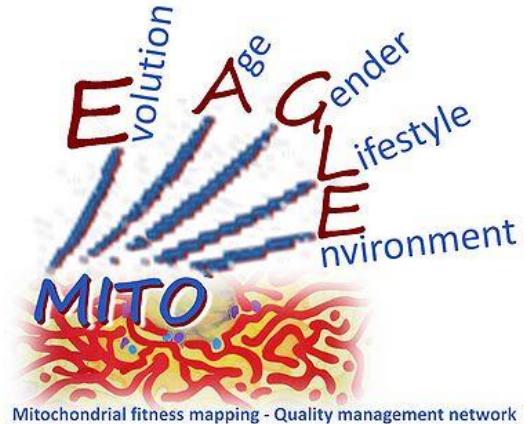


MitoEAGLE Conference and MC/WG Meeting – jointly
organized by MiPsociety and MitoEAGLE
September 18-21 Jurmala, Latvia



Mitochondria-Targeted Antioxidants in Aging related functional changes in the heart and aorta: MitoTEMPO improves aged-cardiovascular performance

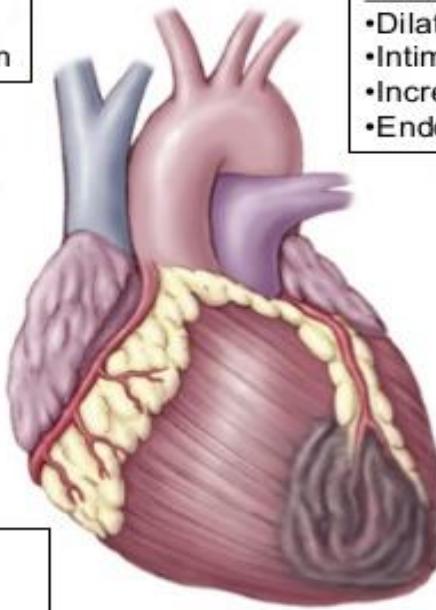
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Aging related Cardiac Alterations

Aging is accumulation of numerous modifications at different levels of the cardiovascular system, resulting in adverse remodelling of the heart and blood vessels

Age-associated cardiac changes



The diagram illustrates the gross anatomy of the human heart, showing the left ventricle, the right atrium, the left atrium, and the major blood vessels including the superior and inferior vena cava, the aorta, and the pulmonary veins.

Impaired contractility

- Decreased reserve
- Norepinephrine dysregulation

Abnormal rhythmicity

- Increase in arrhythmia
- Atrial fibrillation

LV hypertrophy

- Increased wall thickness
- Cardiomyocyte hypertrophy
- Heart failure

Vascular changes

- Dilation of large arteries
- Intimal media thickening
- Increased stiffness
- Endothelial dysfunction

Vascular-ventricular mismatching

- Decreased LV elastance
- Diminished cardiac reserve

Diastolic dysfunction

- Decreased early diastolic filling
- Increased late diastolic filling
- Impaired ability of LV to relax

Aging and Oxidative Stress

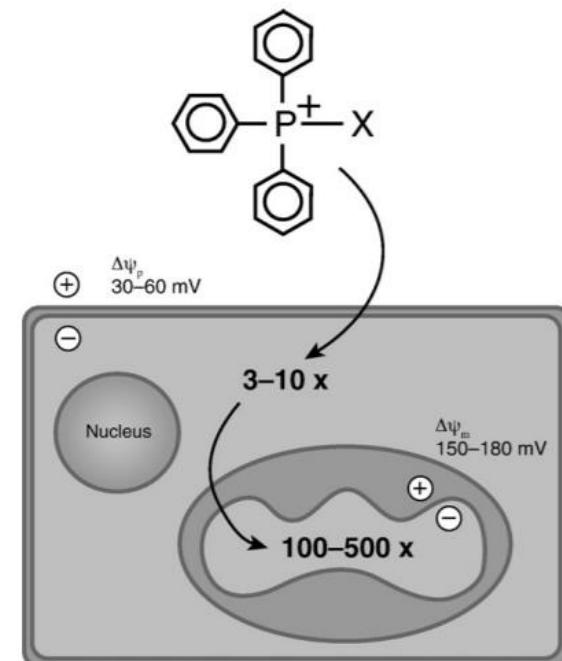
- In 1972 Denham Darman suggested that free radicals cause damage of mitochondria a key determinant of aging processes.
- Unbalanced ROS leading to cellular dysfunction
- Mitochondria the main source of ROS production

Therefore maintain mitochondrial function is good strategy to protect heart during aging.

