residual myocardial damage after reversal of experimental renovascular hypertension

Alfonso Eirin[a], Barbara J. Williams[a], Behzad Ebrahimi[a], Xin Zhang[a], John A. Crane[a], Amir Lerman[b], Stephen C. Textor[a], and Lilach O. Lerman[a,b]





Oxygenation



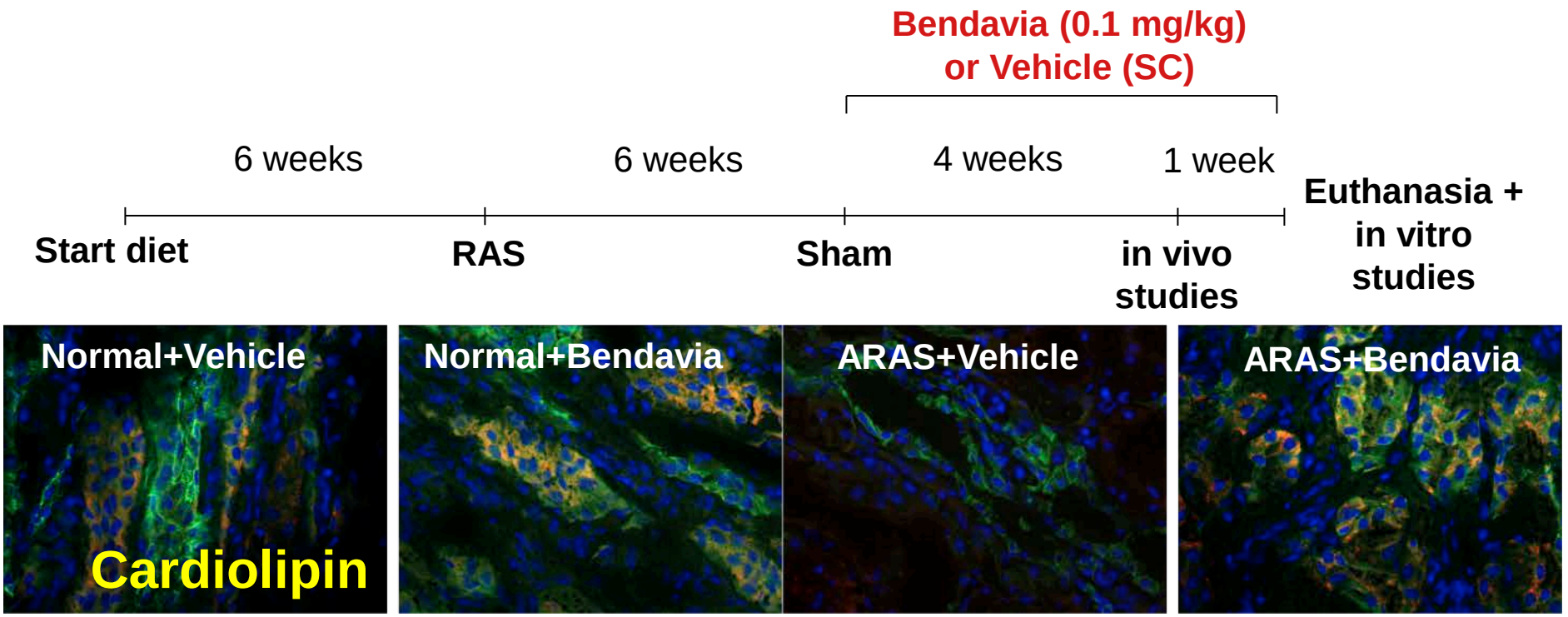
Eirin A et al, J Hypertens 32: 154-65, 2014

