

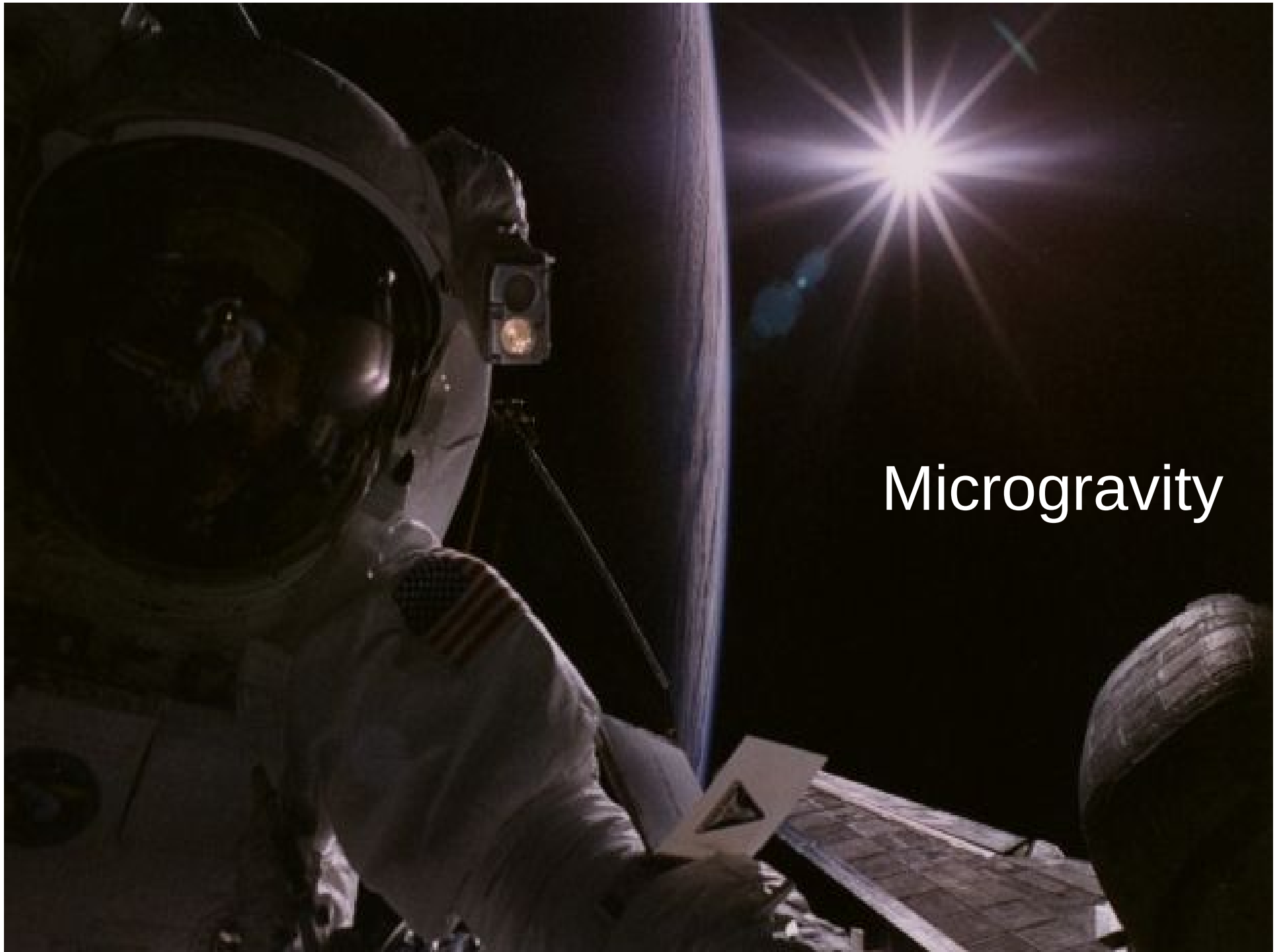
Cardiovascular Adaptations in the Spaceflight Environment

Christian M. Westby, Ph.D.
Universities Space Research Association
NASA Cardiovascular Laboratory
Houston, TX



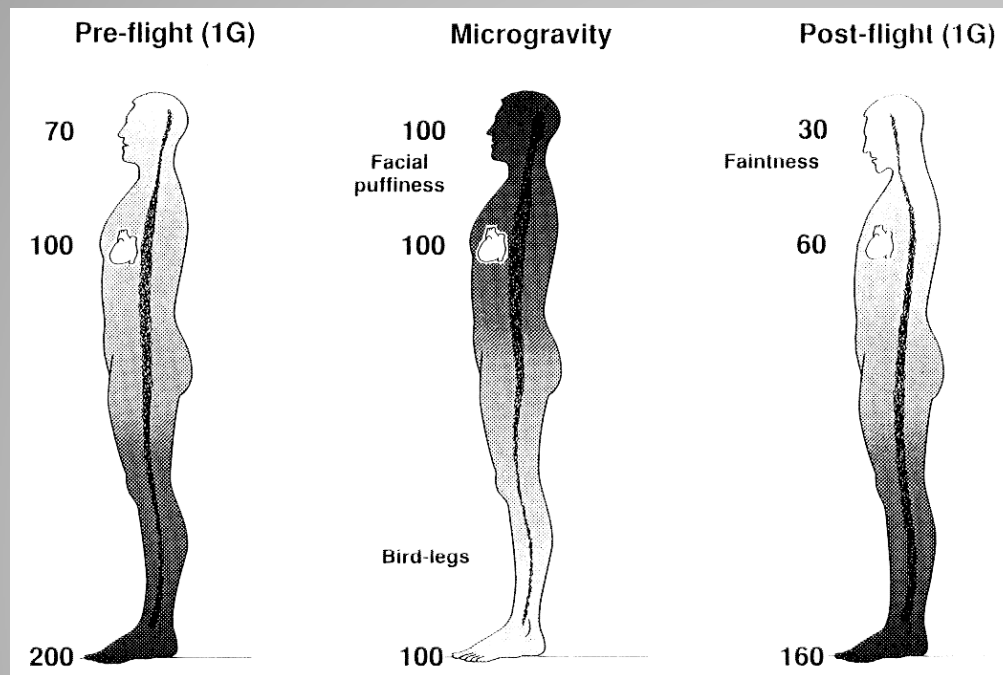
Overview

- **Microgravity**
 - Orthostatic hypotension
 - Sympathetic activation
 - Cardiac function
 - Vascular function
- **Space Radiation**



Microgravity

Volume Distribution in Humans



- 70 % of blood volume is below heart
- 19x more blood in capacitance vessels than resistance vessels