Mitochondrial Targeted Antioxidants

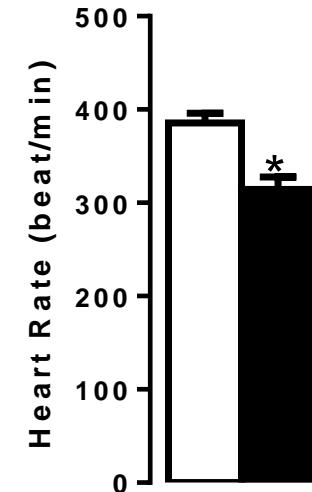
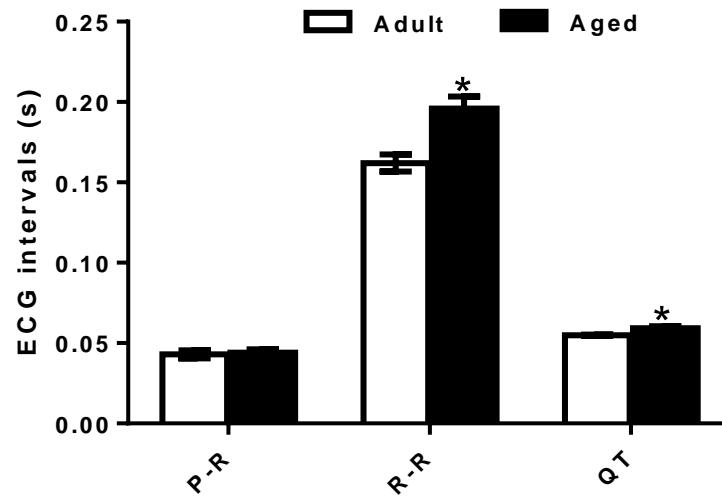
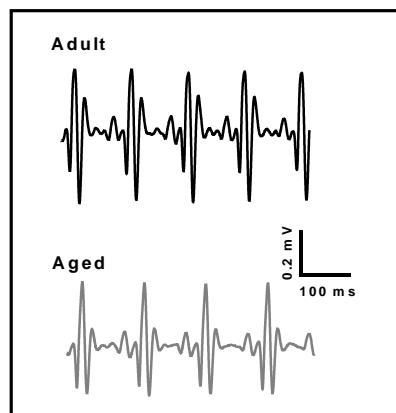
- Decreasing mitochondrial ROS prevents myocardial dysfunction
- Low molecular weight antioxidants (α -Tocopherol, N-acetylcysteine) decreased mitochondrial damage *in vitro*, but their effects *in vivo* is limited
- Antioxidants can be targeted to mitochondria by several methods
 - Hydrophobicity and positive charge
 - Binding with high affinity to intramitochondrial structure
 - Metabolic conversions by specific mitochondrial enzymes

MitoTEMPO conjugated with lipophylic cation TPMP and accumulates 100-500 fold in mitochondria

