Cardiovascular Adaptations in the Spaceflight Environment

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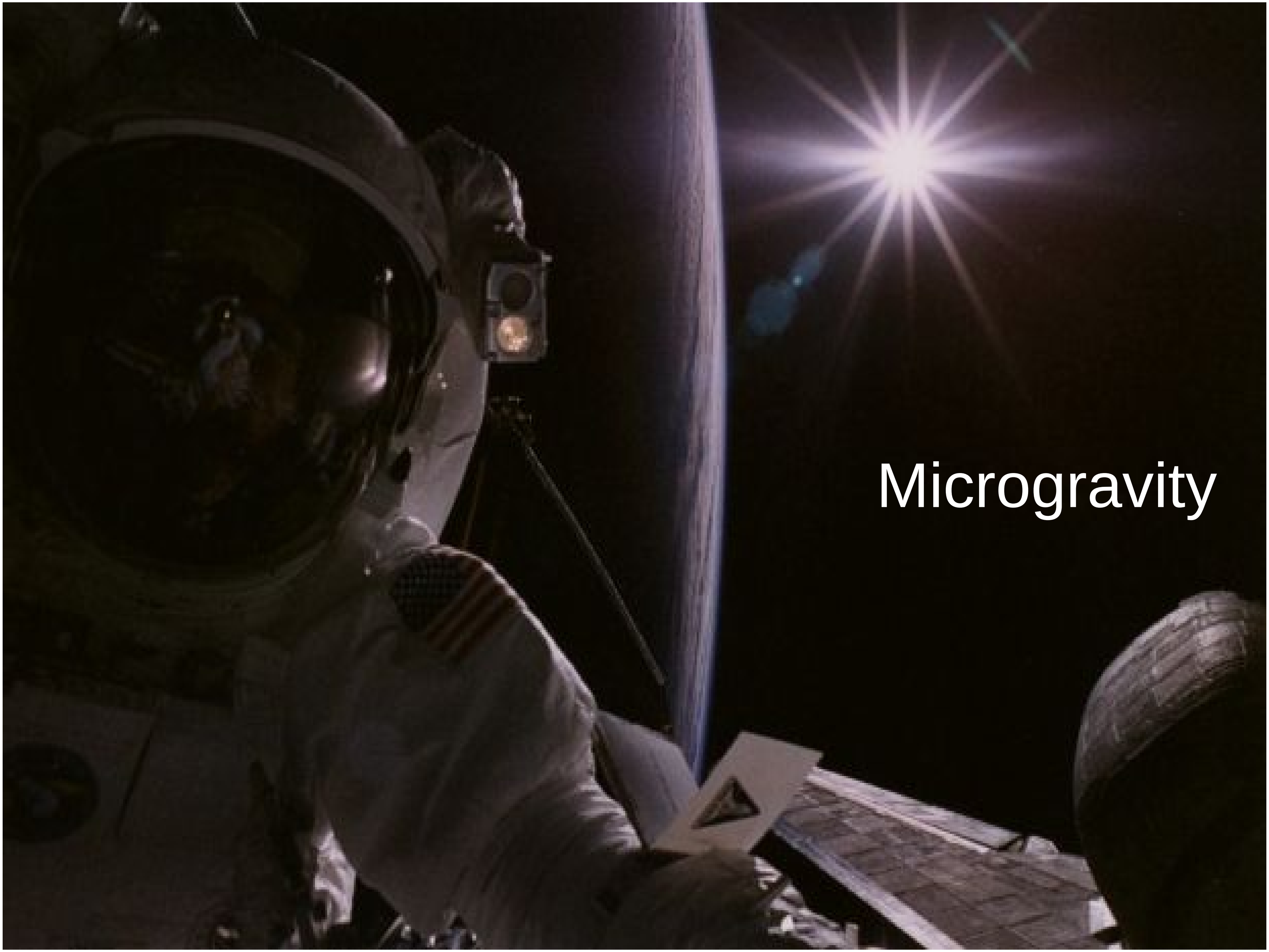
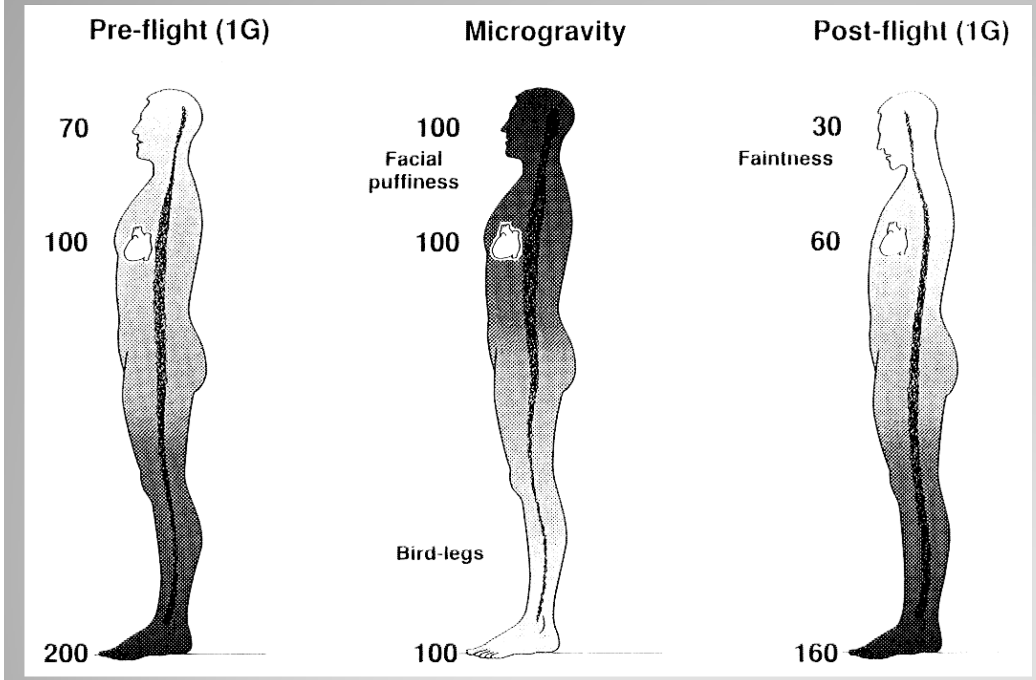
Overview