Example of cephalad fluid shift



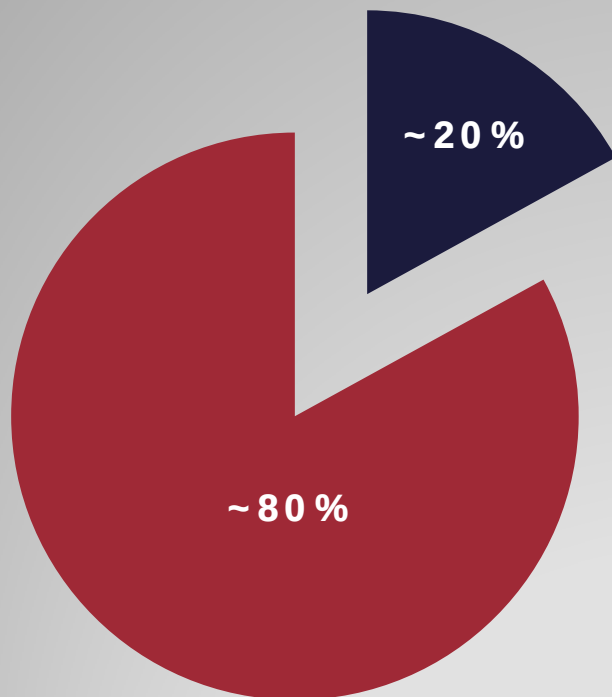
Pre-flight



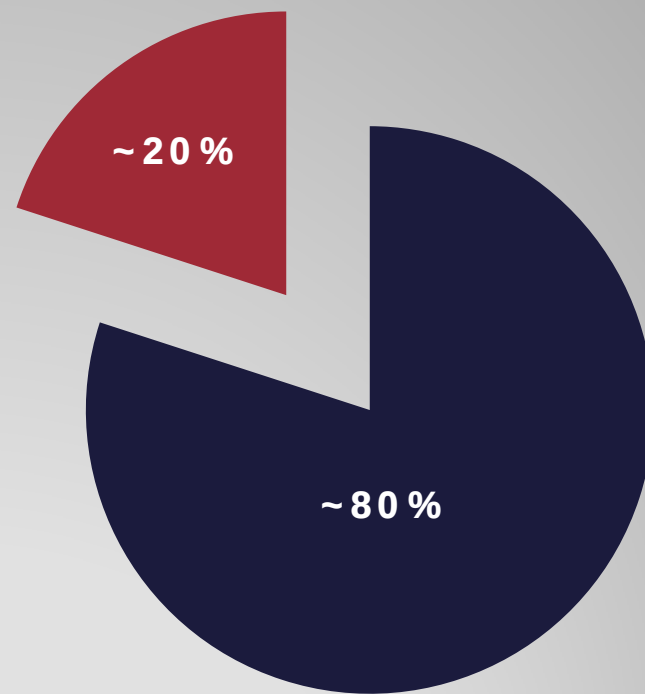
Day-2 in flight

Orthostatic Tolerance

Females

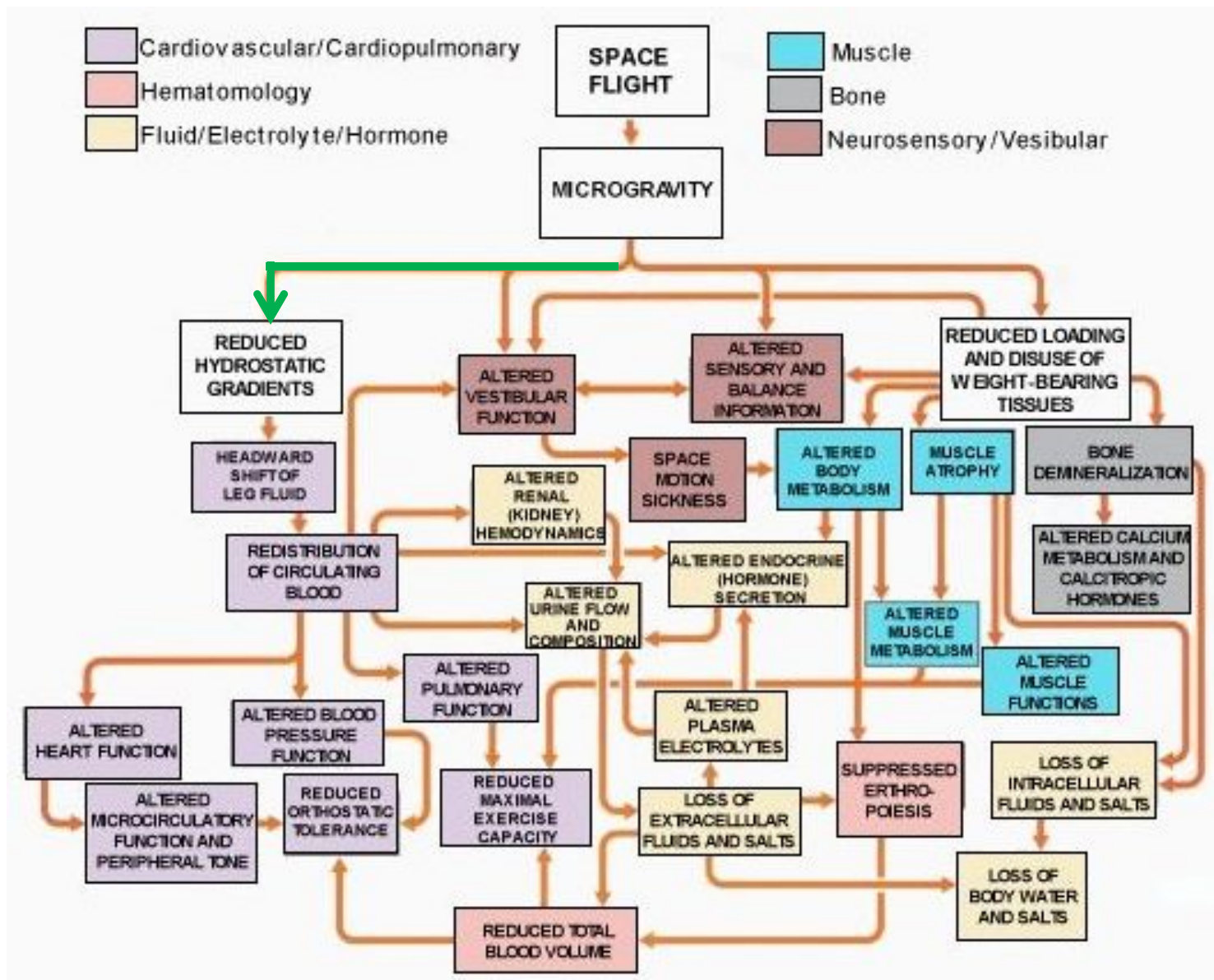


Males



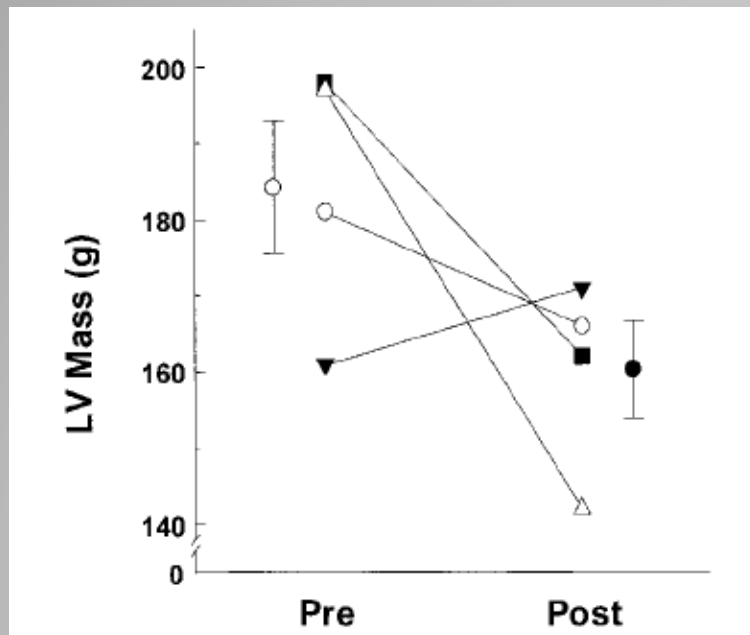
 Presyncopal

 Non-presyncopal



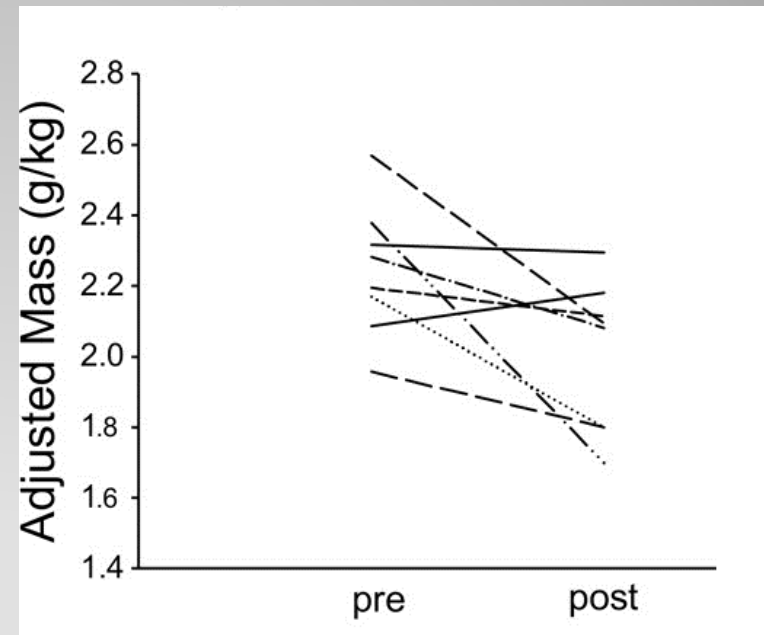
Cardiac Atrophy

Men



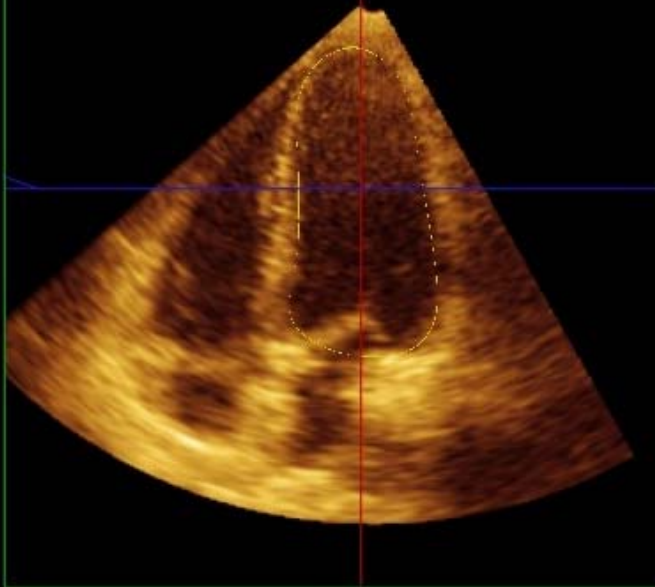
Perhonen MA et al. J Appl Physiol 91: 645-653, 2001

Women

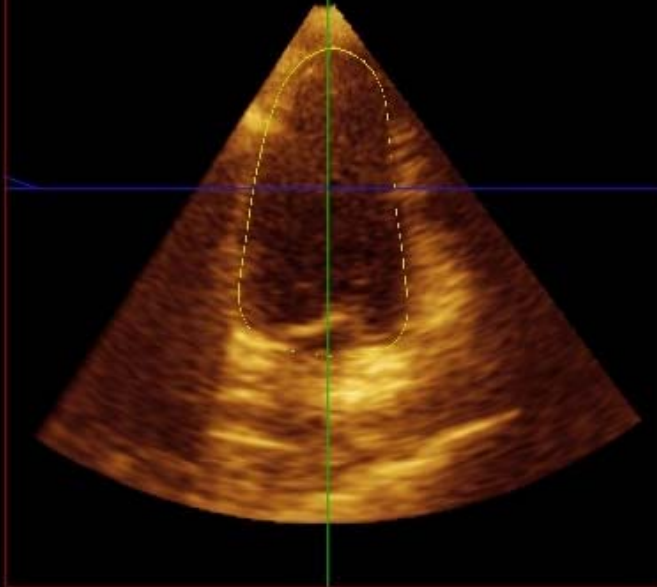


Dorfman T A et al. J Appl Physiol 2007;103:8-16

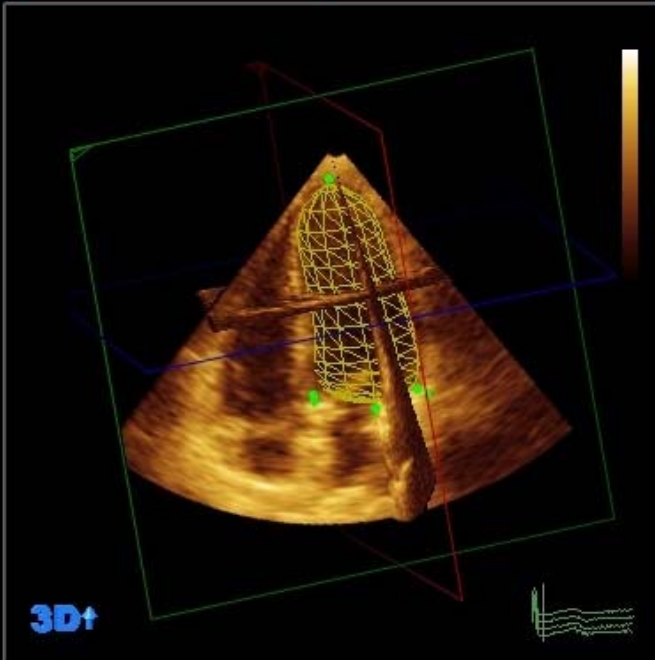
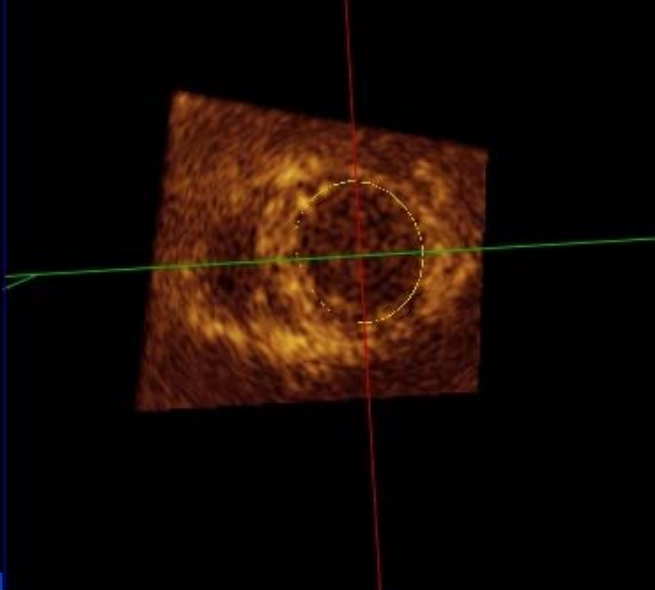
Apical 4 chamber