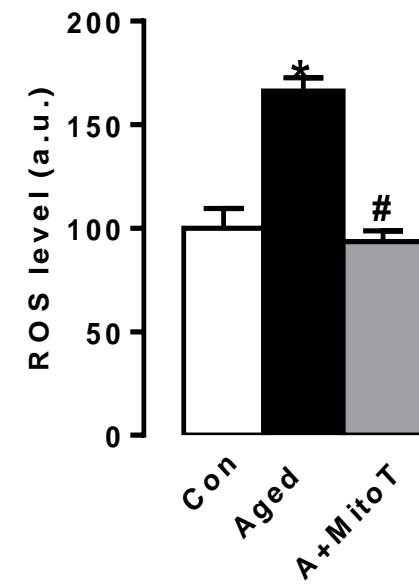
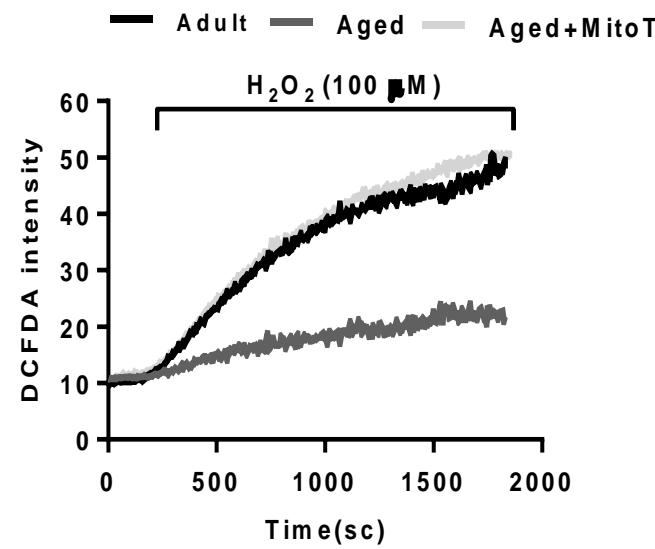
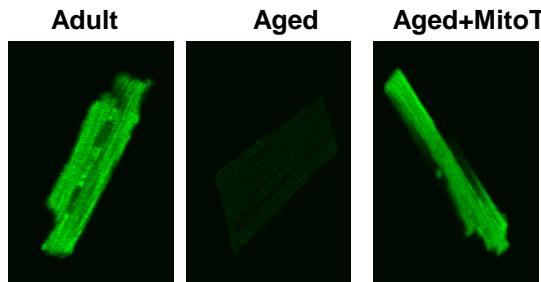


General findings of experimental animals (6- vs. 24- month)

Groups	Body Weight (g)	Heart Weight/Body Weight	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	TAS (mM Trolox)	TOS ($\mu\text{M H}_2\text{O}_2$)
Adult-rats						
(n=30)	330 \pm 11	0.43 \pm 0.02	119 \pm 2	75 \pm 0.6	1.05 \pm 0.11	0.25 \pm 0.06
Aged-rats (n=35)	380 \pm 8.3*	0.52 \pm 0.02*	143 \pm 4*	83 \pm 1.1*	0.37 \pm 0.09*	0.77 \pm 0.22*