EUROPEAN SOCIETY OF CARDIOLOGY®

Cardiovascular Research

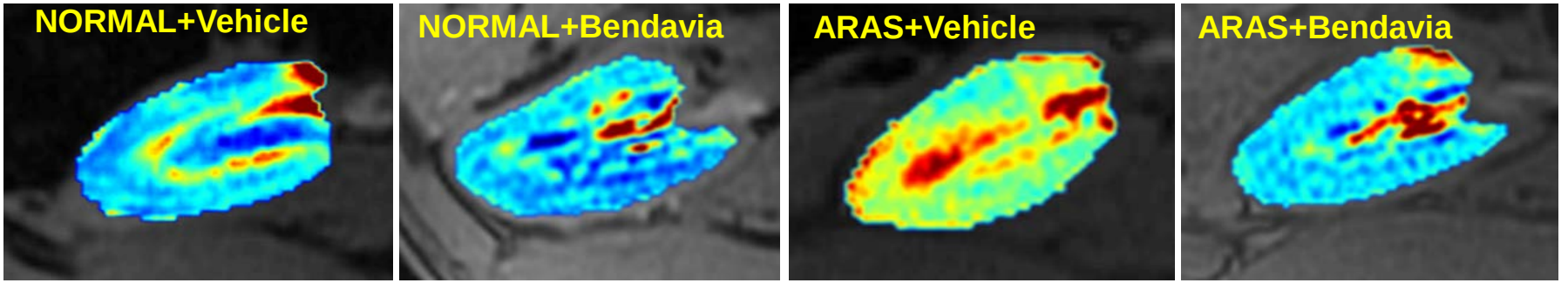
Mitochondrial protection restores renal function in swine atherosclerotic renovascular disease

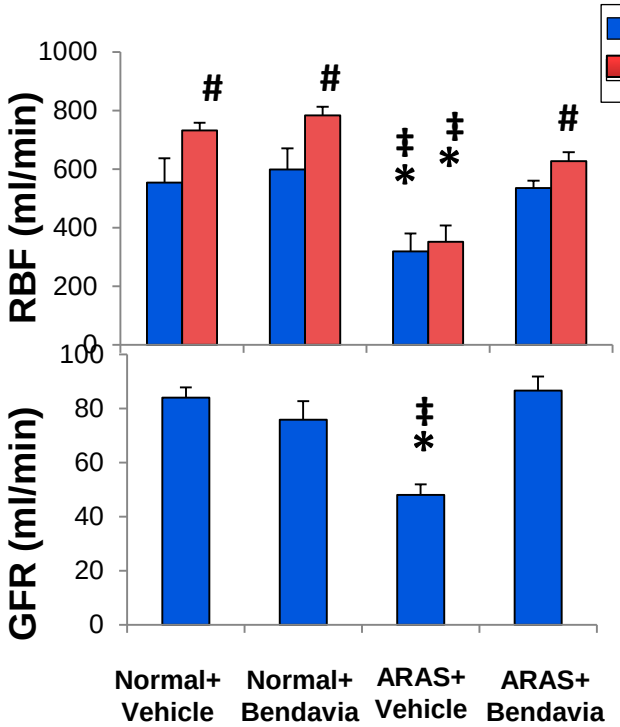
Alfonso Eirin[1], Behzad Ebrahimi[1], Xin Zhang[1], Xiang-Yang Zhu[1], John R. Woollard[1], Quan He[2], Stephen C. Textor[1], Amir Lerman[3], and Lilach O. Lerman[1,3*]