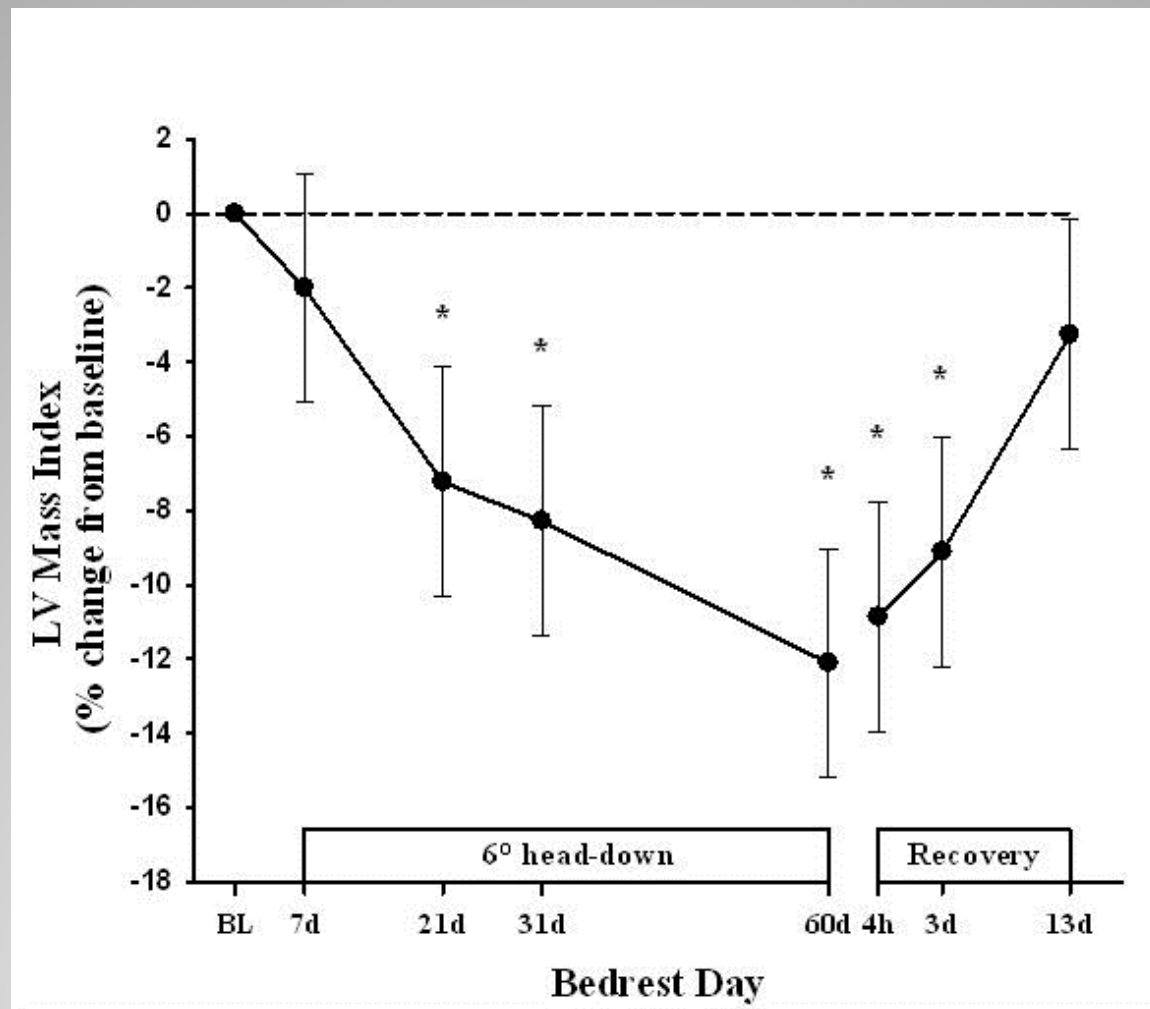
Apical 2 chamber



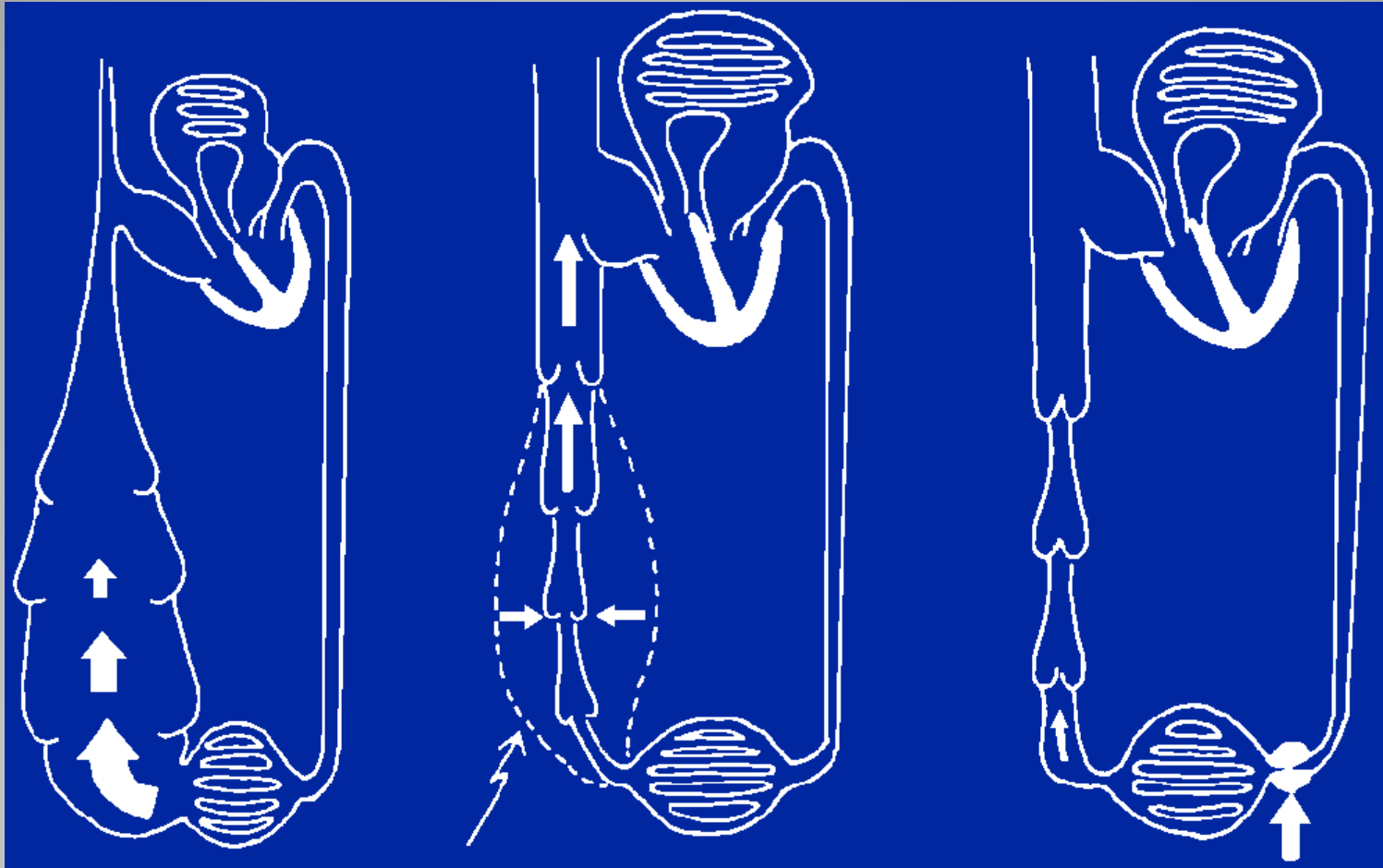
Parasternal short axis



Cardiac Atrophy Time Course



Mobilization of blood

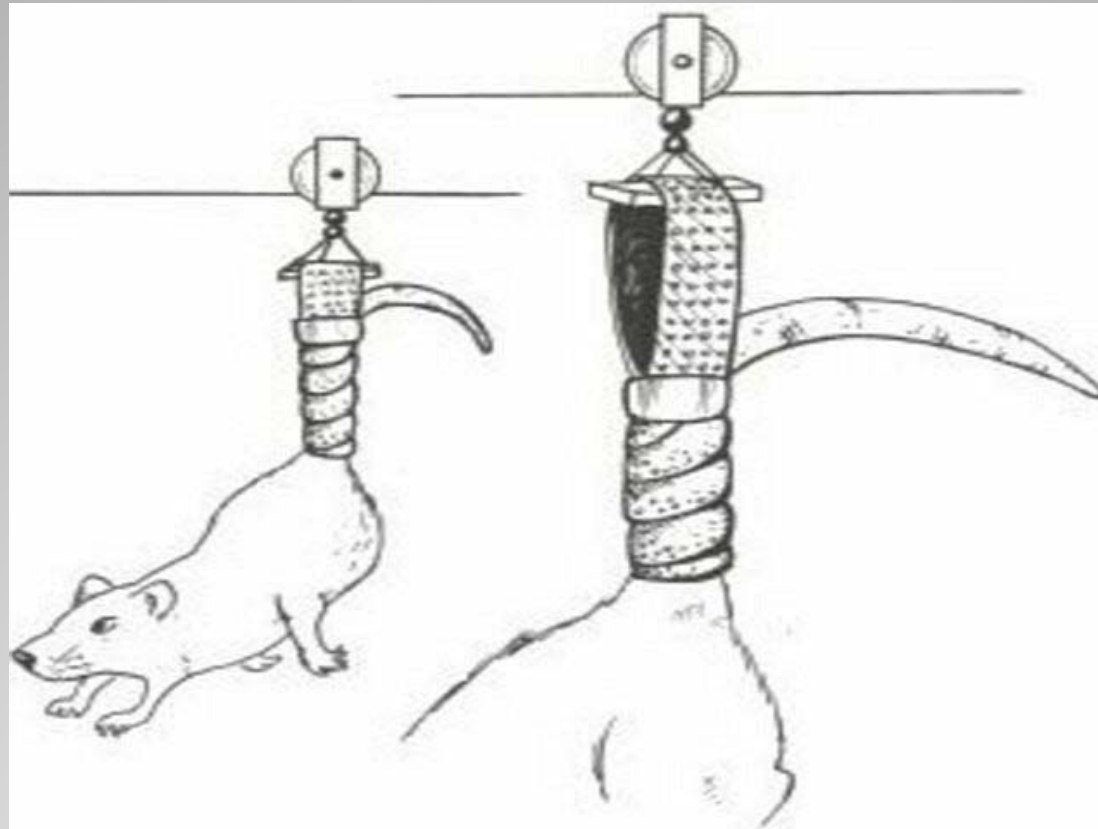


Orthostasis

Venous constriction
expels volume

Arterial Constriction
reduces inflow rate

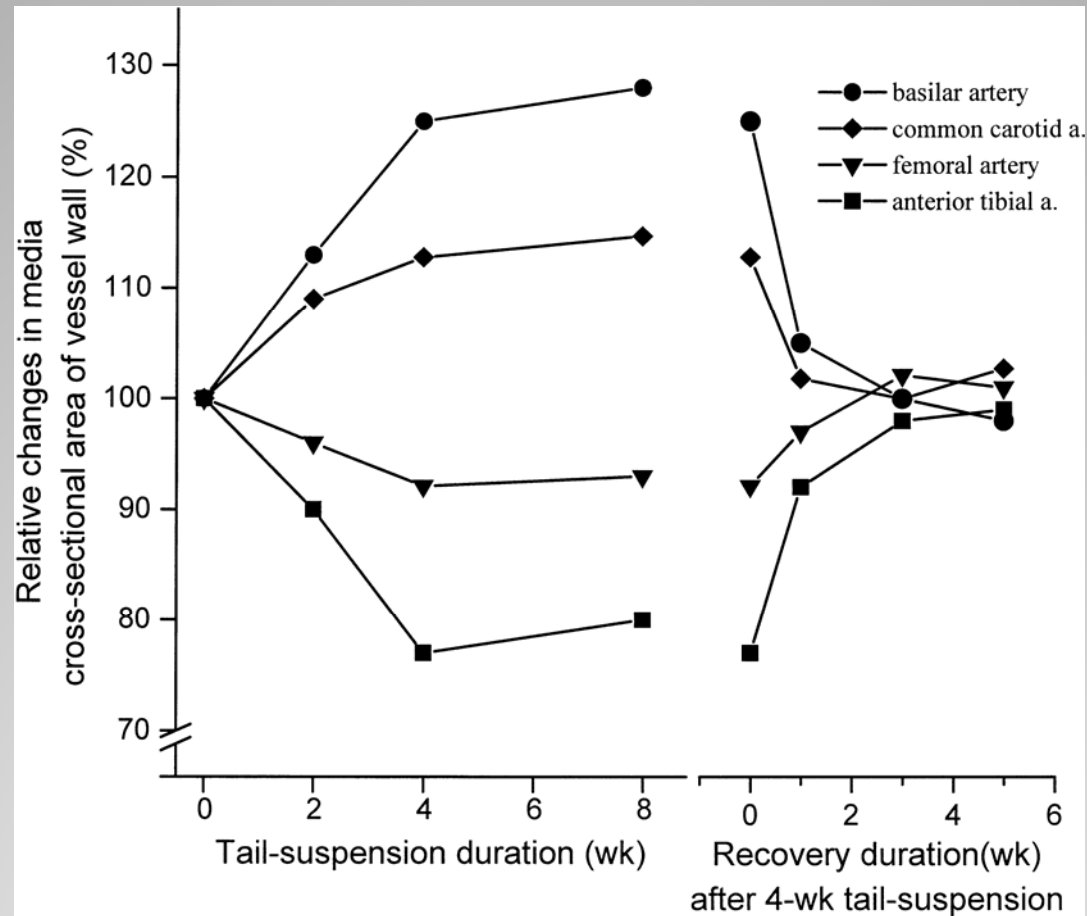
Rat suspended hind limb model



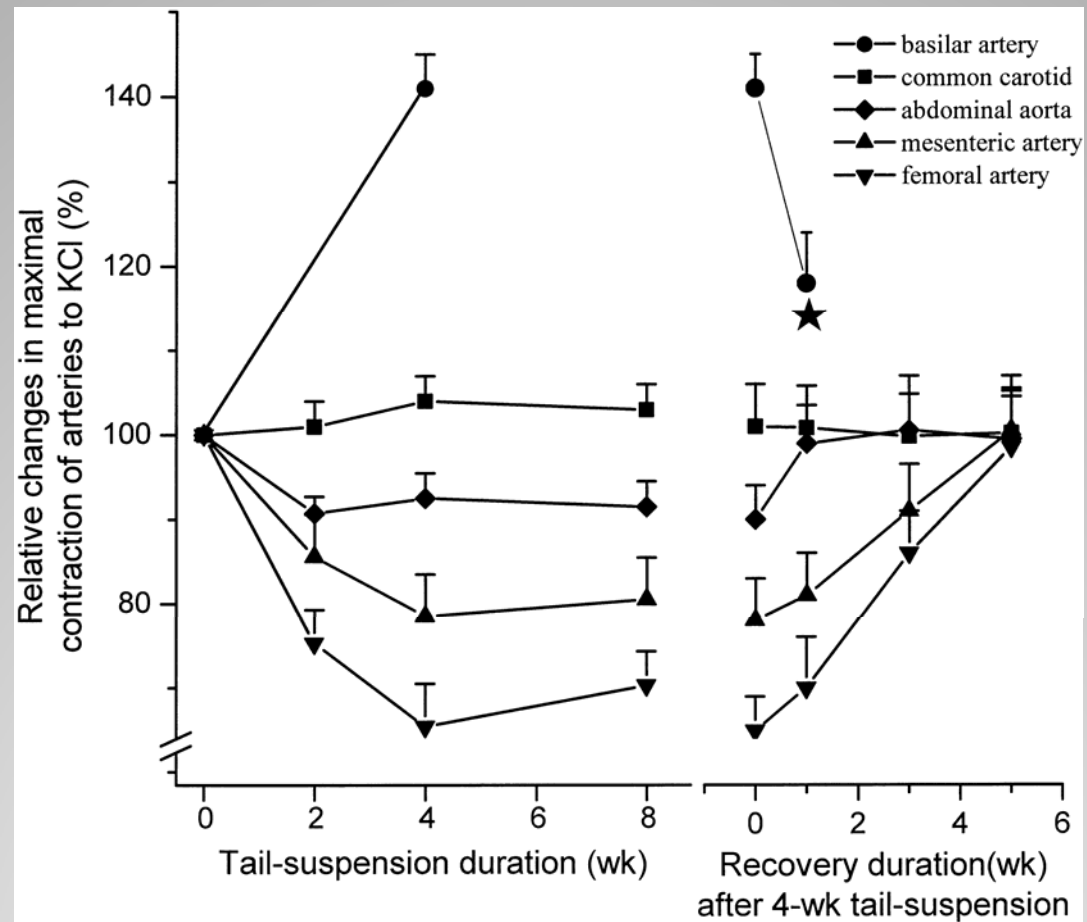
USRA

Zhang LF et. al. J Gravit Physiol. 1996;3(2):5-8

Arterial Remodeling



Arterial Function



Specific Aims

To compare venous responses before and after bed rest:

1. Between the hand and foot
2. Between men and women

Subject Characteristics

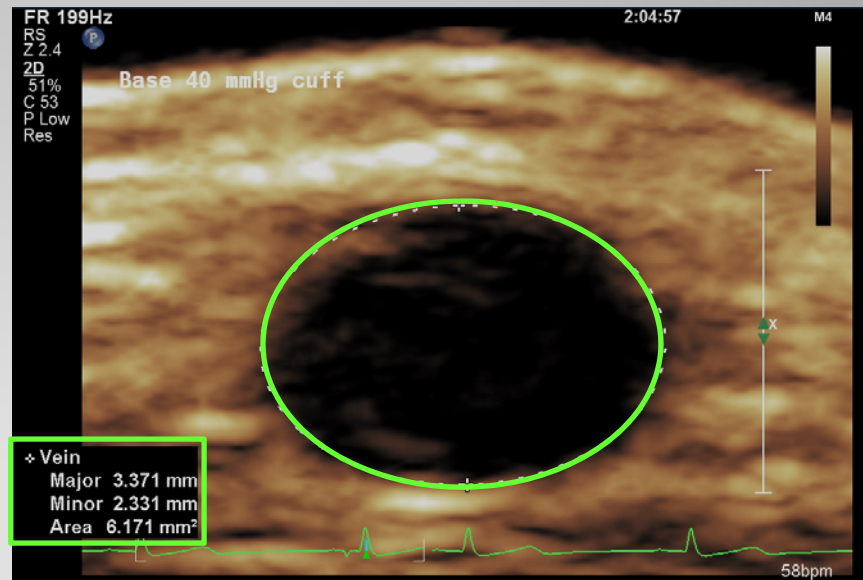
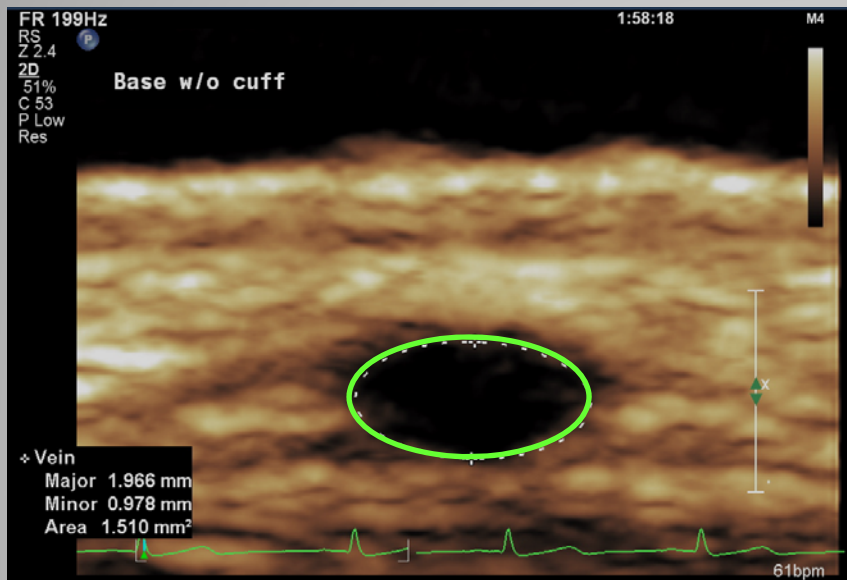
Variable (pre bedrest)	Male (n=16)	Female (n=10)
Age, yr	34 ± 2	37 ± 2
Body mass, kg	79.8 ± 2.4	61.3 ± 3.1 *
BMI, kg / m ²	26.6 ± 0.5	23.8 ± 0.9 *
Systolic BP, mmHg	122 ± 2	104 ± 2 *
Diastolic BP, mmHg	80 ± 2	67 ± 2 *
VO ₂ max, ml / kg / min	29.5 ± 1.9	24.7 ± 1.6