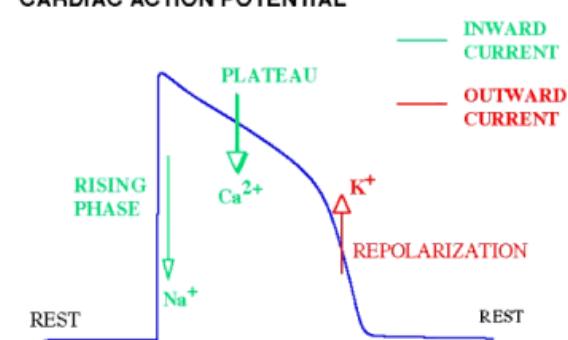
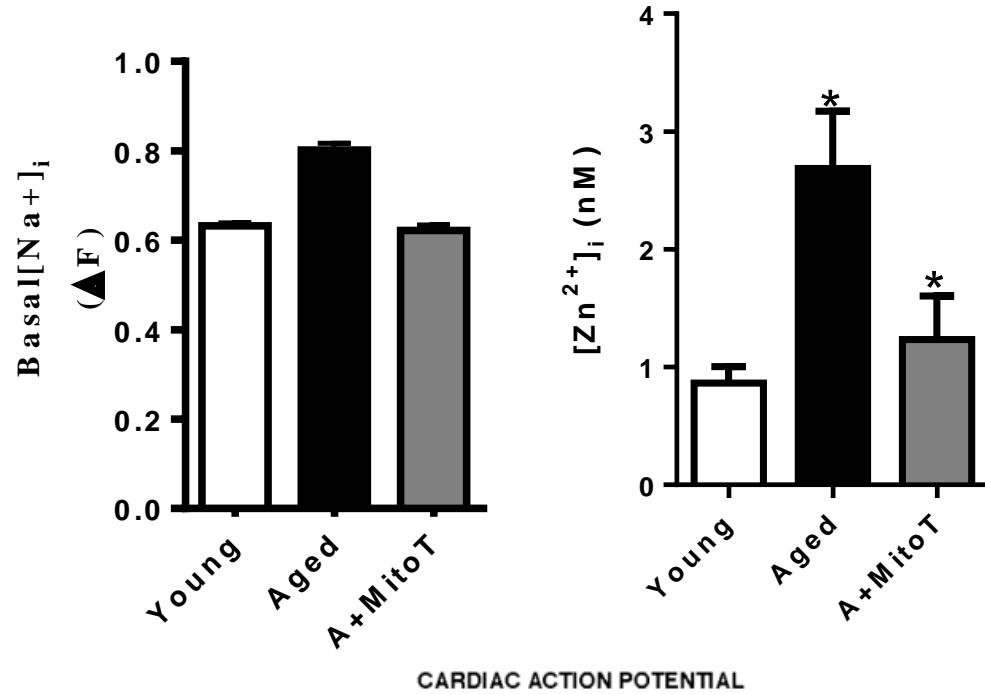
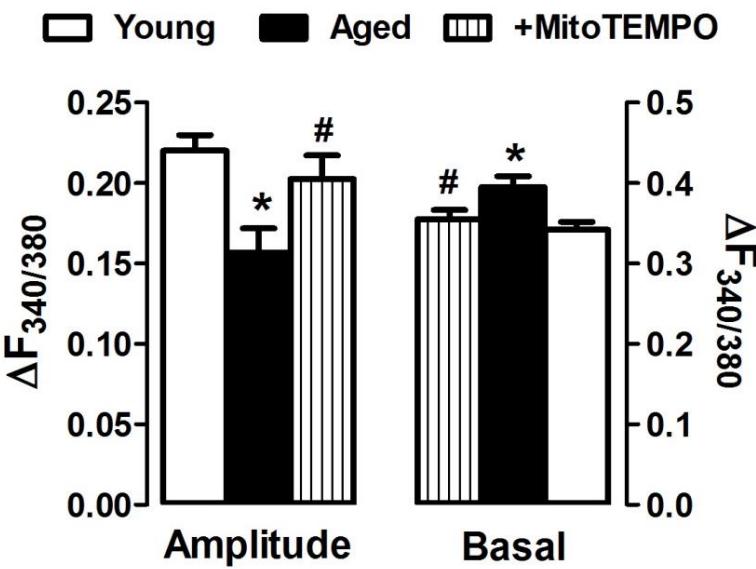