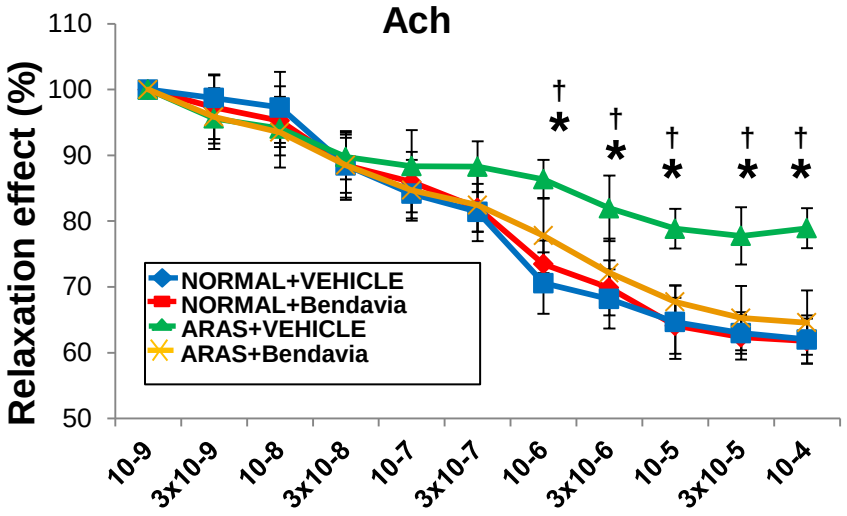


Renal Function After 4 Weeks of SC Bendavia

BOLD-MRI

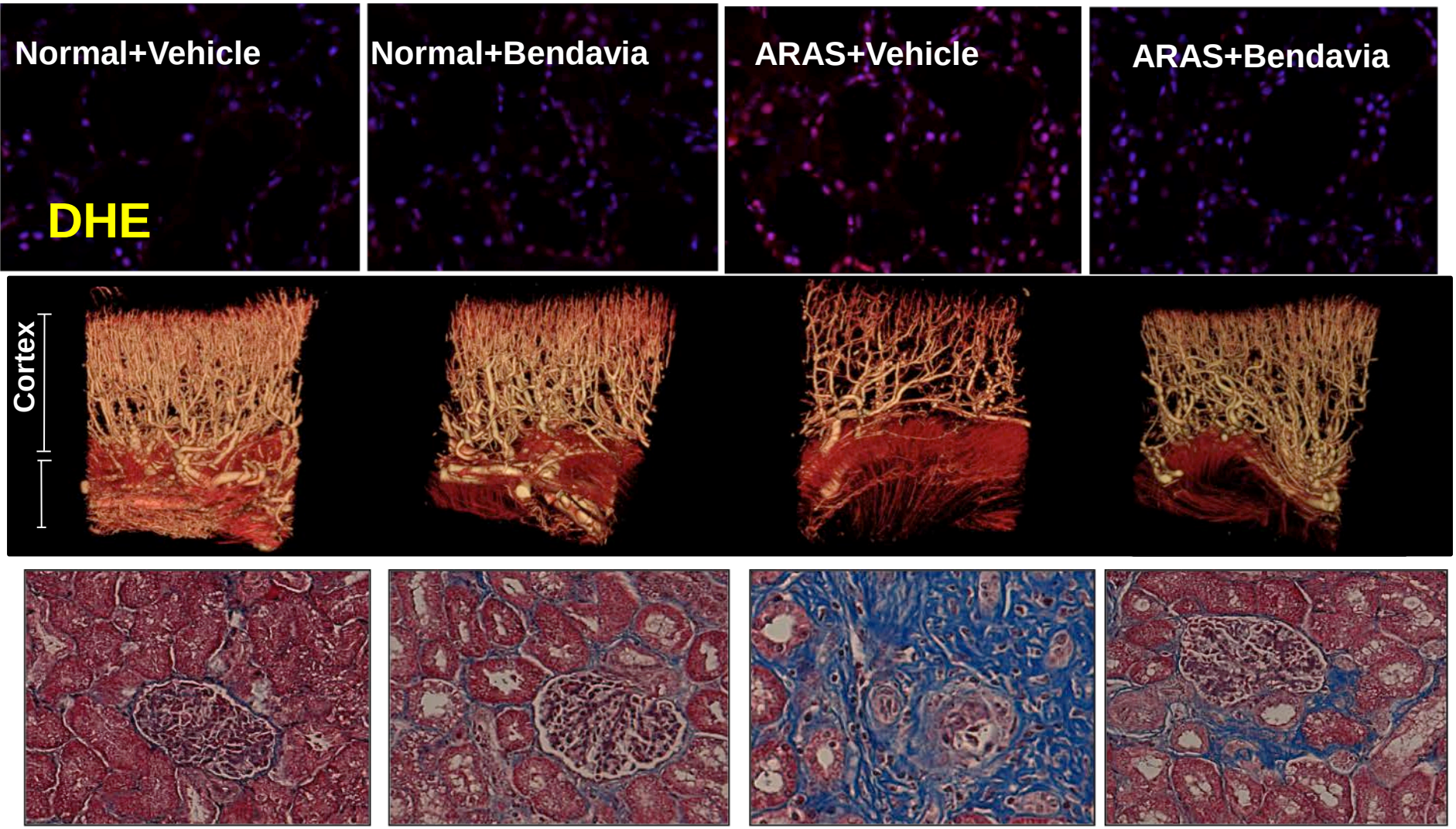