Mean ± SEM; *p < 0.05



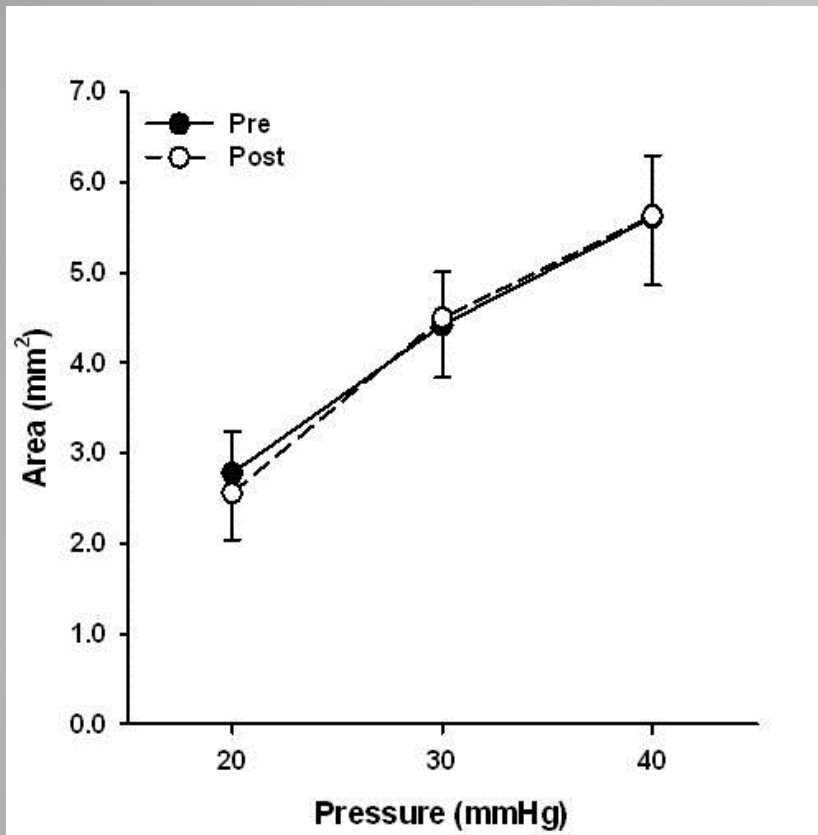


Vascular Ultrasound

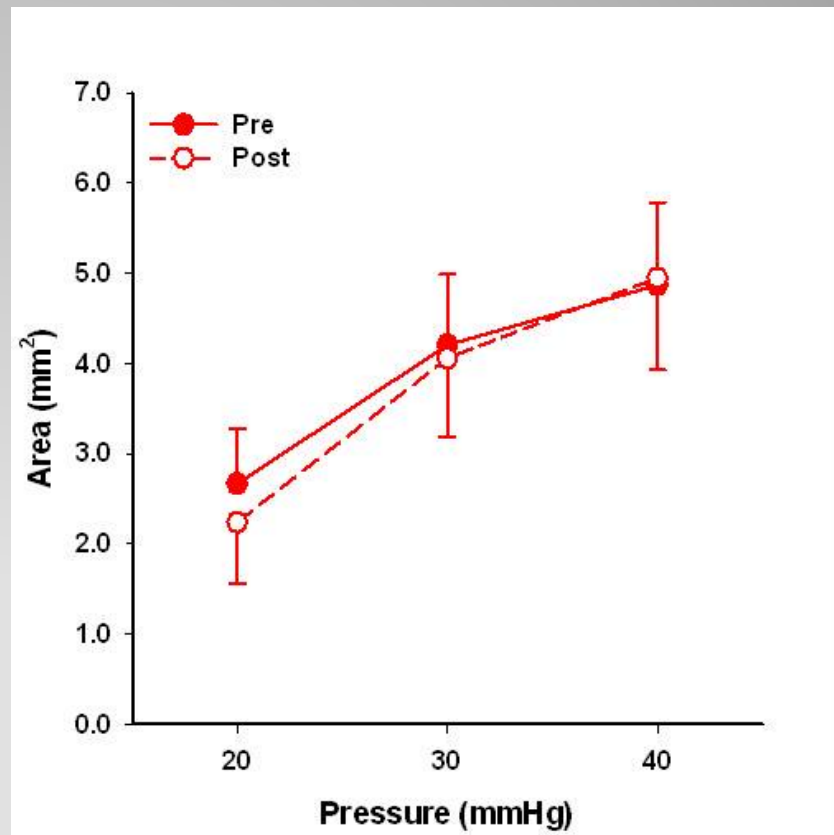


Dorsal Hand Vein

Male

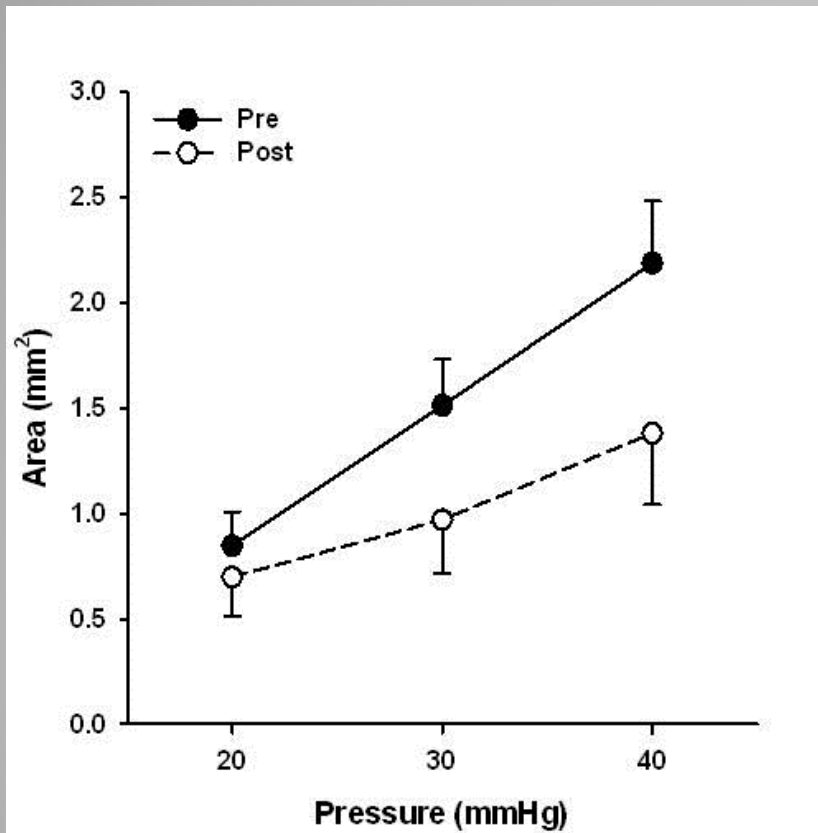


Female

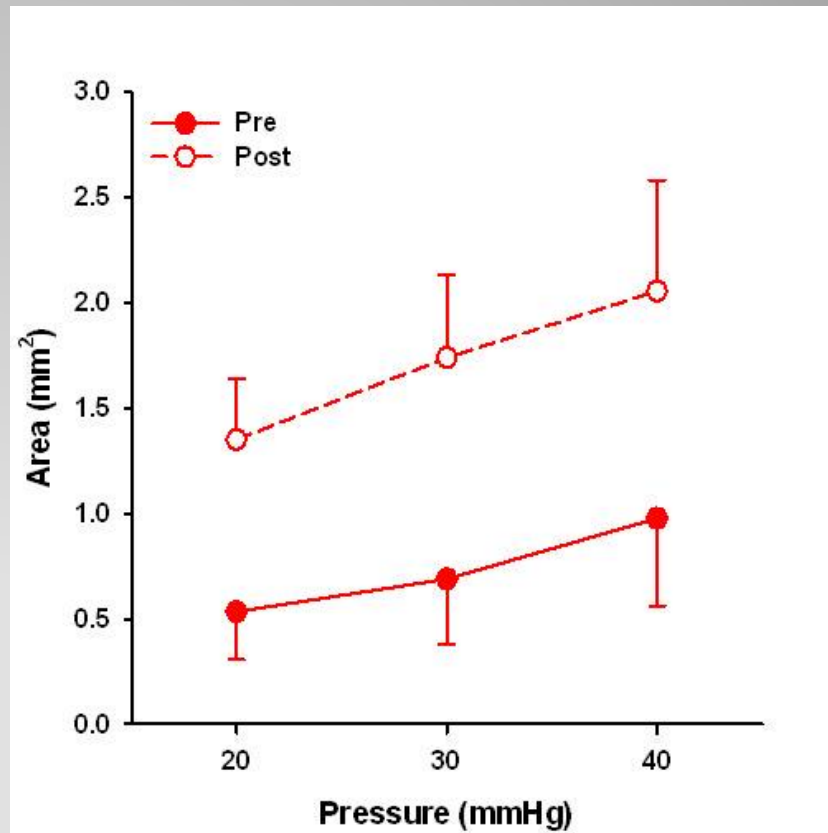


Dorsal Foot Vein

Male



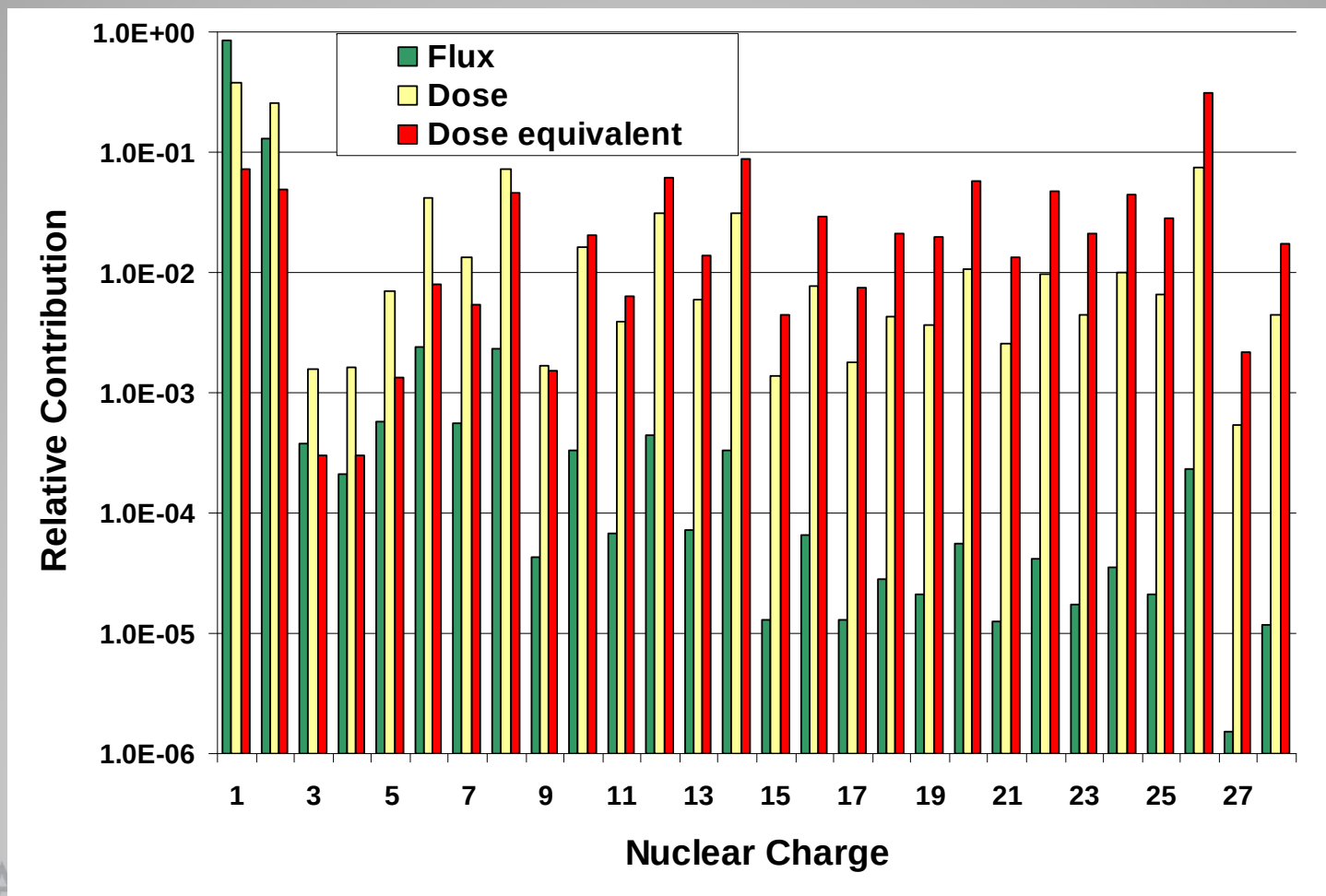
Female



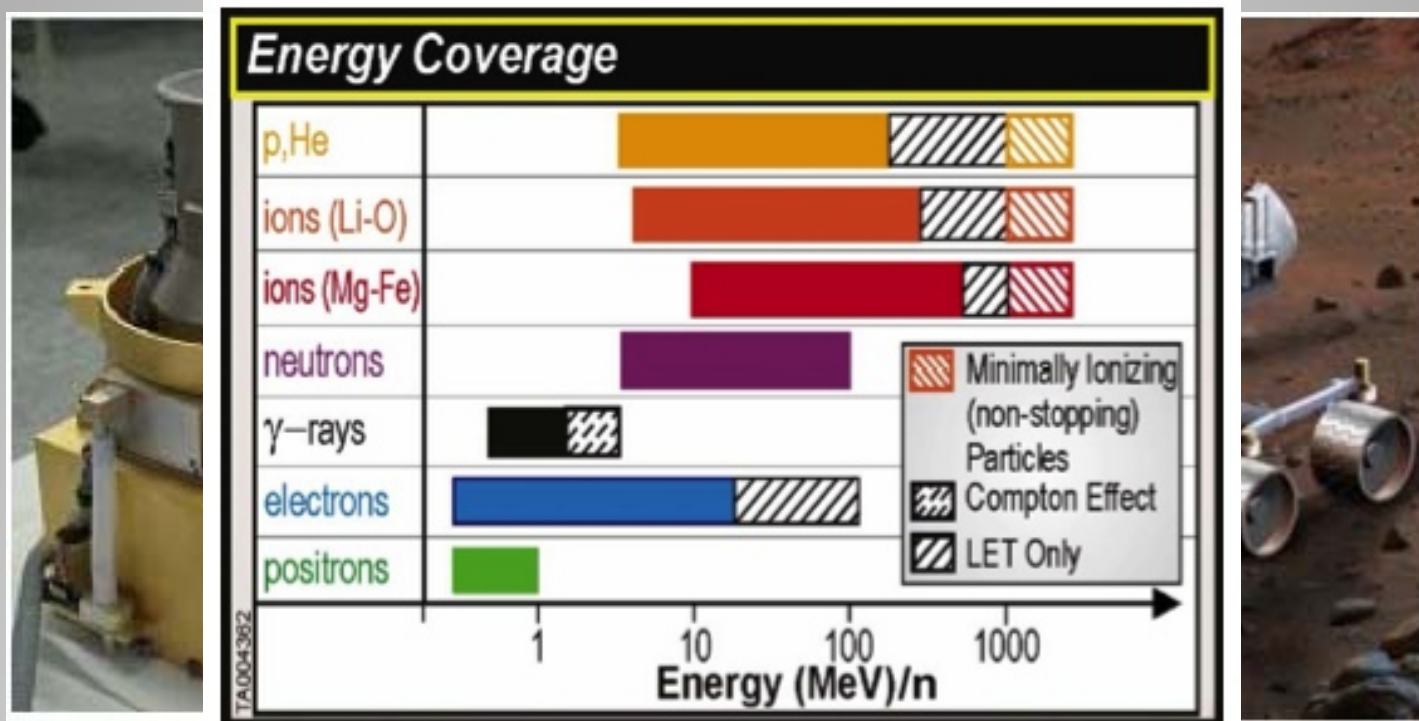


Space Radiation

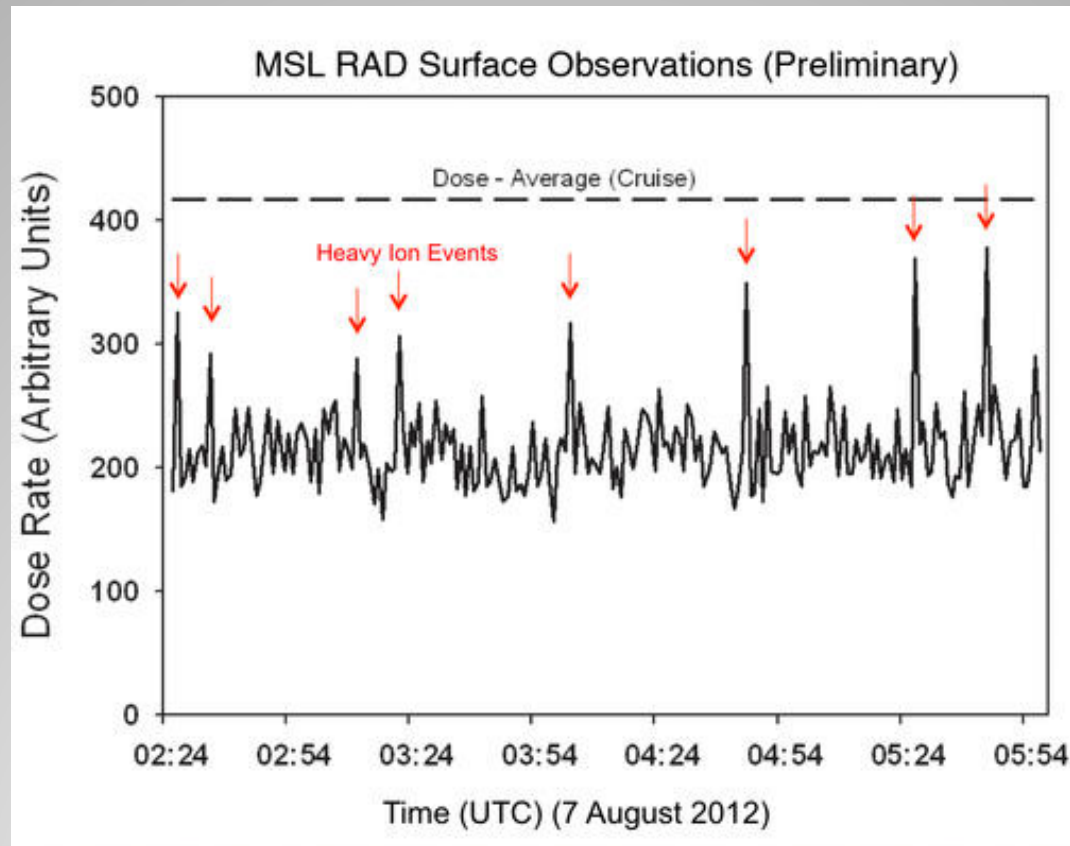
Ion Species



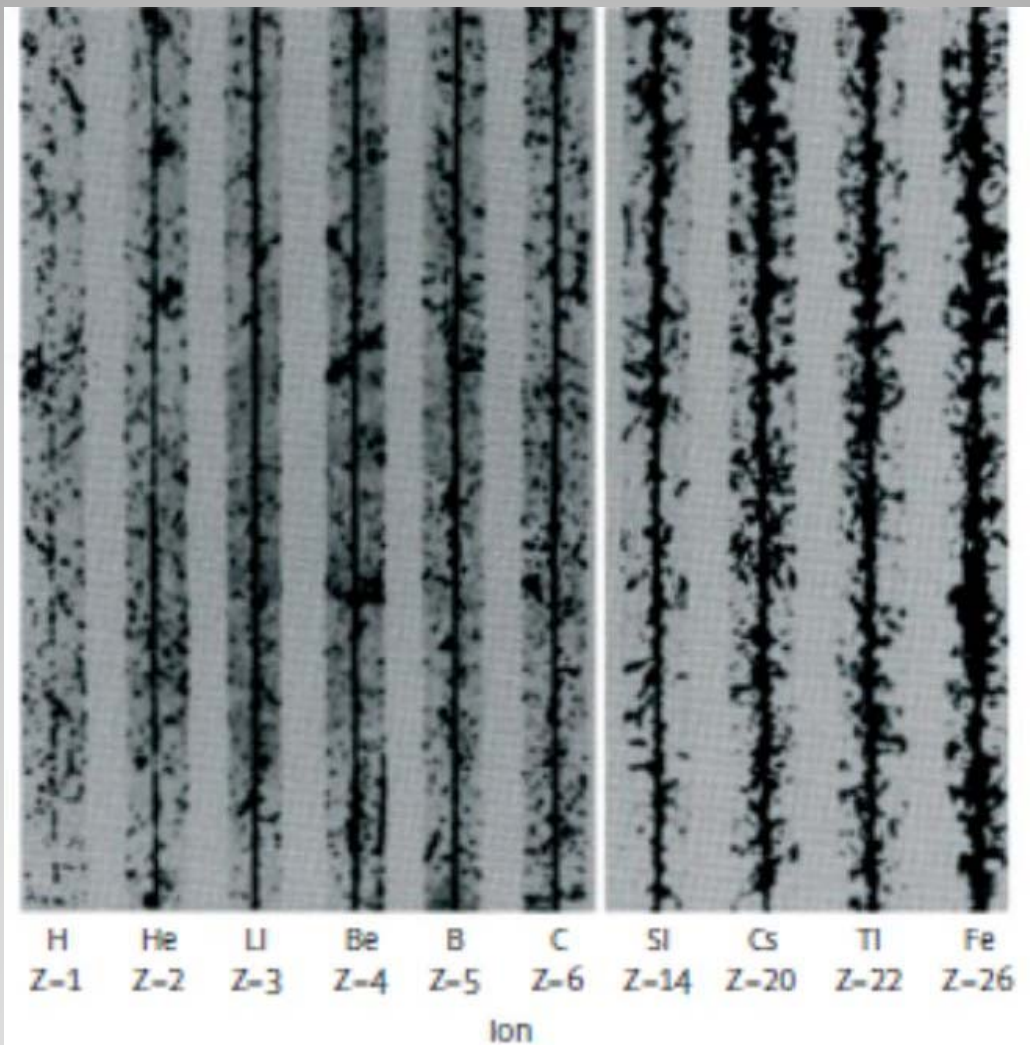
RAD on Curiosity