- **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**

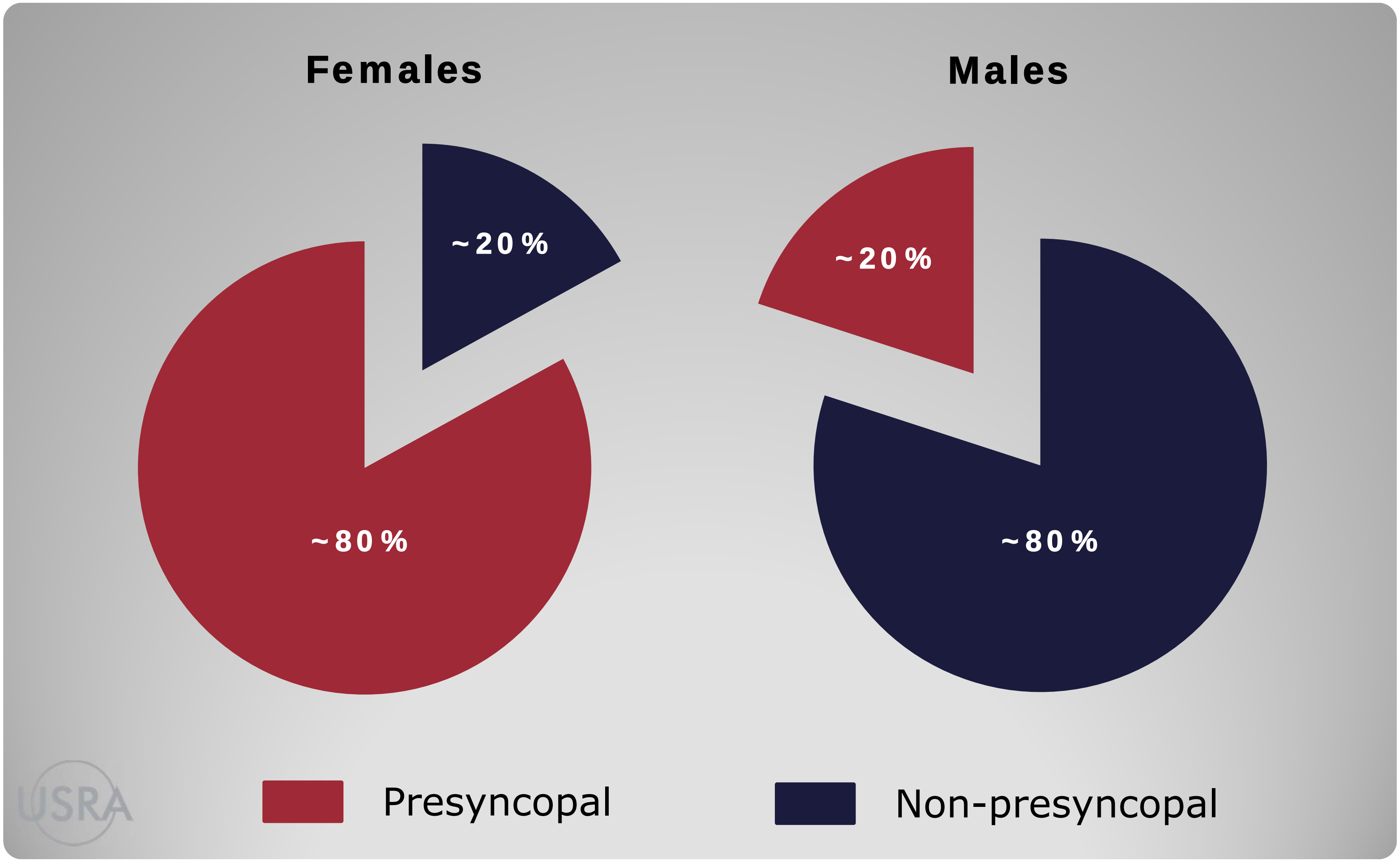
Rowell L.B., 1986

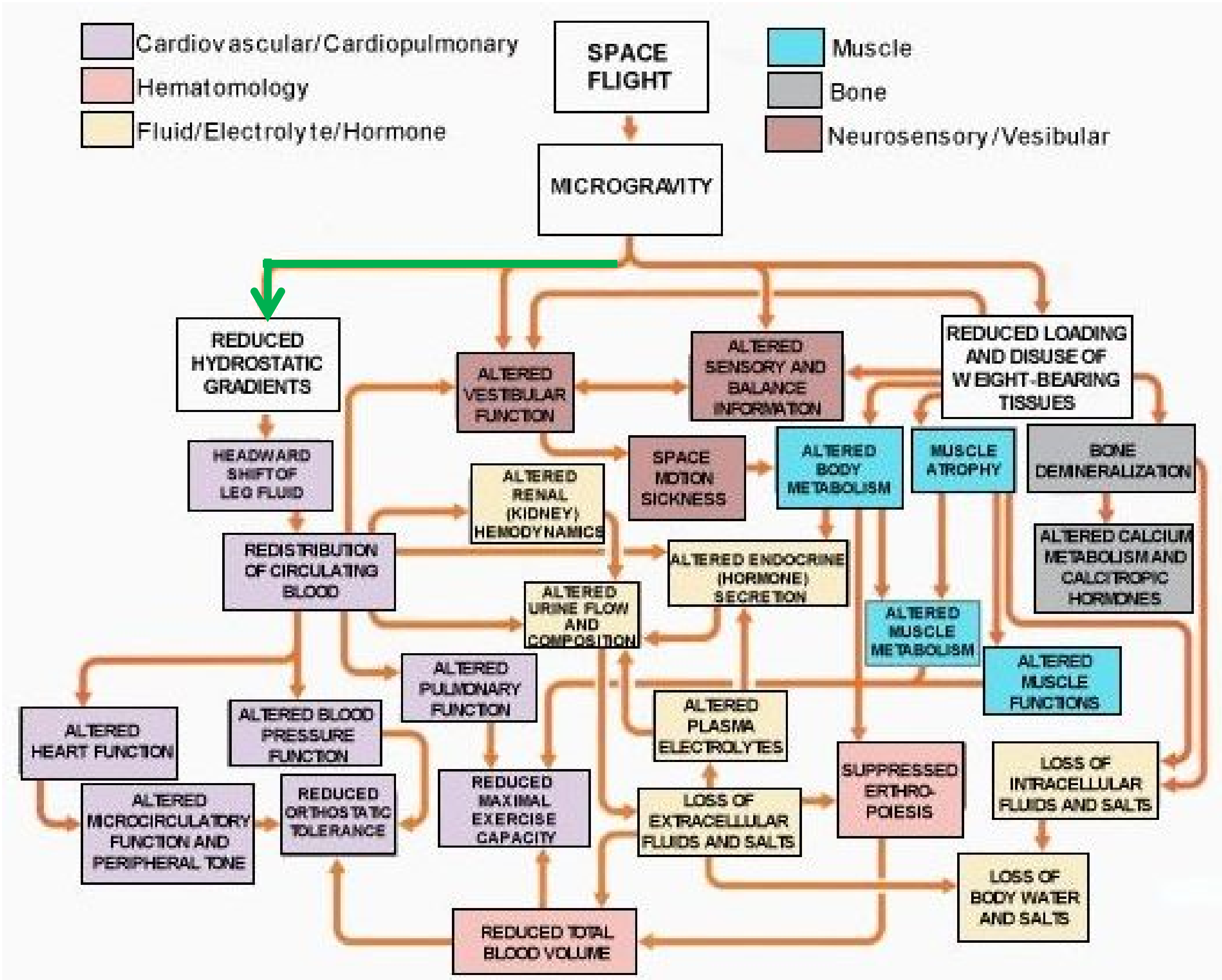
Example of cephalad fluid shift

Pre-flight

Day-2 in flight

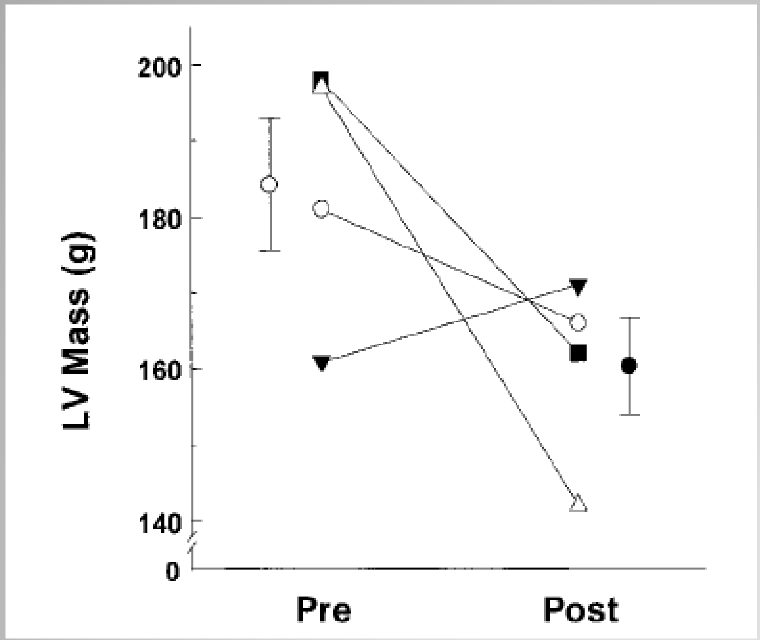
Orthostatic Tolerance




Cardiovascular/Cardiopulmonary
Hematomology
Fluid/Electrolyte/Hormone
SPACE FLIGHT
Muscle
Bone
Neurosensory/Vesibular
MICROGRAVITY
REDUCED HYDROSTATIC GRADIENTS
ALTERED VESTIBULAR FUNCTION
ALTERED SENSORY AND BALANCE INFORMATION
REDUCED LOADING AND DISUSE OF WEIGHT-BEARING TISSUES
HEADWARD SHIFT OF LEG FLUID
ALTERED RENAL (KIDNEY) HEMODYNAMICS
SPACE MOTION SICKNESS
ALTERED BODY METABOLISM
MUSCLE ATROPHY
BONE DEMINERALIZATION
REDISTRIBUTION OF CIRCULATING BLOOD
ALTERED ENDOCRINE (HORMONE) SECRETION
ALTERED CALCIUM METABOLISM AND CALCITROPIC HORMONES
ALTERED URINE FLOW AND COMPOSITION
ALTERED MUSCLE METABOLISM
ALTERED MUSCLE FUNCTIONS
ALTERED PULMONARY FUNCTION
ALTERED HEART FUNCTION
ALTERED BLOOD PRESSURE FUNCTION
ALTERED PLASMA ELECTROLYTES
SUPPRESSED ERTHROPOIESIS
LOSS OF INTRACELLULAR FLUIDS AND SALTS
ALTERED MICROCIRCULATORY FUNCTION AND PERIPHERAL TONE
REDUCED ORTHOSTATIC TOLERANCE
REDUCED MAXIMAL EXERCISE CAPACITY
LOSS OF EXTRACELLULAR FLUIDS AND SALTS
LOSS OF BODY WATER AND SALTS
REDUCED TOTAL BLOOD VOLUME