Mitotempo treatment reduces ROS level in senescent cardiomyocytes

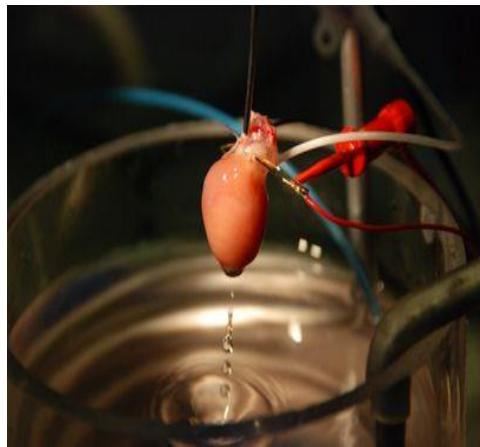


mitoTempo: 1 μM - 1-Hour

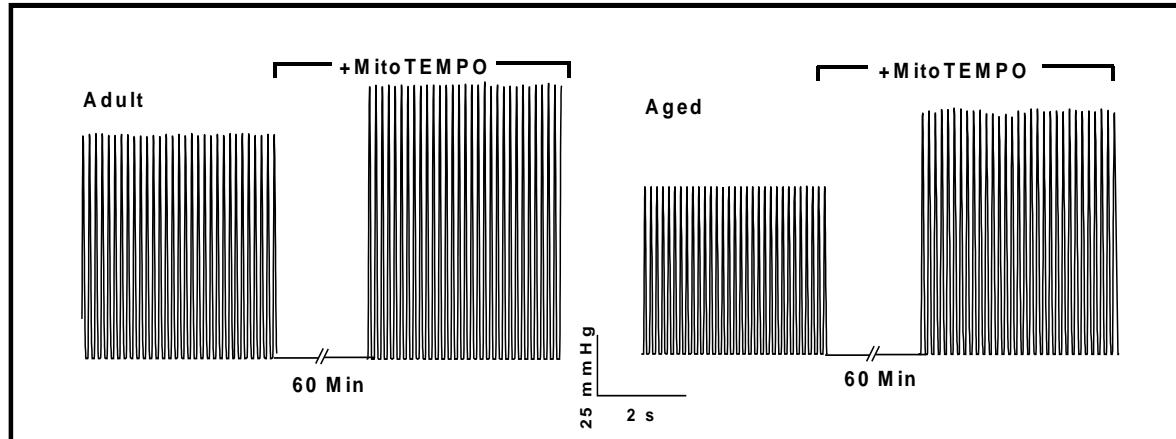
Mitotempo restores cytosolic Na^+ , Ca^{2+} and Zn^{2+} levels in senescent cardiomyocytes



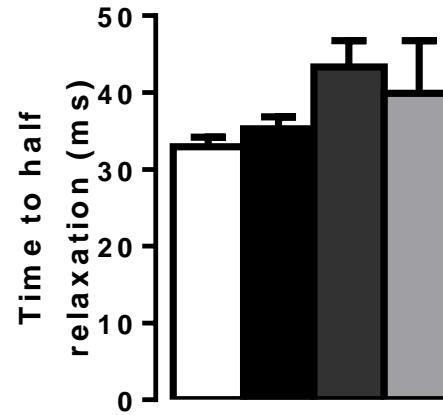
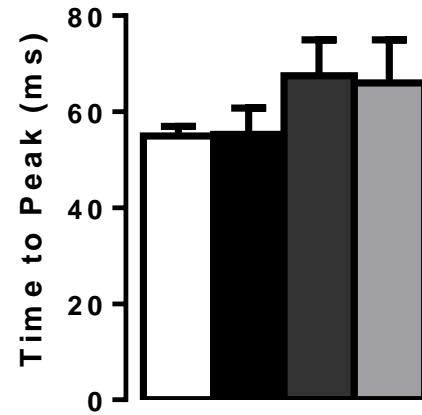
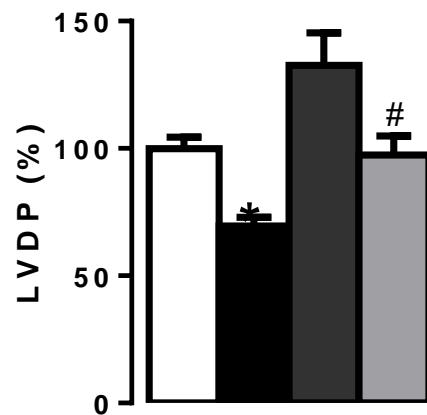
Mitotempo improves Left Ventricular function in senescent cardiomyocytes