First Look on Mars

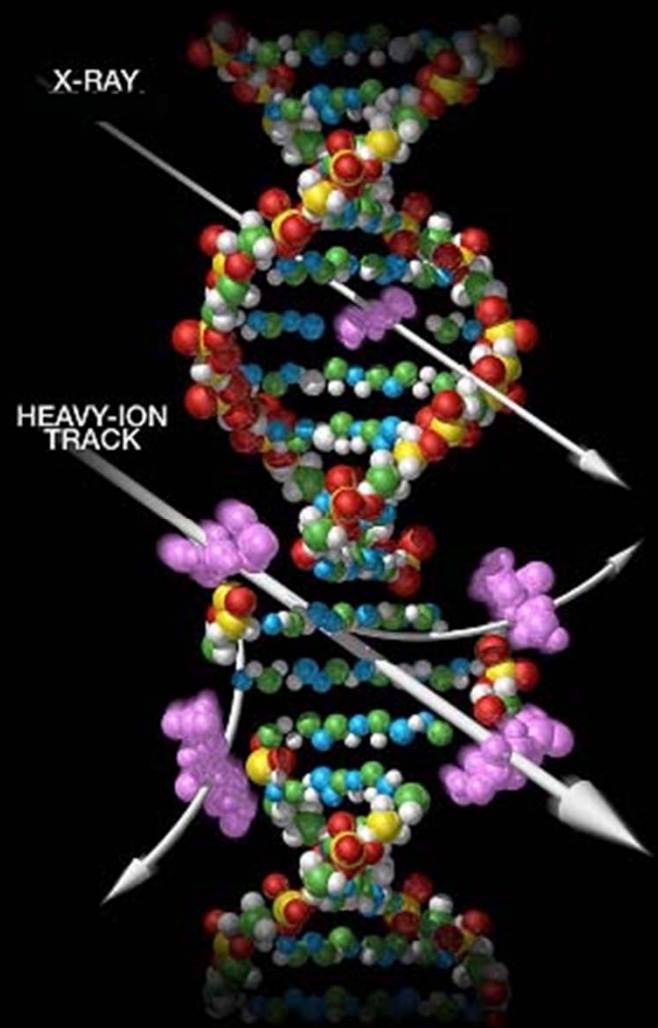


Ion Particle Tracks



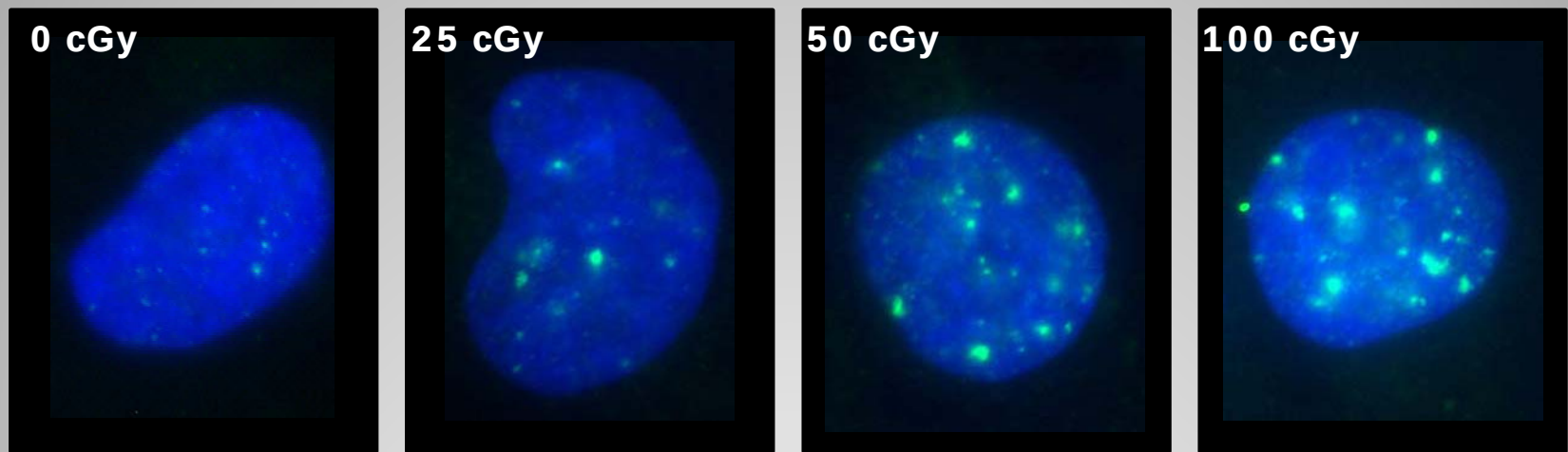
USRA

Cucinotta and Durante 2006



DNA Repair

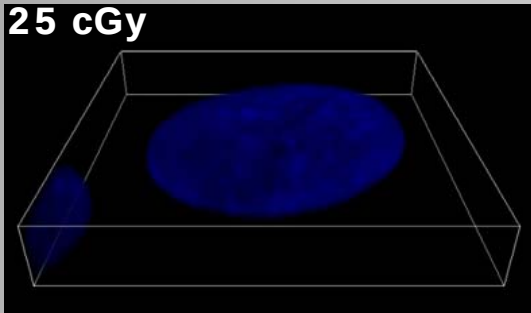
^{56}Fe [600 MeV/u]



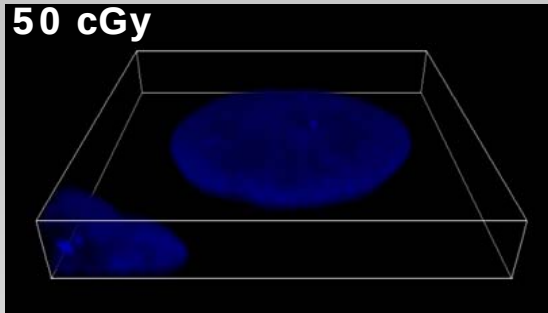
Track Structure

^{56}Fe [600 MeV/u]

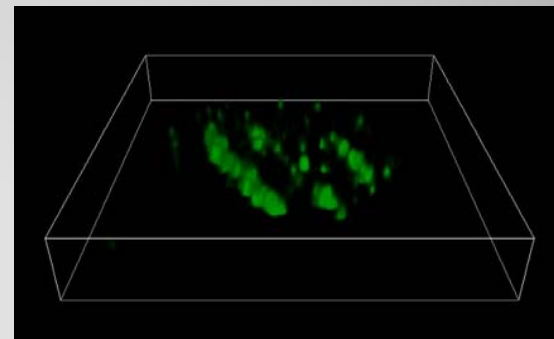
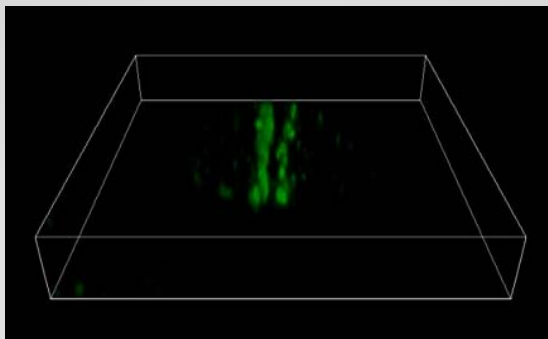
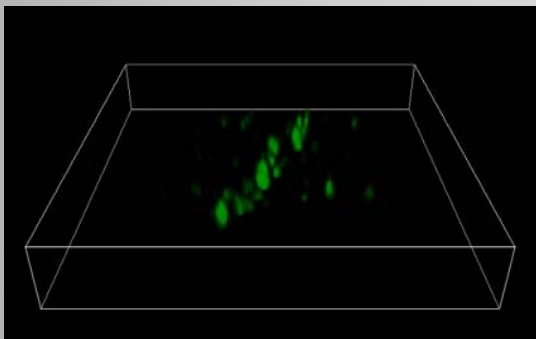
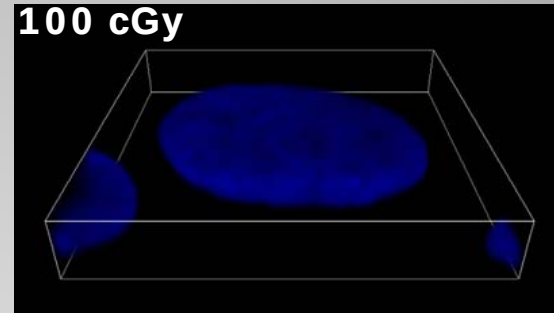
25 cGy