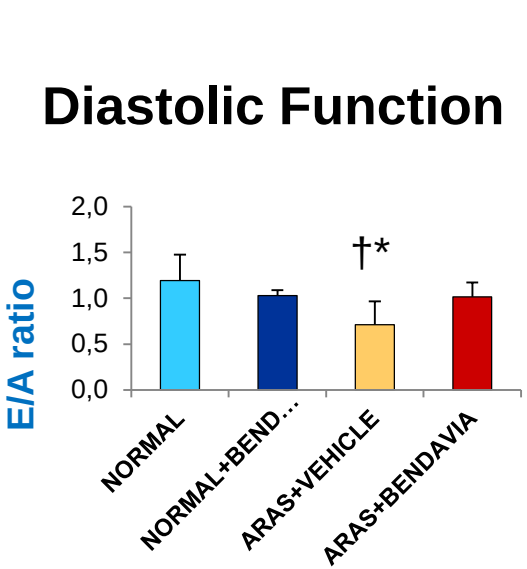


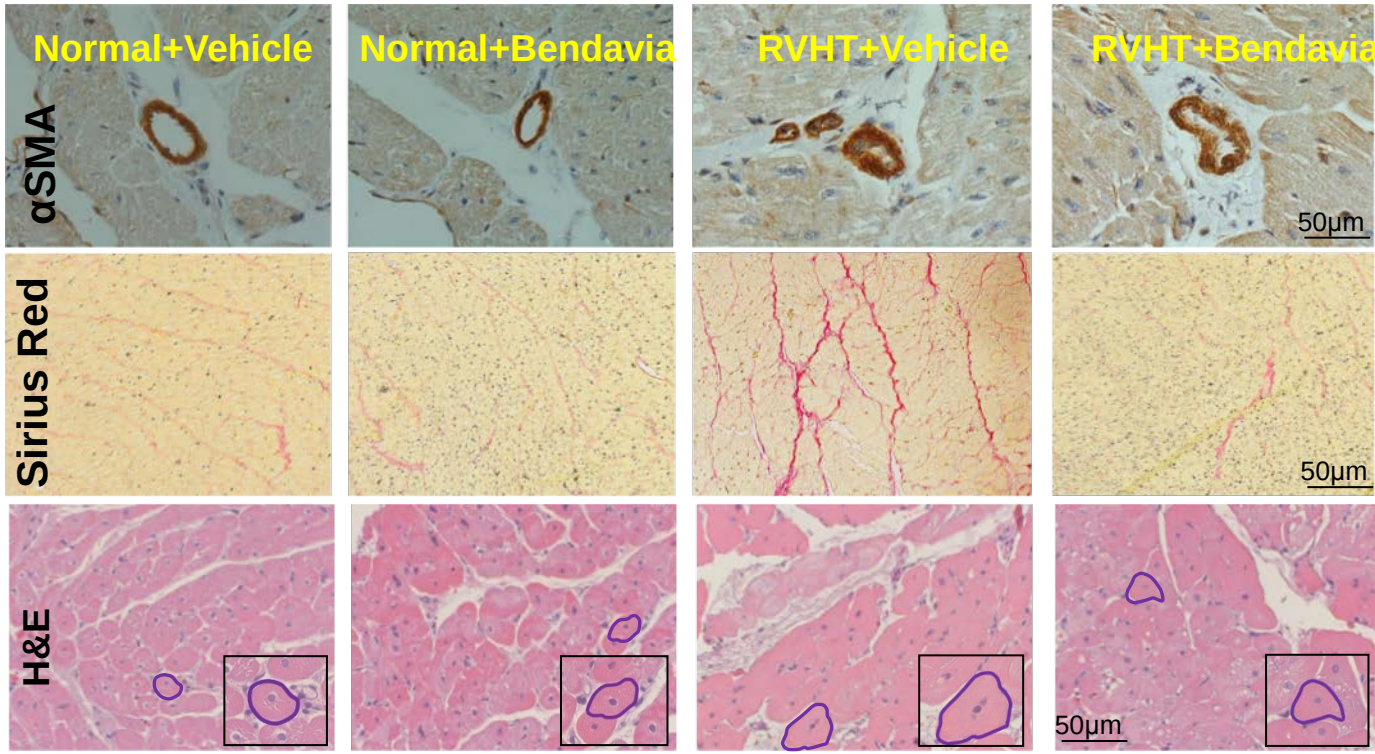
** p<0.05 vs. Normal+Vehicle, ‡ p<0.05 vs. ARAS+Bendavia, # p<0.05 vs. Baseline*