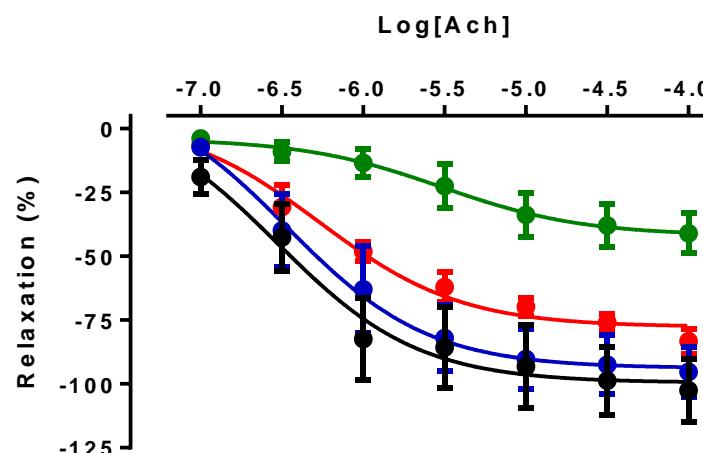
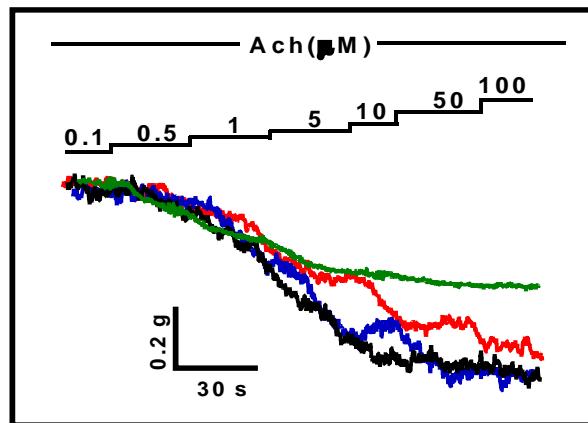
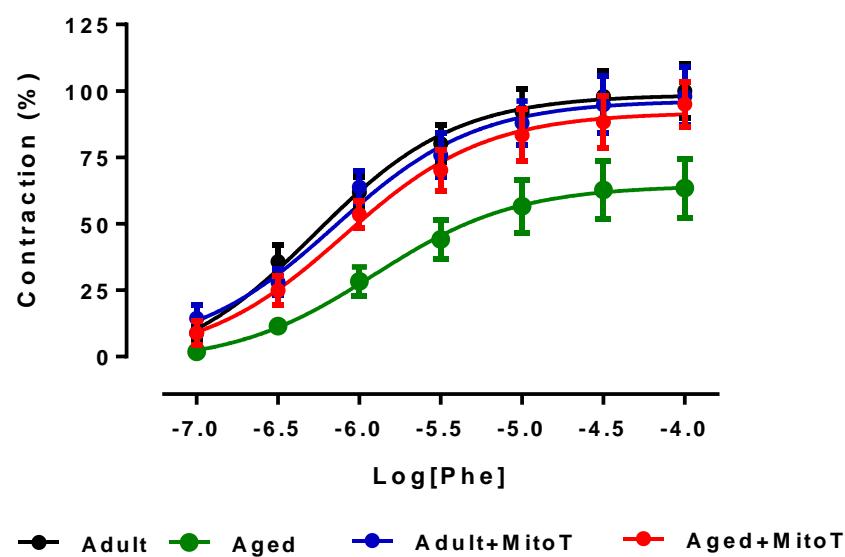
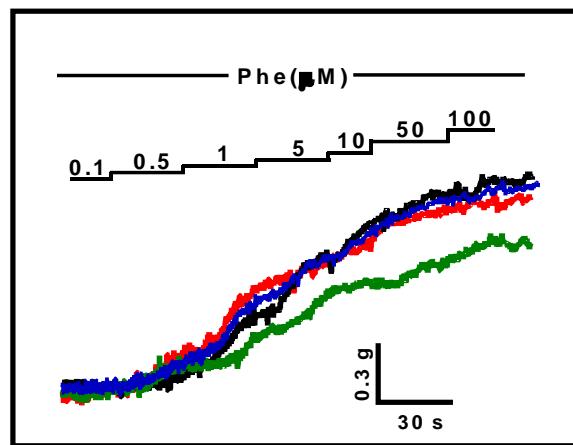
Langendorff perfusion



■ Adult ■ Aged ■ Adult+MitoT ■ Aged+mitoT



Mitotempo improves contraction-relaxation function of aortic rings in senescent cardiomyocytes



TURAN's Lab

KİTAPVAN EGE
ÖĞRENCİ LABORATUVARI

Prof. Dr. Turan Ege'nin Biyografisi

"BÜYÜK MÜZELERİN SİSTEMİ"
ANKARA İŞ YÖNETİMİ
DEĞİŞİMİ