50 cGy

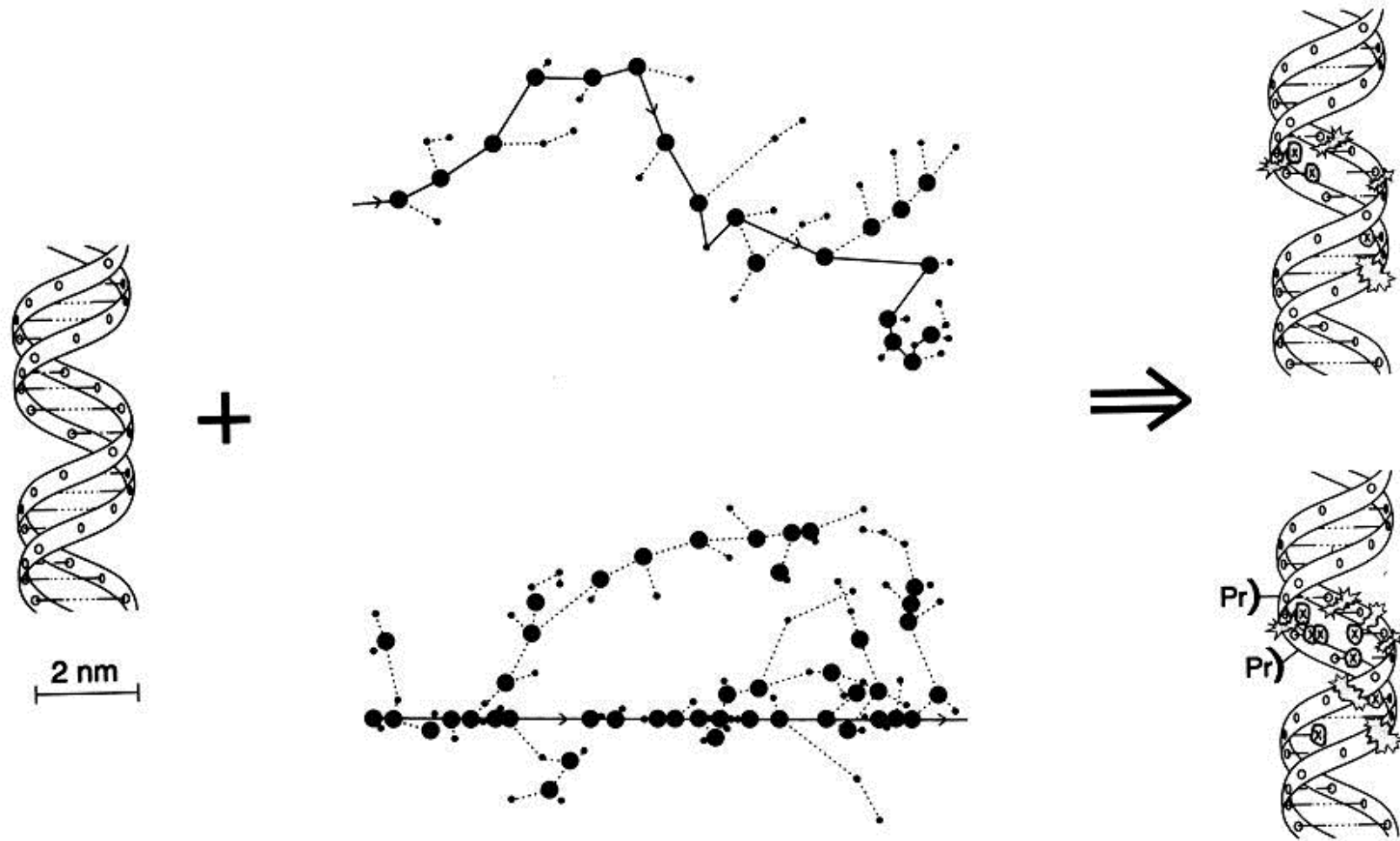


100 cGy

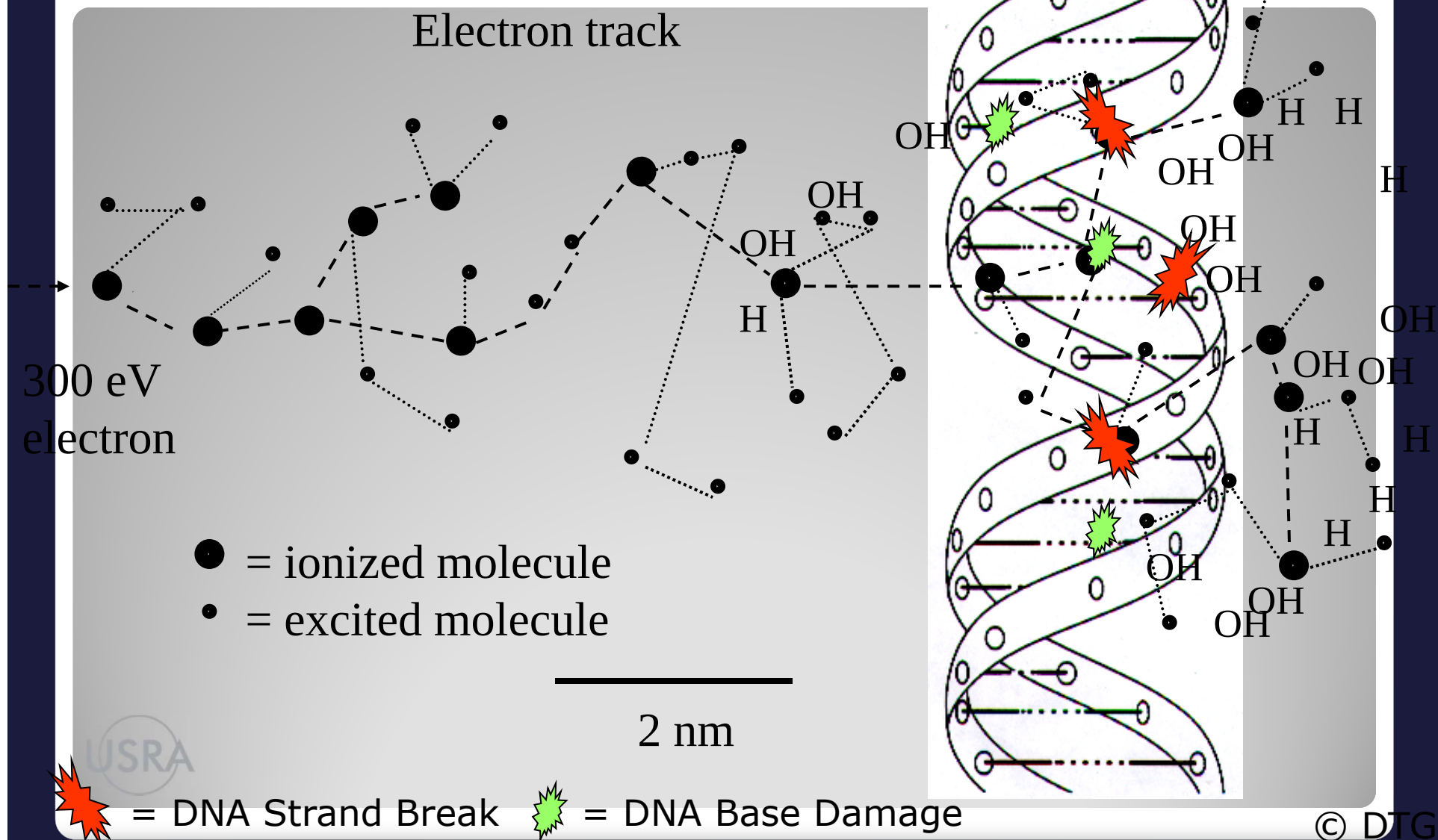


USRA

Clustered Lesions



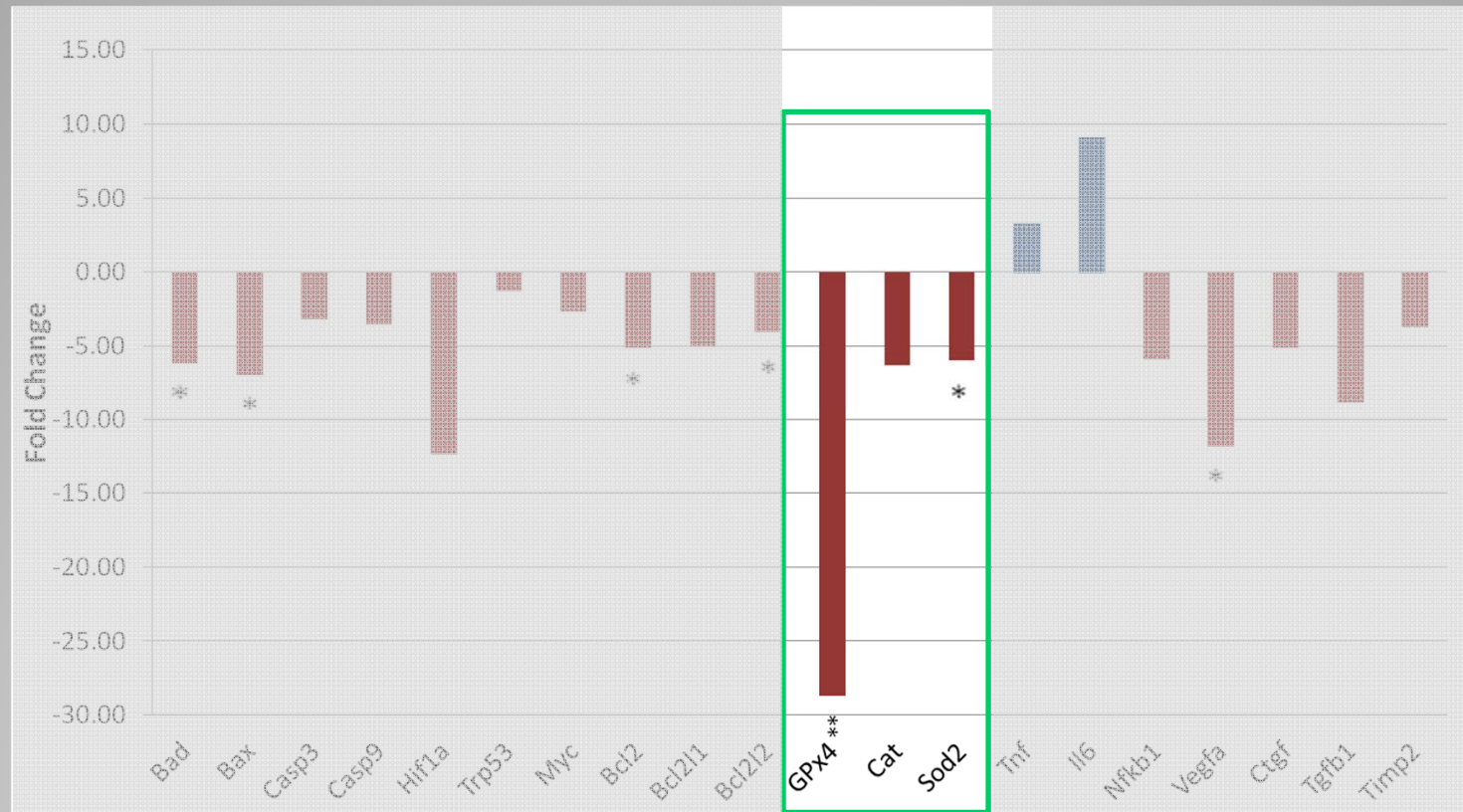
Secondary Effects



**OXIDATIVE MECHANISMS OF
MYOCARDIAL TISSUE REMODELING IN A
MODEL OF HIGH DIETARY HEME IRON
EXPOSED TO RADIATION**



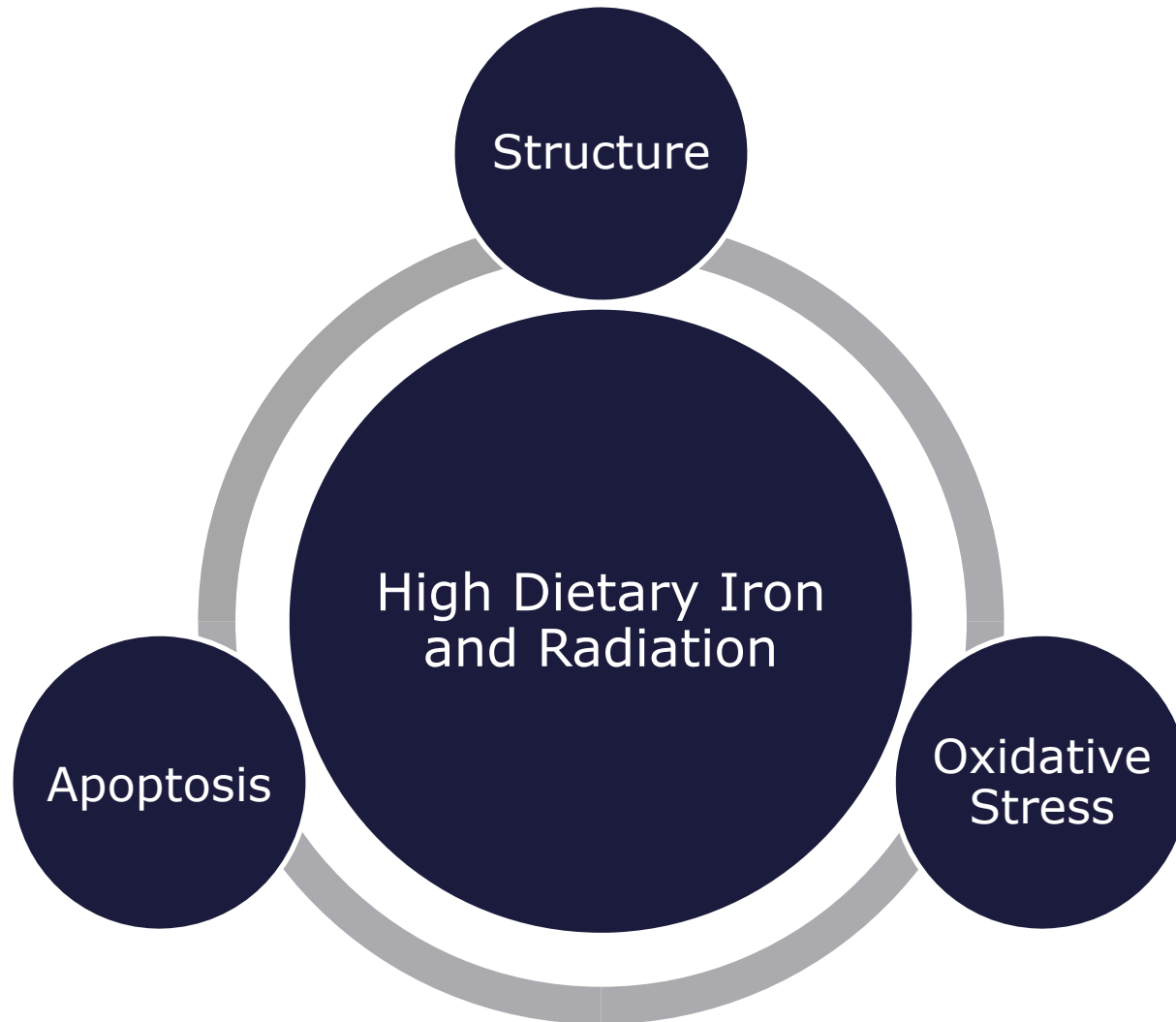
Radiation, Oxidation, & Cardiac Myocyte



Gene expression in mice 4hr after irradiation with ^{137}Cs .
6 Gy compared to sham.