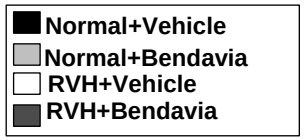
Bendavia Decreases Stenotic Kidney Injury

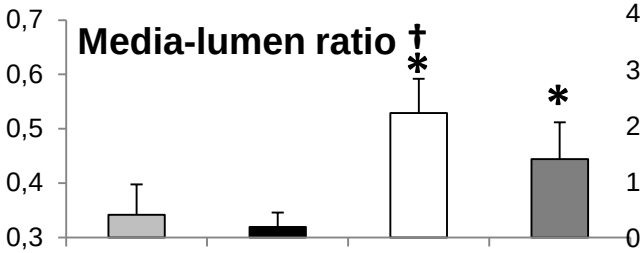


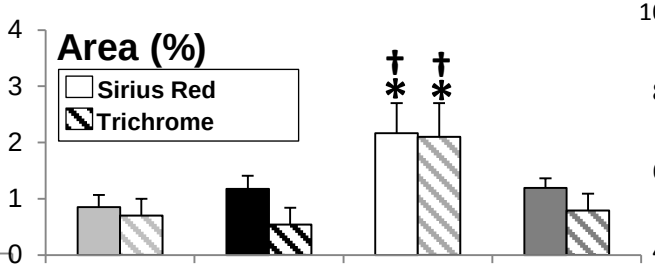
Attenuated myocardial remodeling in renovascular hypertension (RVHT)

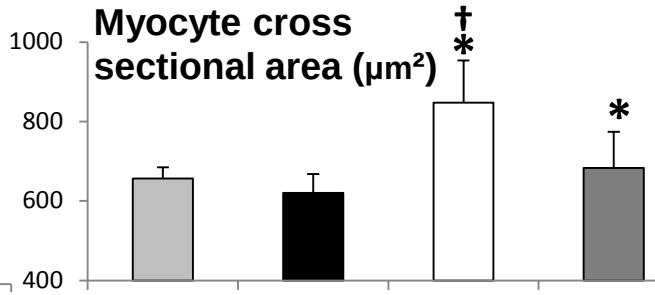












Clinical Trials

A Phase 2a, Randomized, Placebo-controlled, Single Center Trial to Evaluate the Impact of Intravenous Bendavia-131 on Ischemia Reperfusion Injury in Atherosclerotic Renal Artery Stenosis in Patients Undergoing Percutaneous Transluminal Angioplasty of the Renal Artery (PTRA)

ClinicalTrials.gov Identifier: NCT01755858, IRB: 12-002947

EMBRACE-STEMI Study:

Evaluation of the ***M***yocardial effects of ***B***endavia for reducing ***R***eperfusion injury in patients with ***A***cute ***C***oronary ***E***vents — ***ST***-wave ***E***levation ***M***yocardial ***I***nfarction.

A phase 2a, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability and efficacy of intravenous Bendavia on reperfusion injury in patients treated with standard therapy including primary percutaneous coronary intervention and stenting for ST-segment elevation myocardial infarction

Conclusions

- **The mitochondria are fundamental therapeutic targets in ischemia**
- **Mitochondrial-targeted peptides possess a unique potential to decrease ischemic damage in the kidney and heart**
  - ***Acute***
  - ***Chronic***

Questions?