

Myocardial infarctions (MI, “heart attacks”)

- MIs resulting from atherosclerosis are among the most common cause of death in the developed world - 1.25 million people suffer heart attacks a year in the USA of which ~ 0.5 million are fatal.
- Infarction - tissue death due to oxygen starvation due to blockage of blood supply due to plaques in the blood vessels

Ischemic Reperfusion Injury and Myocardial Infarctions

- Patients who suffer from AMI need immediate reperfusion to remove the occluding thrombosis and reperfuse the anoxic heart tissue.
- Restored oxygen and inflammatory immune cells in the newly restored blood flow lead to ROS buildup and cellular damage as well as apoptotic cell death at the site of reperfusion. Reperfusion injury is a prominent cause of death following coronary artery bypass procedures (in 25% of cases).

If ischemia means lack of oxygen, how can ischemic heart cells produce ROS?

- Ischemia renders the heart tissue ~90% anoxic. However remaining oxygen could still sufficiently cause leakage through the respiratory cytochromes leading to superoxide production.
- Experiments with mitochondrial inhibitors in ischemic cardiomyocytes indicate that the ROS produced during ischemia occurs during the semiquinone reduction stage (ie at electron transfer after Complex I and before Complex IV).
- How to measure in intact heart?

Electron Paramagnetic Resonance (EPR) Spectroscopy

- Analogous to MRI except uses signal from unpaired electrons instead of protons
- Due to their paramagnetic nature, certain ROS species can be detected by EPR - often using spin-traps to stabilize the radical species.
- EPR can detect electron spins at low concentration and the resonance frequency of the signal can provide structural information about the species being detected.

Reperfusion-Induced Cell Death: Cause or Effect?

- Necrotic or damaged cells and tissue are observed during reperfusion following ischemia - are they damaged during reperfusion or does the damage merely manifest itself during the reperfusion phase?
- Can reducing ROS influx reduce reperfusion damage?
Antioxidant clinical trials with Vit E and carotene in smokers with myocardial infarcts showed little promise despite promising results in whole organ model systems.
- Even if antioxidants work, how to deliver optimally, given restricted blood flow and non-homogenous areas of infarction?

SOD mimetics as candidates to reduce I/R-induced inflammation

Excessive production of superoxide (O_2^-) can lead to inflammation through various pathways, including generation of peroxynitrite ($ONOO^-$). A, adrenaline; LTB₄, leukotriene B₄; MnSOD, manganese superoxide dismutase; NA, noradrenaline; NO, nitric oxide.

SOD mimetics as candidates to reduce I/R-induced inflammation

Removal of superoxide affects the inflammatory cascade through at least three main pathways:

first, inhibition of peroxynitrite formation and sparing of nitric oxide;
second, inhibition of neutrophil infiltration at the site of inflammation;
third, inhibition of pro-inflammatory cytokine release.