Cardiac Specific Aims

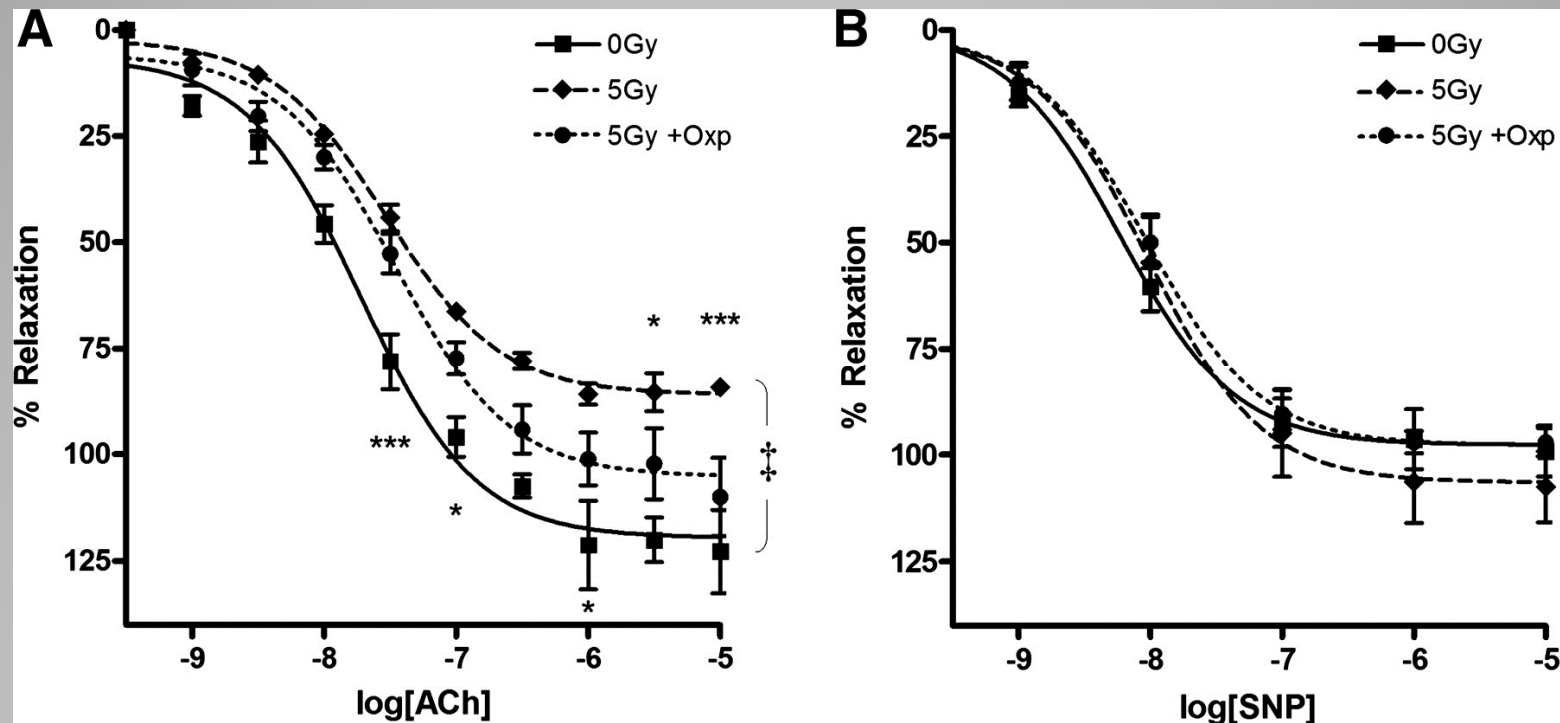
- **Aim 1:** To determine the short-term consequences of the independent and combined effects of gamma radiation and elevated body iron stores on measures of cardiac structure.
- **Aim 2:** Identify and compare the effects of gamma radiation and elevated body iron stores on the genetic and epigenetic regulation of proteins associated with cardiac structure and function.



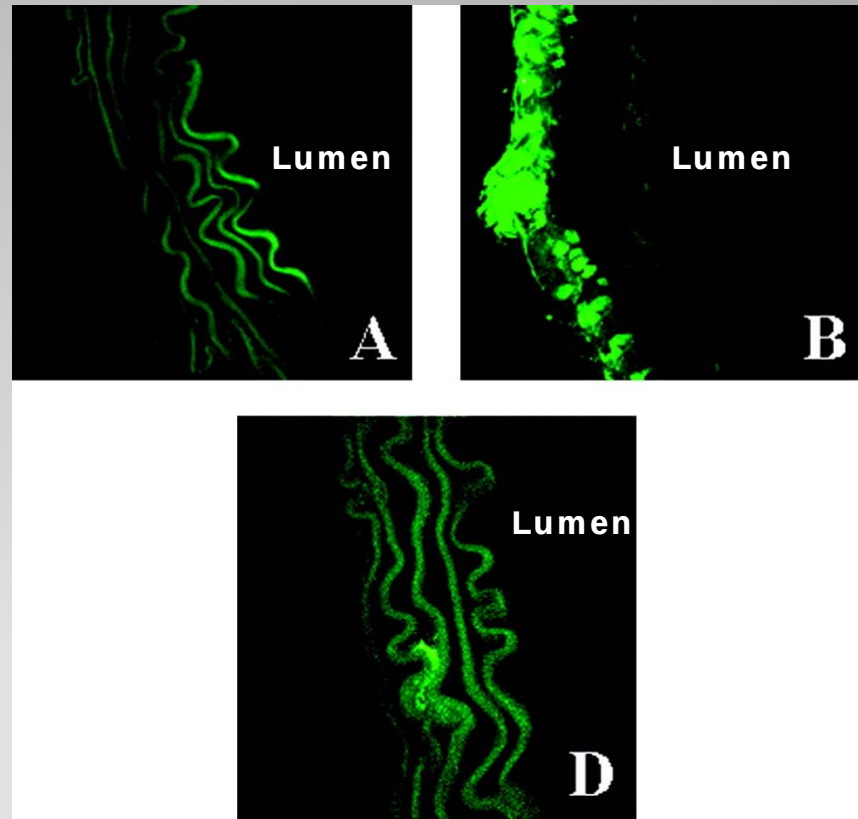
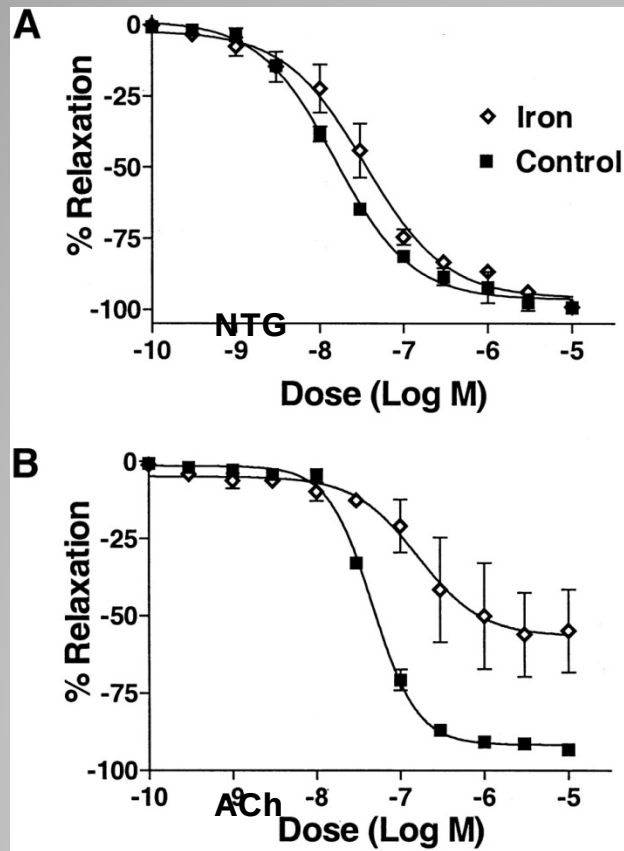
**HIGH DIETARY HEME IRON COMBINED
WITH IRRADIATION PROMOTES A
PROATHEROGENIC ENDOTHELIAL CELL
PHENOTYPE DUE TO INCREASED
OXIDATIVE STRESS**



Radiation, Endothelial Dysfunction, and Oxidative Stress



High Iron, Endothelial Dysfunction, and Oxidative Stress



Vascular Specific Aims

- **Aim 1:** To determine the short-term consequences of the independent and combined effects of exposure to gamma radiation and elevated body iron stores on measures of endothelial function.
- **Aim 2:** Identify and compare the effects of gamma radiation and elevated body iron stores on the genetic and epigenetic regulation of proteins associated with endothelial cell barrier function.

Aging, Endothelial Progenitor Cell Function, and HZE Radiation

Christian M. Westby, Ph.D.
JSC Cardiovascular Laboratory
University Space Research Association
Houston, TX, United States



EPC Function

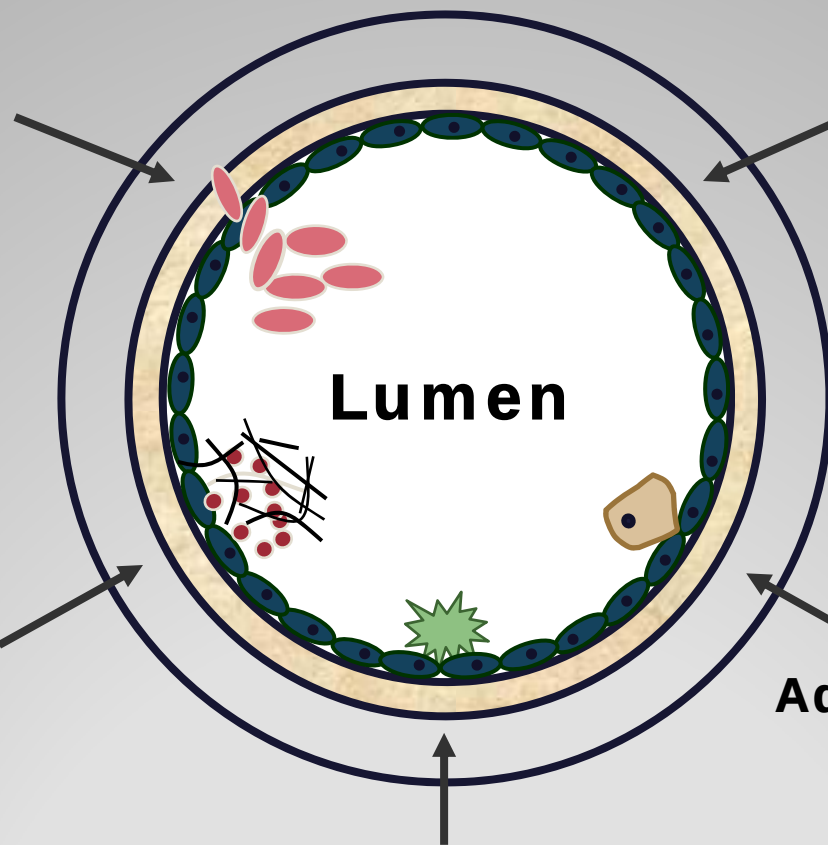
**Endothelial
Vasoregulation**

Lumen

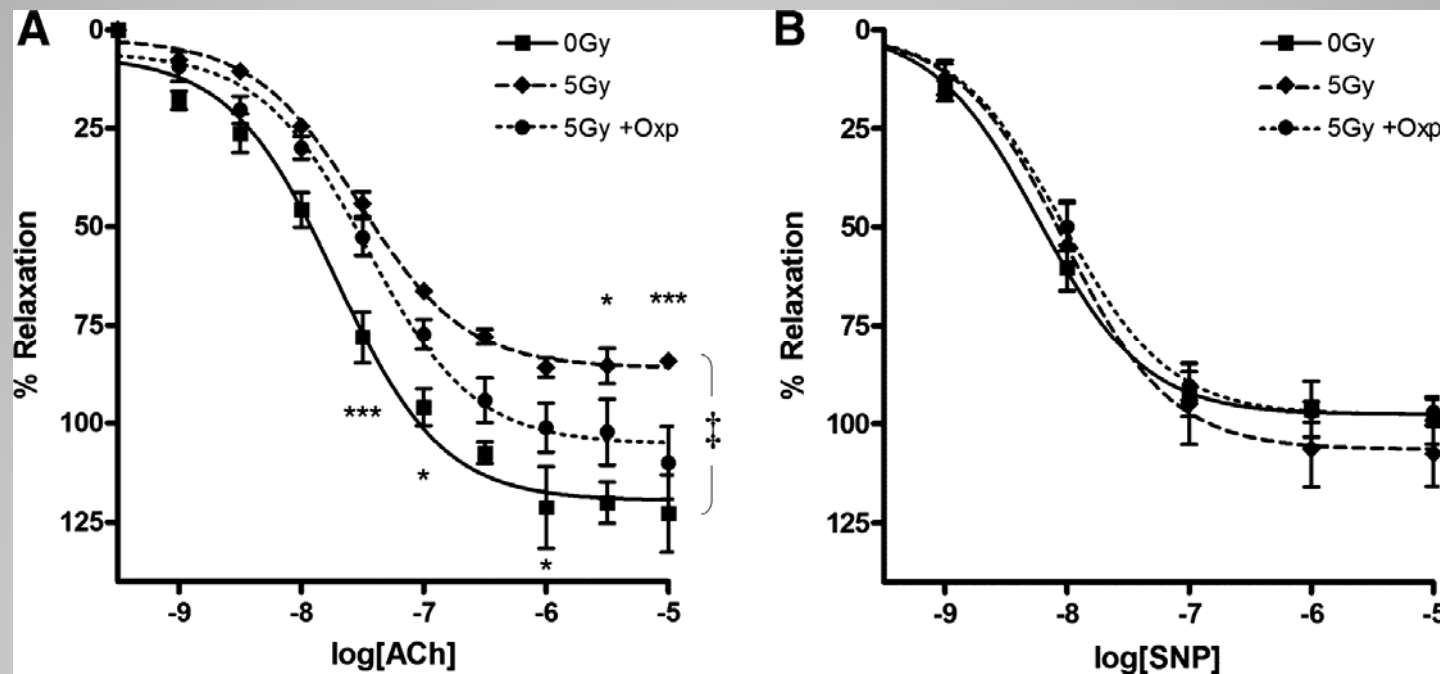
**Endogenous
Fibrinolysis**

**Leukocyte
Adhesion / Migration**

Inflammation / Oxidation



Radiation, Endothelial Dysfunction, and Oxidative Stress



Specific Aims

- **Aim 1:** Determine if exposure low doses of high LET radiation will alter important phenotypic features of circulating endothelial progenitor cells and examine whether these processes are differentially altered in young compared to healthy older adults.
- **Hypothesis:** Exposure to low doses of high LET radiation will impair the function of humans derived circulating endothelial progenitor cells and that the functional phenotype will be less conserved in young compared to older adults.

Methods

- **Subjects**

- 12 young (age 21–34 years) and 12 older (age 56–67 years) healthy, sedentary men

- **Putative EPCs isolated from whole blood**

- DiI-ac-LDL, Willebrand factor, VE-cadherin, CD31, and VEGFR-2

- **Nonadherent fraction will be irradiated using 600 MeV ^{56}Fe**

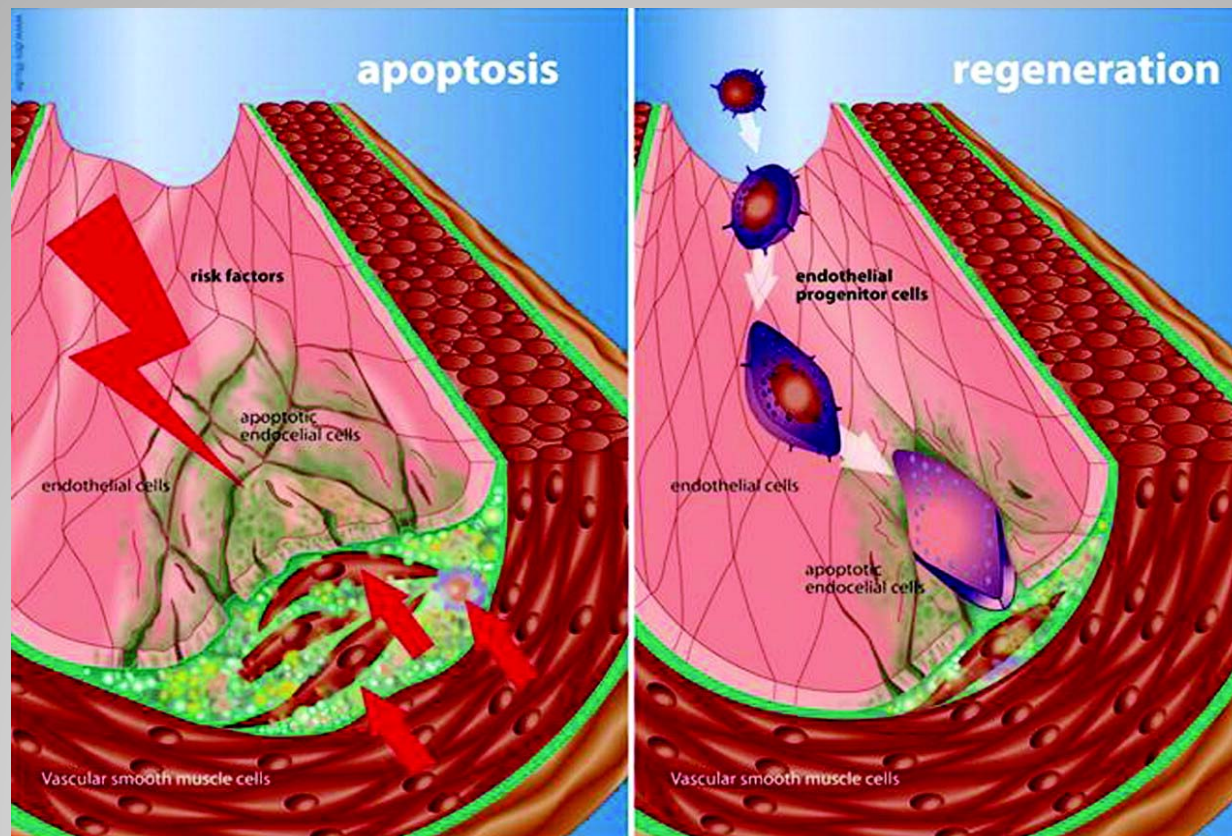
- Dose 0.1, 0.25, 0.5, or 1Gy, at 0.25Gy/min

- **Assays**

- EPC Colony-Forming Assay/Cell Survival, Migration, Angiogenic growth factor.