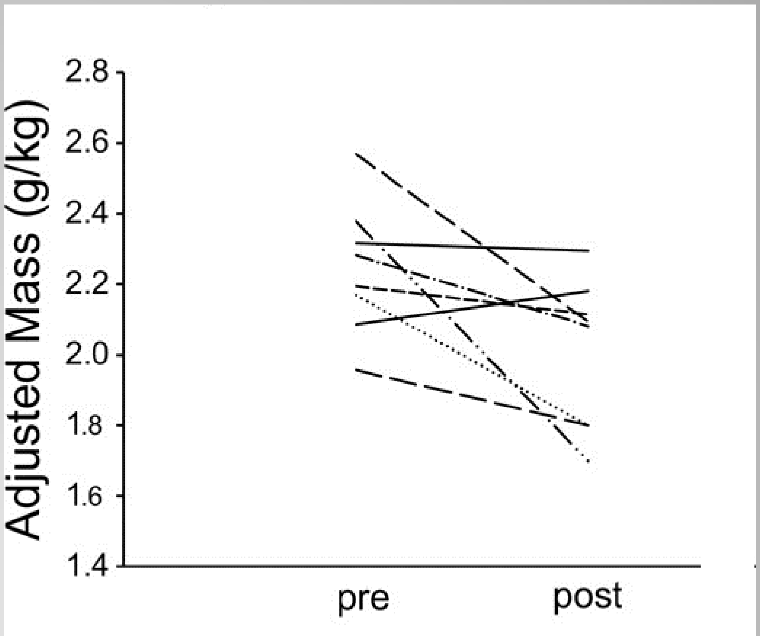
Cardiac Atrophy

Men

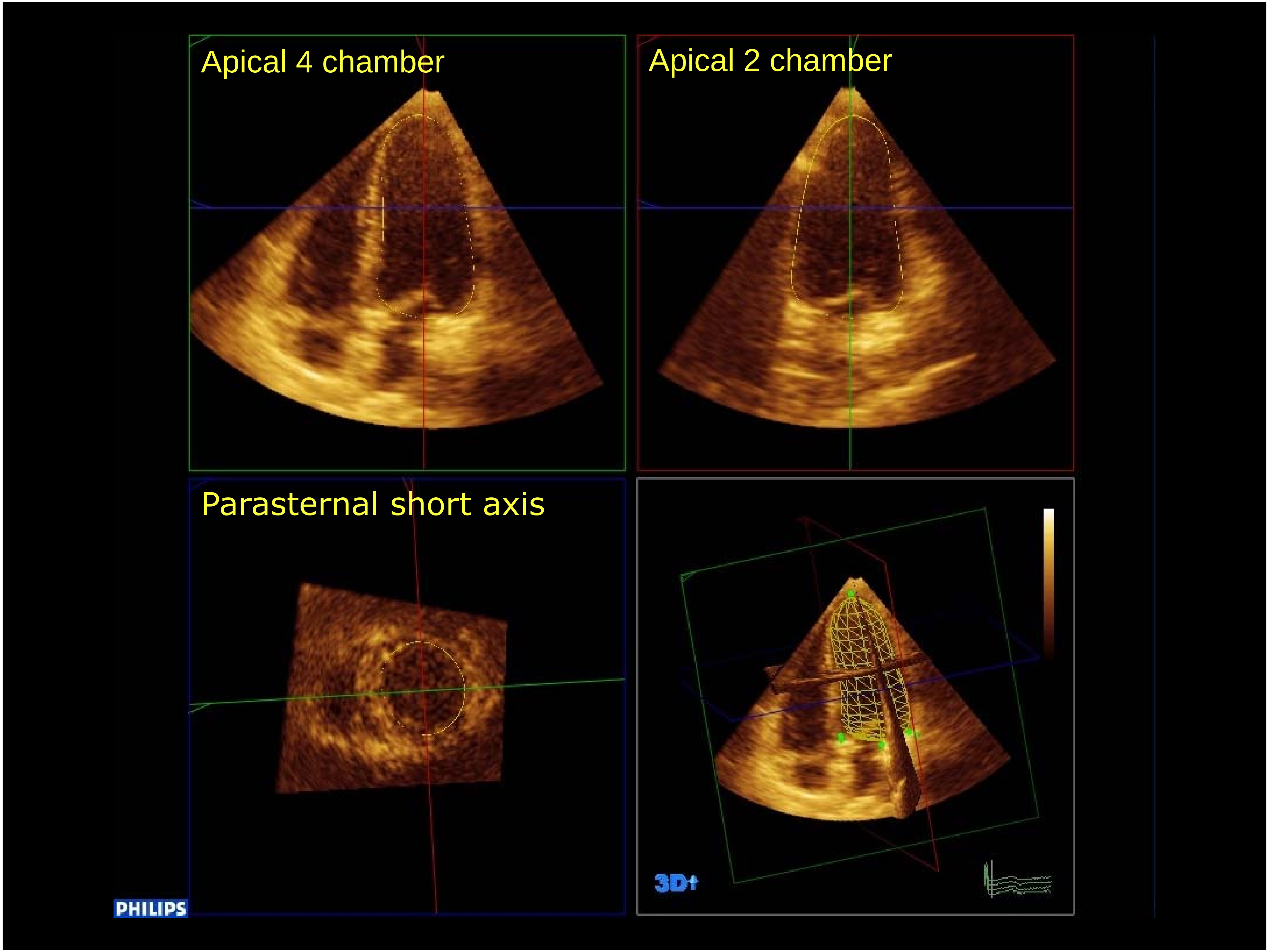


Perhonen MA et al. J Appl Physiol 91: 645-653, 2001

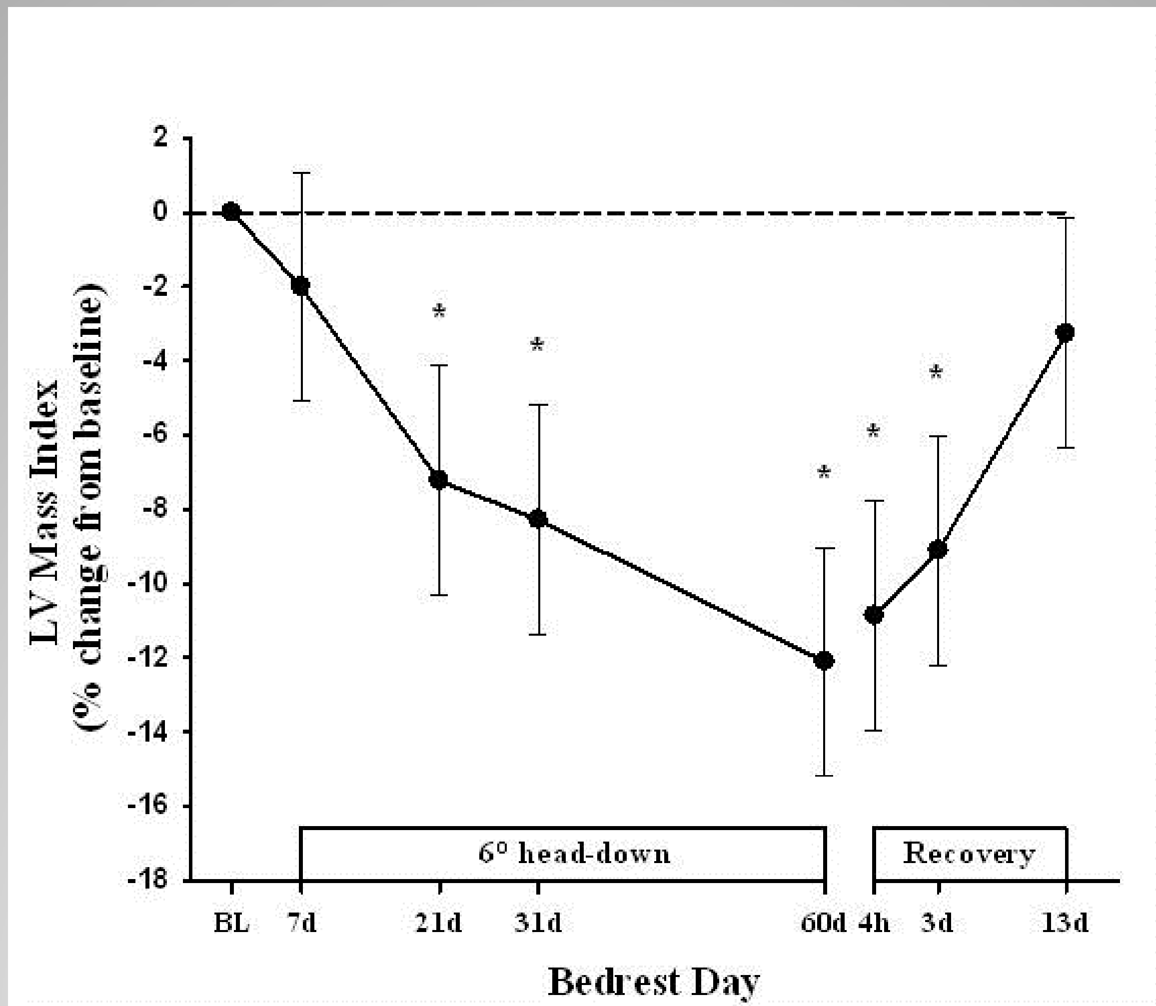
Women



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

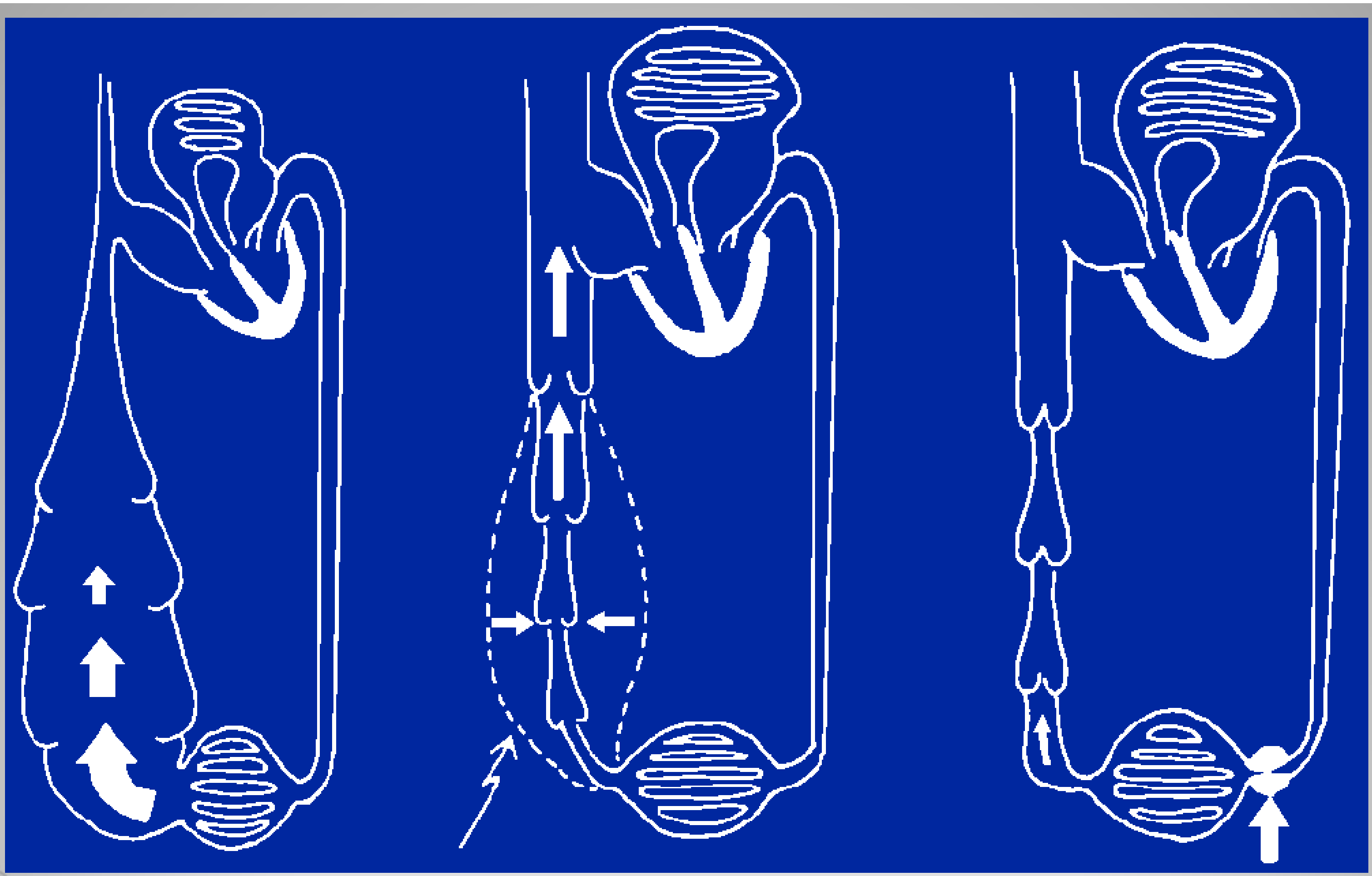

Apical 4 chamber
Apical 2 chamber
Parasternal short axis
3D
PHILIPS

Cardiac Atrophy Time Course



Westby CM et al. In Press 2012

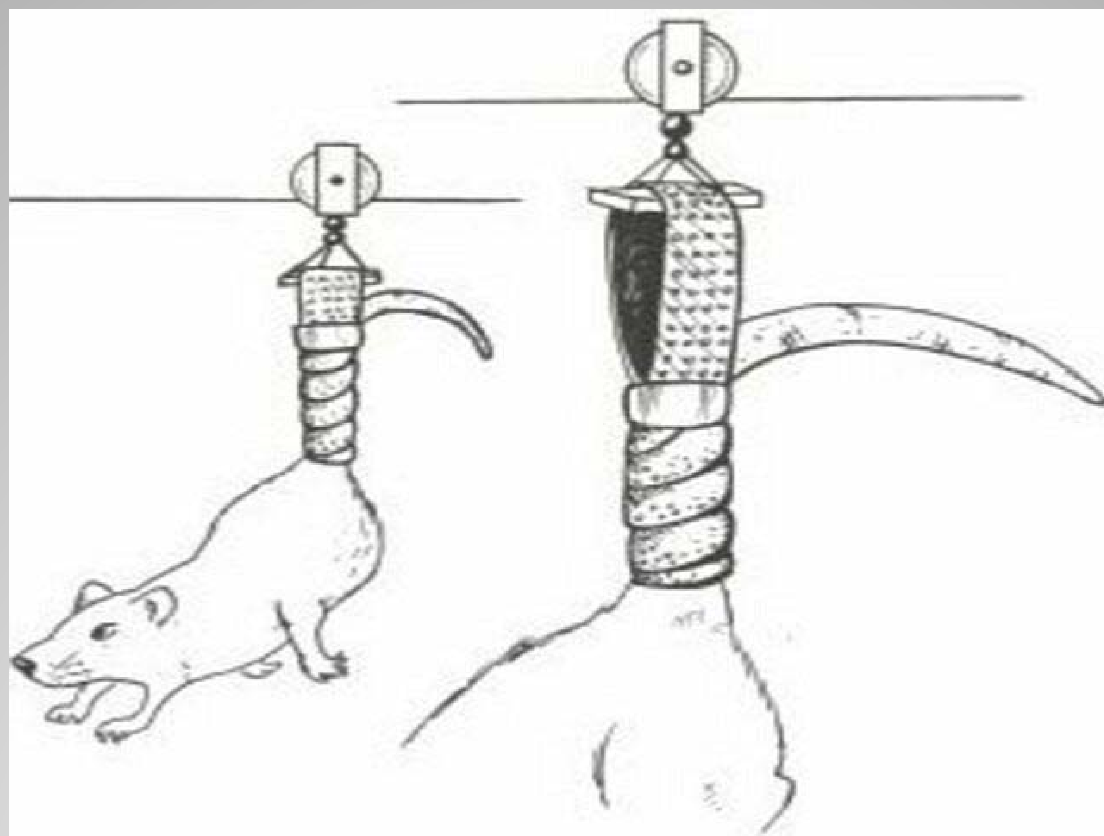
Mobilization of blood



Orthostasis | Venoconstriction expels volume | Arterial Constriction reduces inflow rate