EPCs and Vascular Repair

The balance between endothelial cell apoptosis and endothelial cell regeneration may determine the degree and progression of atherosclerosis



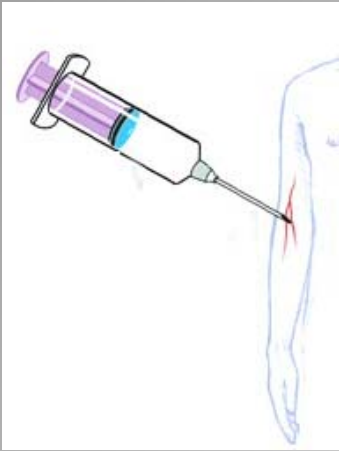
Werner, N. et al. Arterioscler Thromb Vasc Biol 2006

Radiation and EPC Function

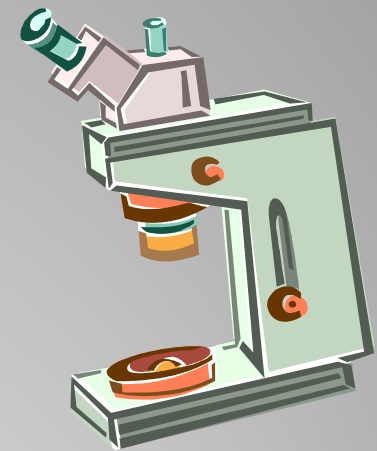
- **EPC Functional Characteristics:**

- Clonogenic Capacity
- Migration
- Angiogenic Growth Factor Release

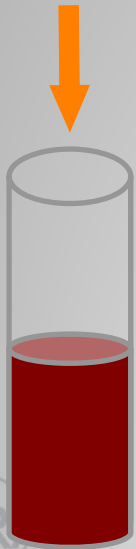
CFU Protocol



EPC Colony Forming Assay



Count Clusters



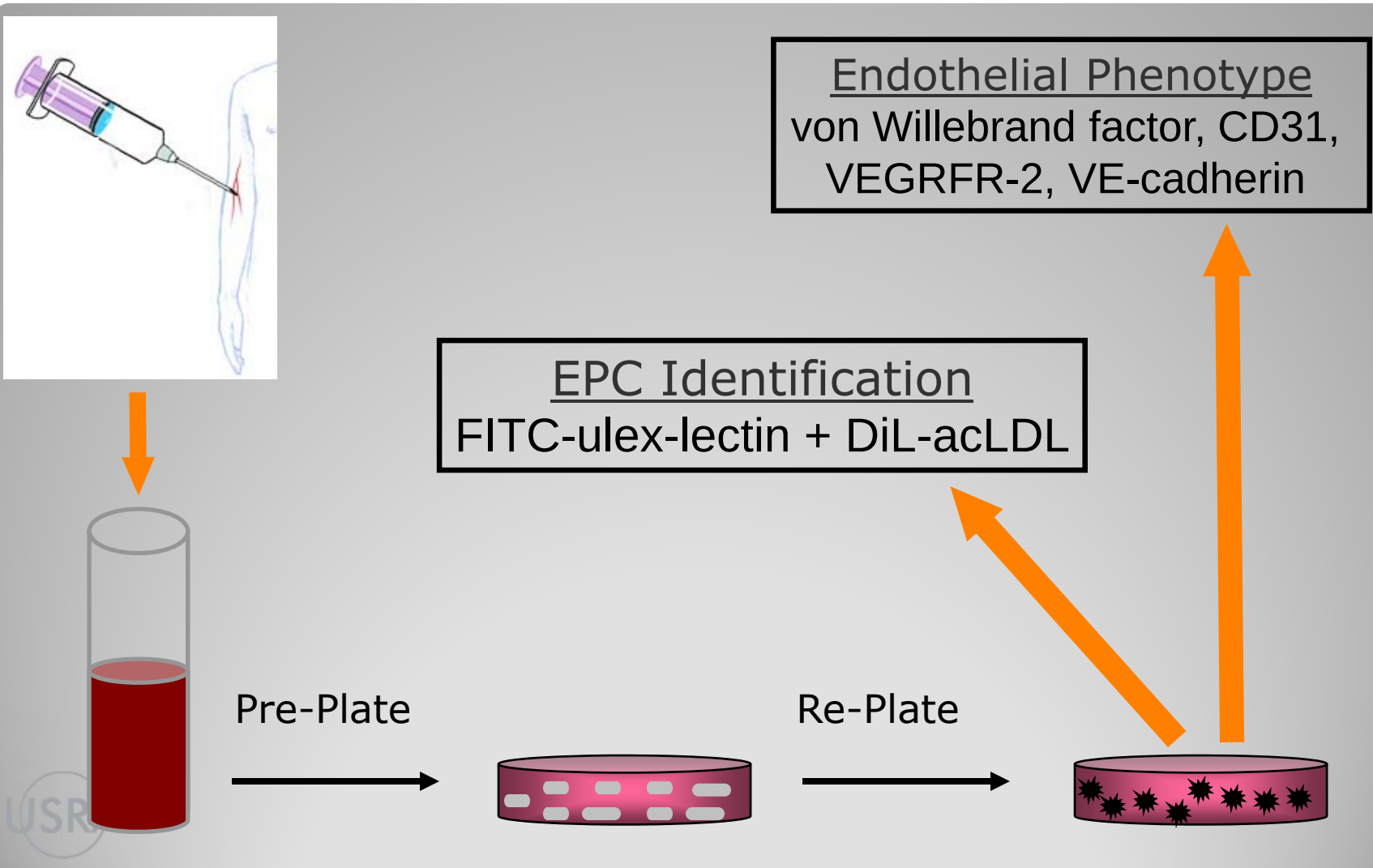
Pre-Plate



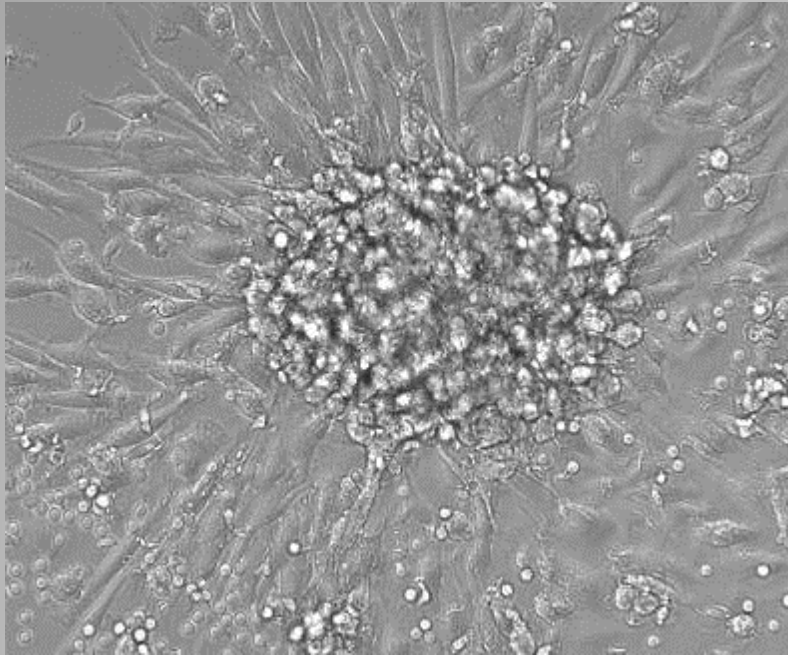
Re-Plate



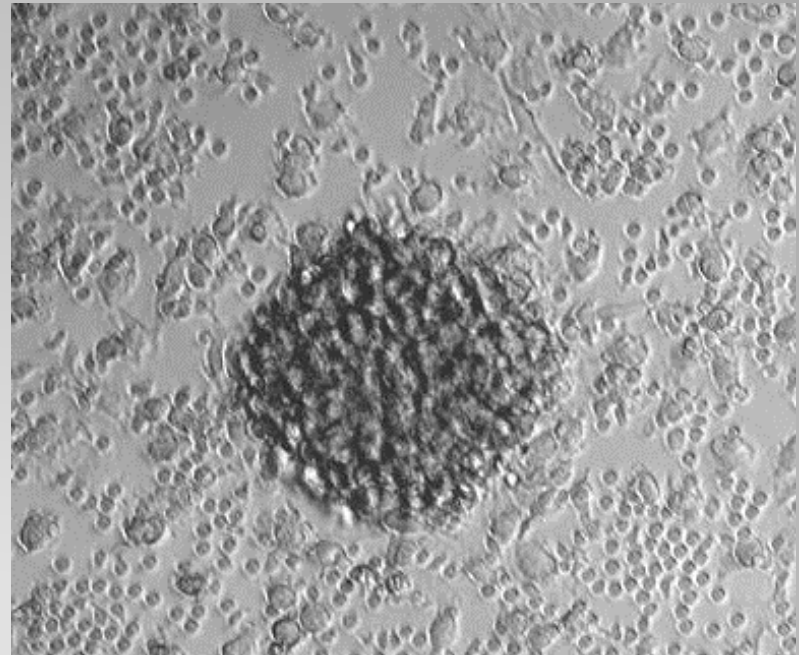
EPC Identification in Culture



Colony Examples



Counted



Not Counted

EPC Migration Protocol

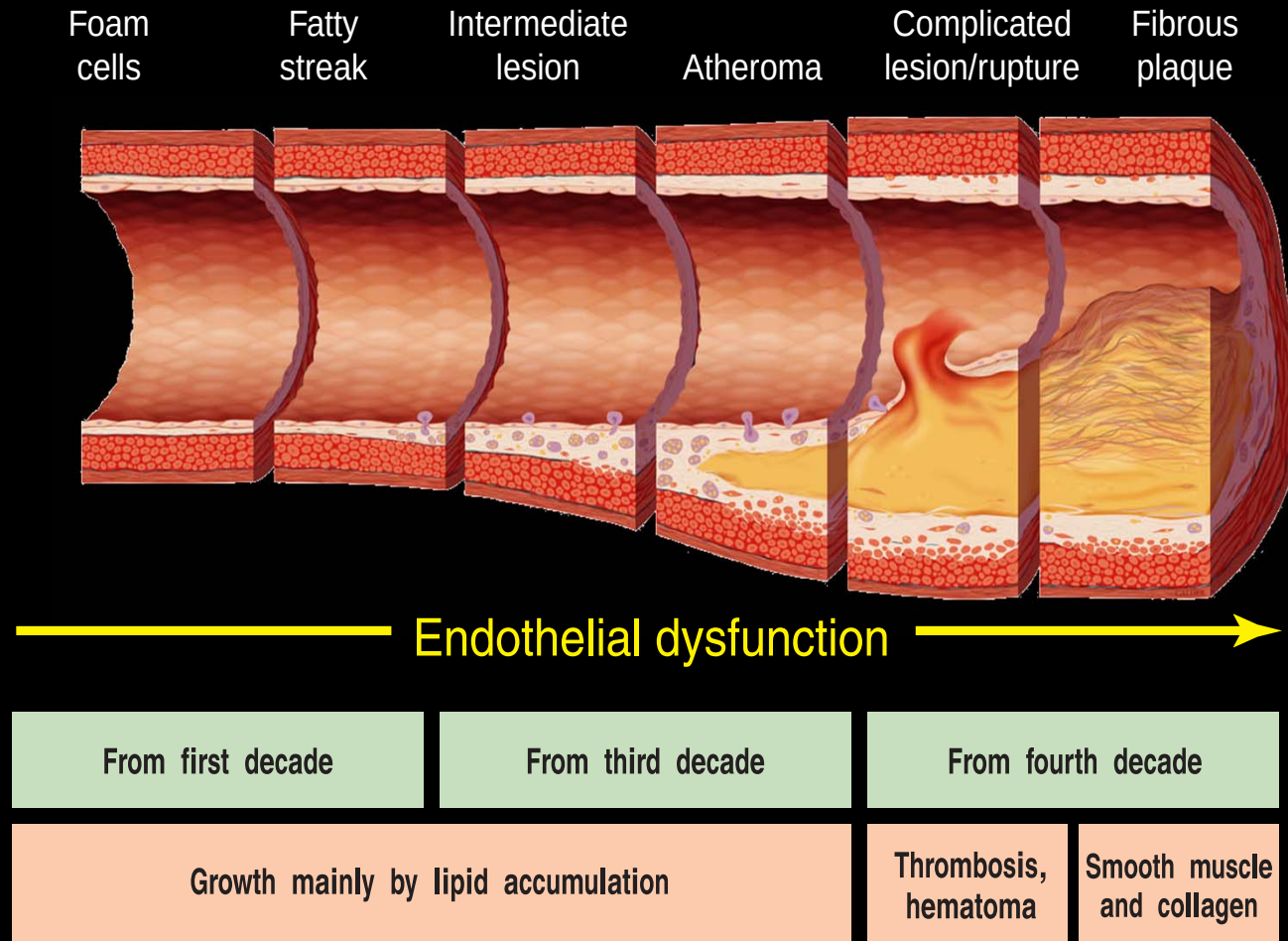
Peripheral Blood Samples Collected:

Preplated for 2 days

**EPC Migration: Modified Boyden
Chamber**



Atherosclerotic Timeline



Adapted from Pepine CJ. *Am J Cardiol.* 1998;82(suppl 10A:23S-27S)

Acknowledgements

- **Cardiovascular Laboratory**
 - Sydney Stein
 - Angela Brown
 - Steven H. Platts, Ph.D.
- **Nutrition Laboratory**
 - Sara Zwart, Ph.D.
- **Radiation / Core Laboratory**
 - Corey A. Theriot, Ph.D.