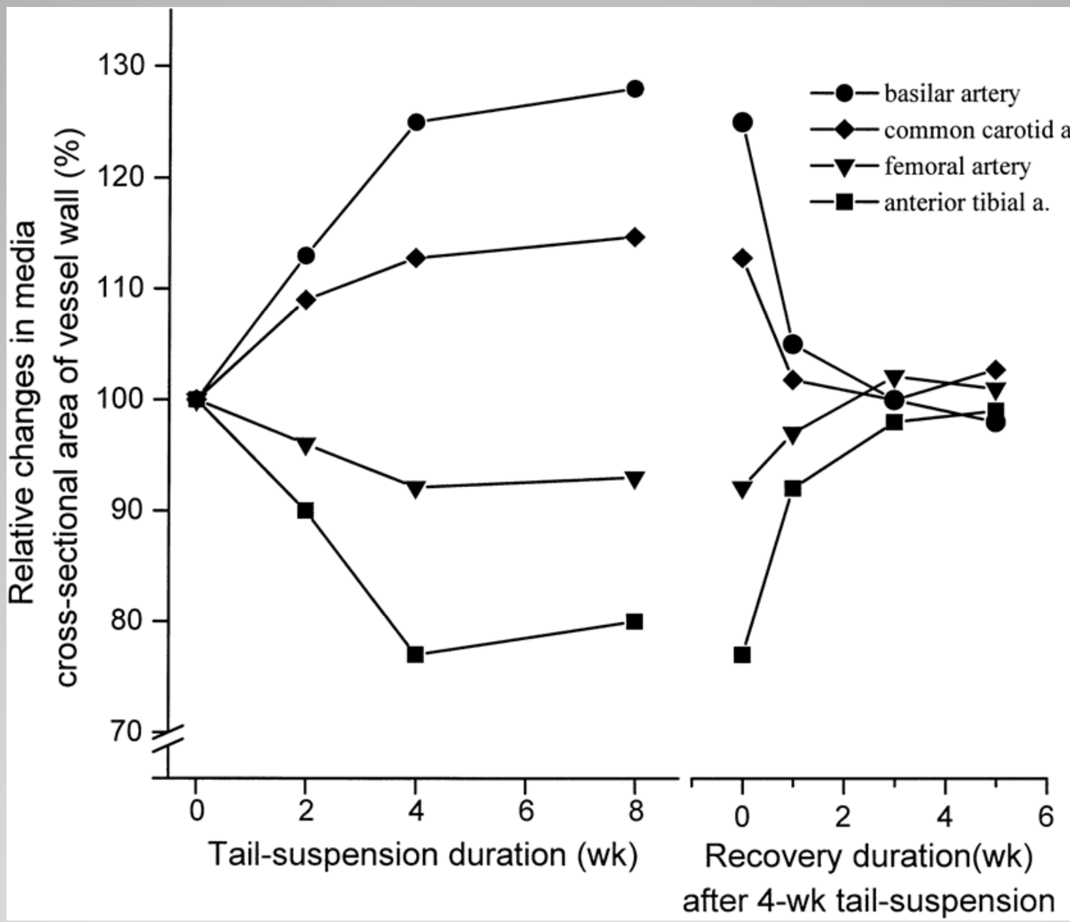
Loring B. Rowell, 1986

Rat suspended hind limb model



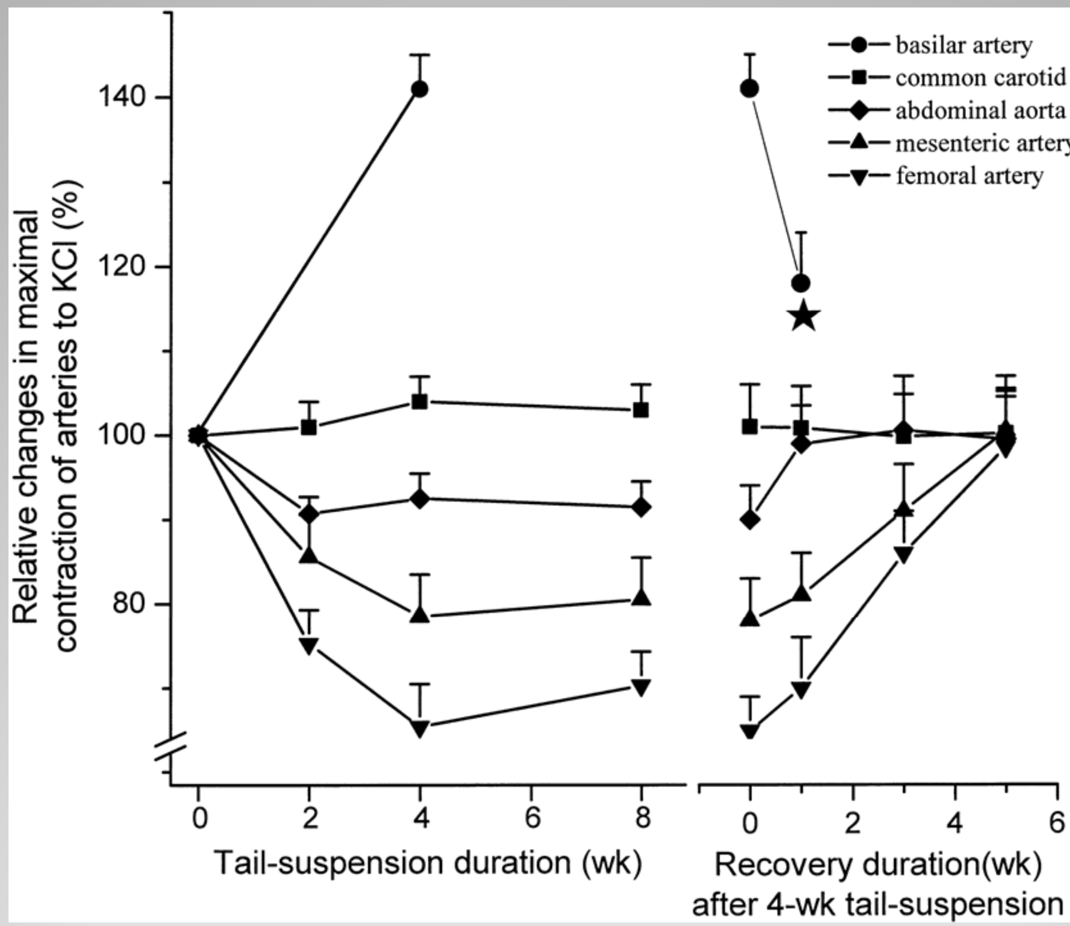
Zhang LF et. al. J Gravit Physiol. 1996;3(2):5-8

Arterial Remodeling



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

Arterial Function



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

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_2max, ml/kg/min	29.5 ± 1.9	24.7 ± 1.6

Mean ± SEM; *$p < 0.05$

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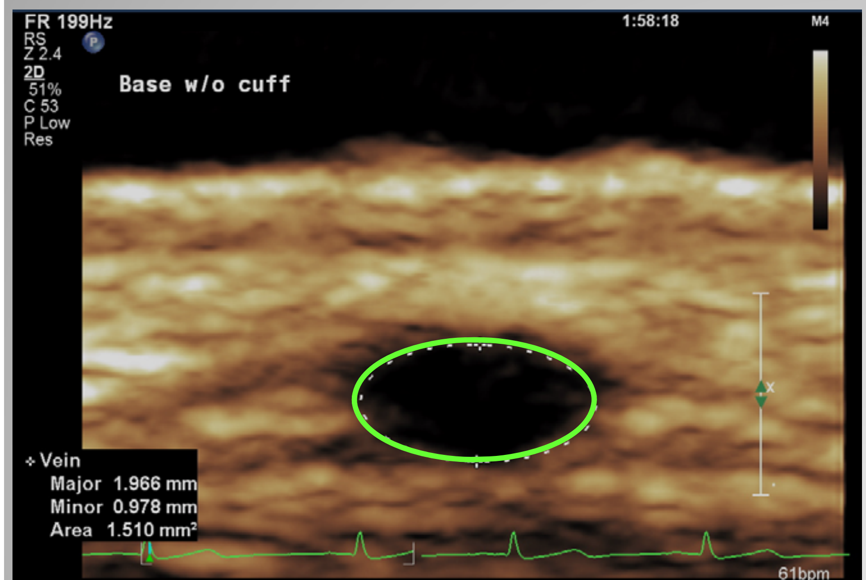
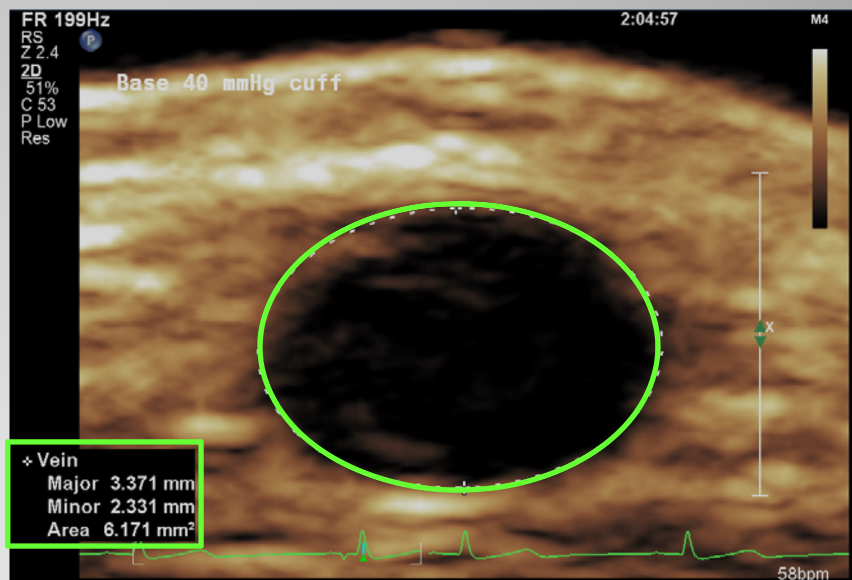
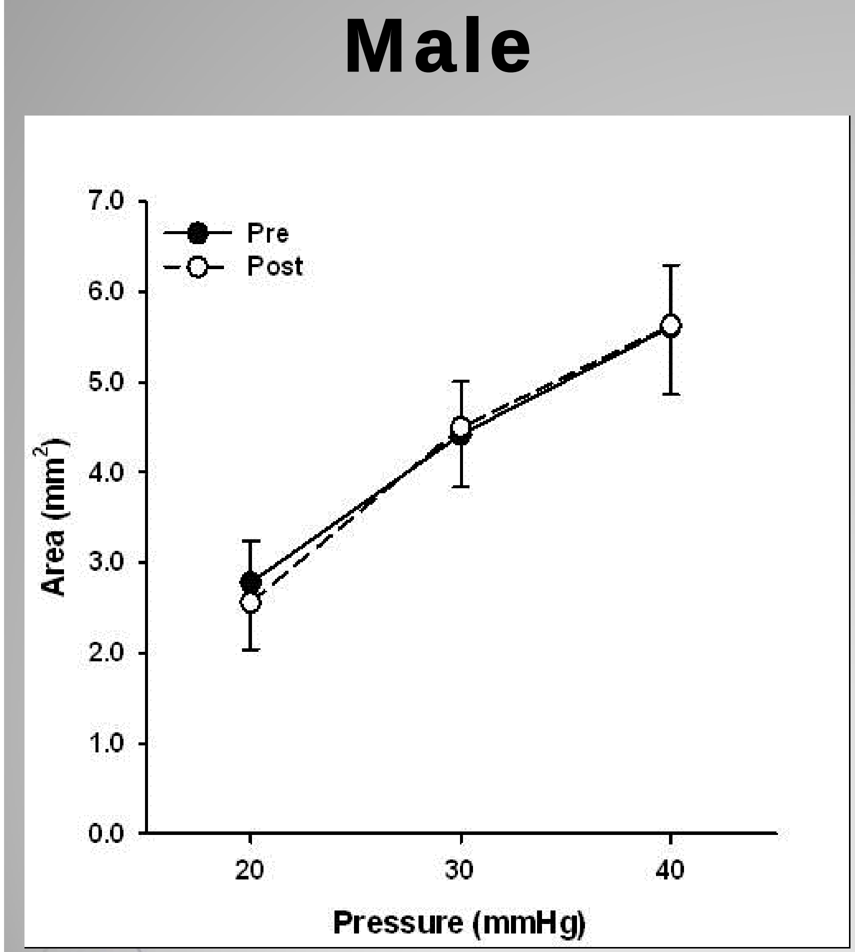
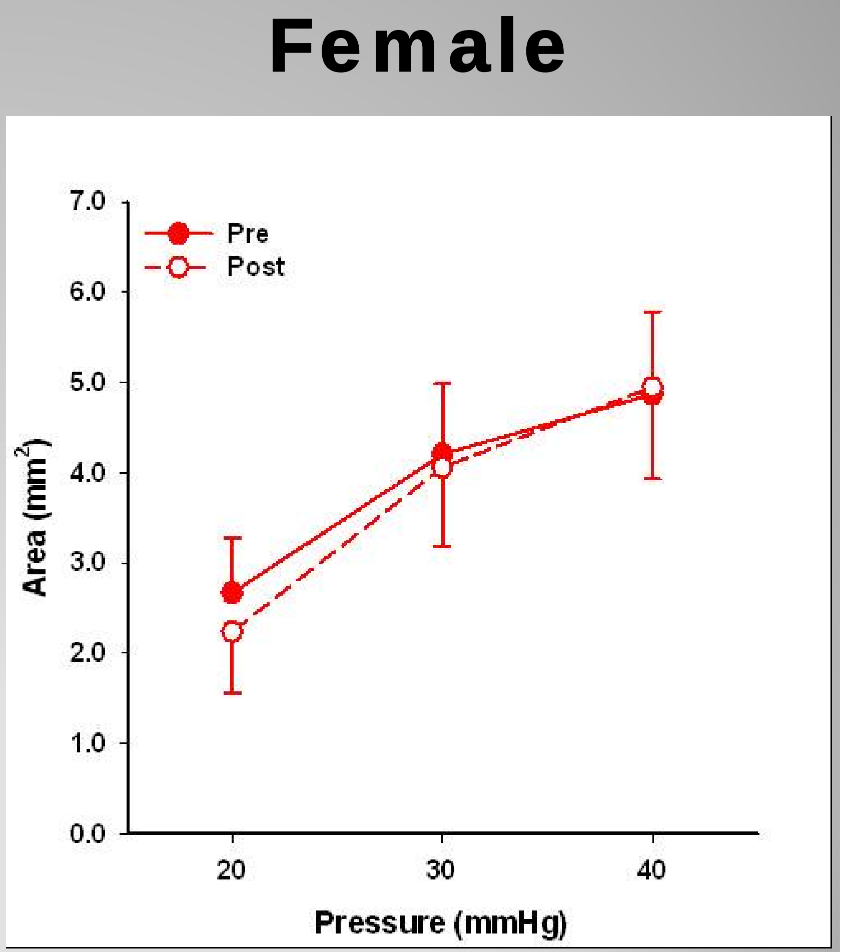
Vascular Ultrasound





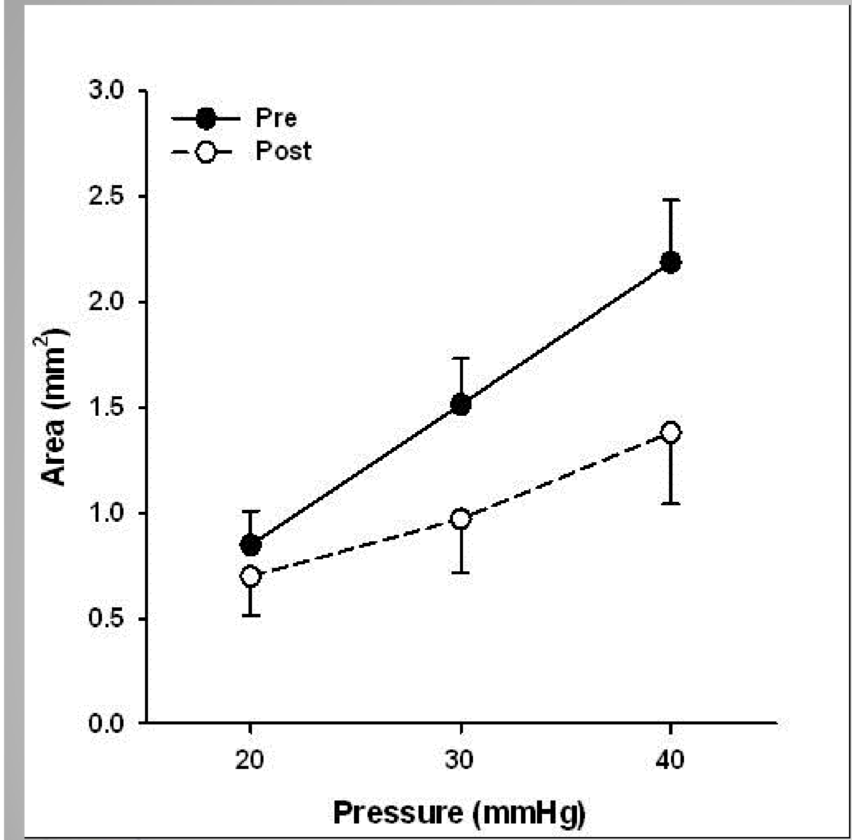
Dorsal Hand Vein



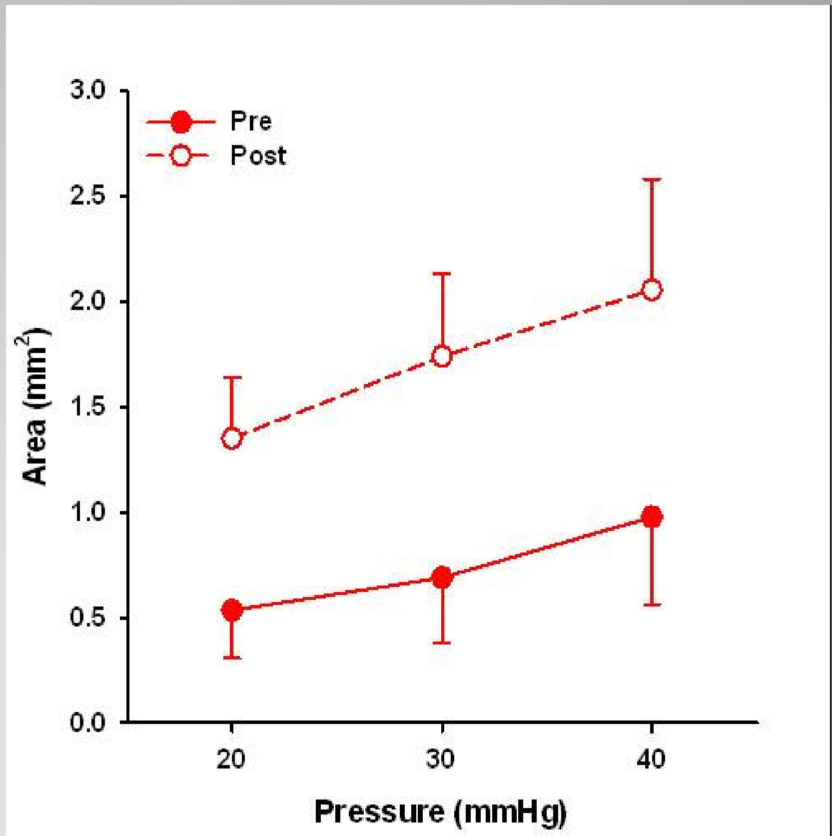


Dorsal Foot Vein

Male

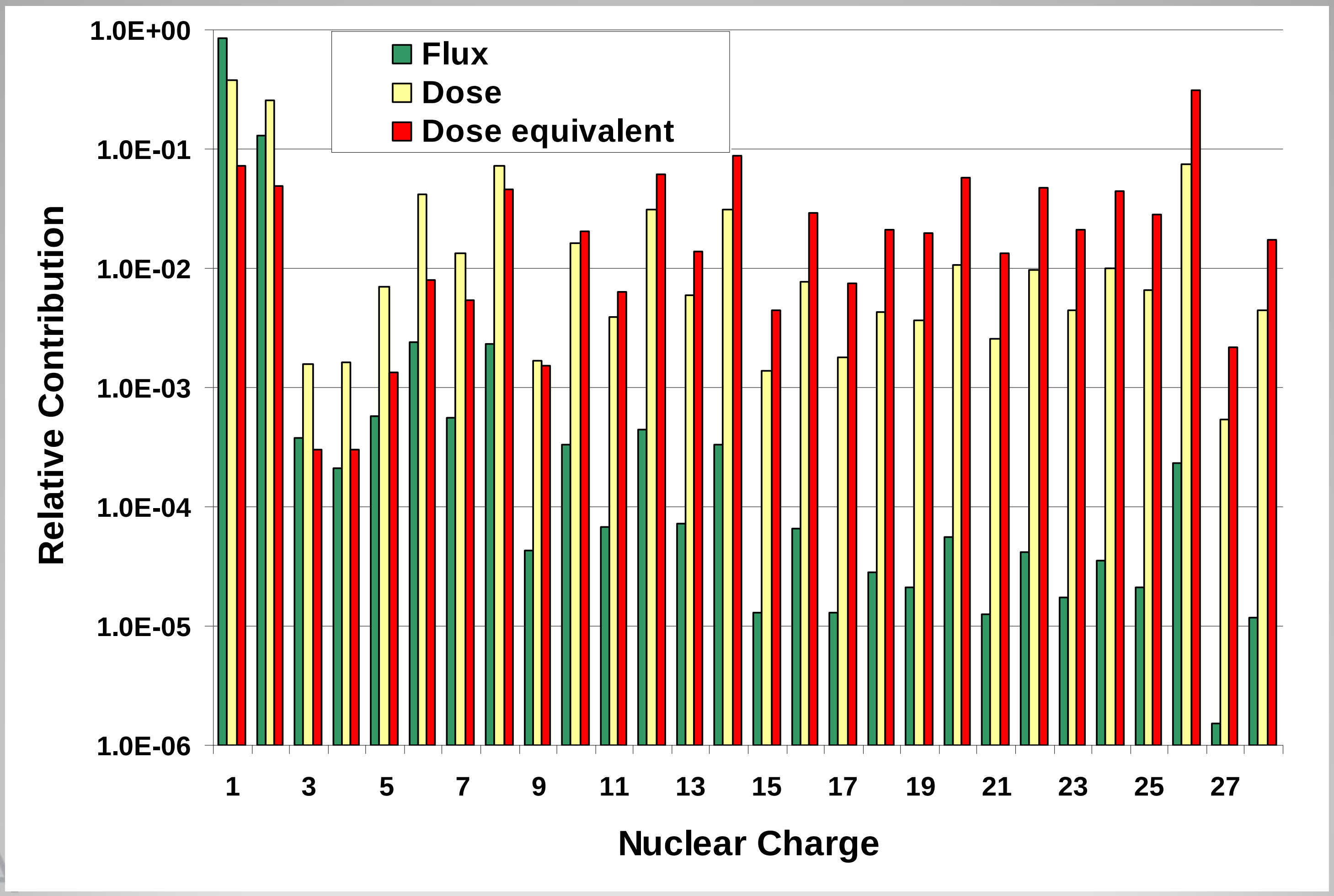


Female



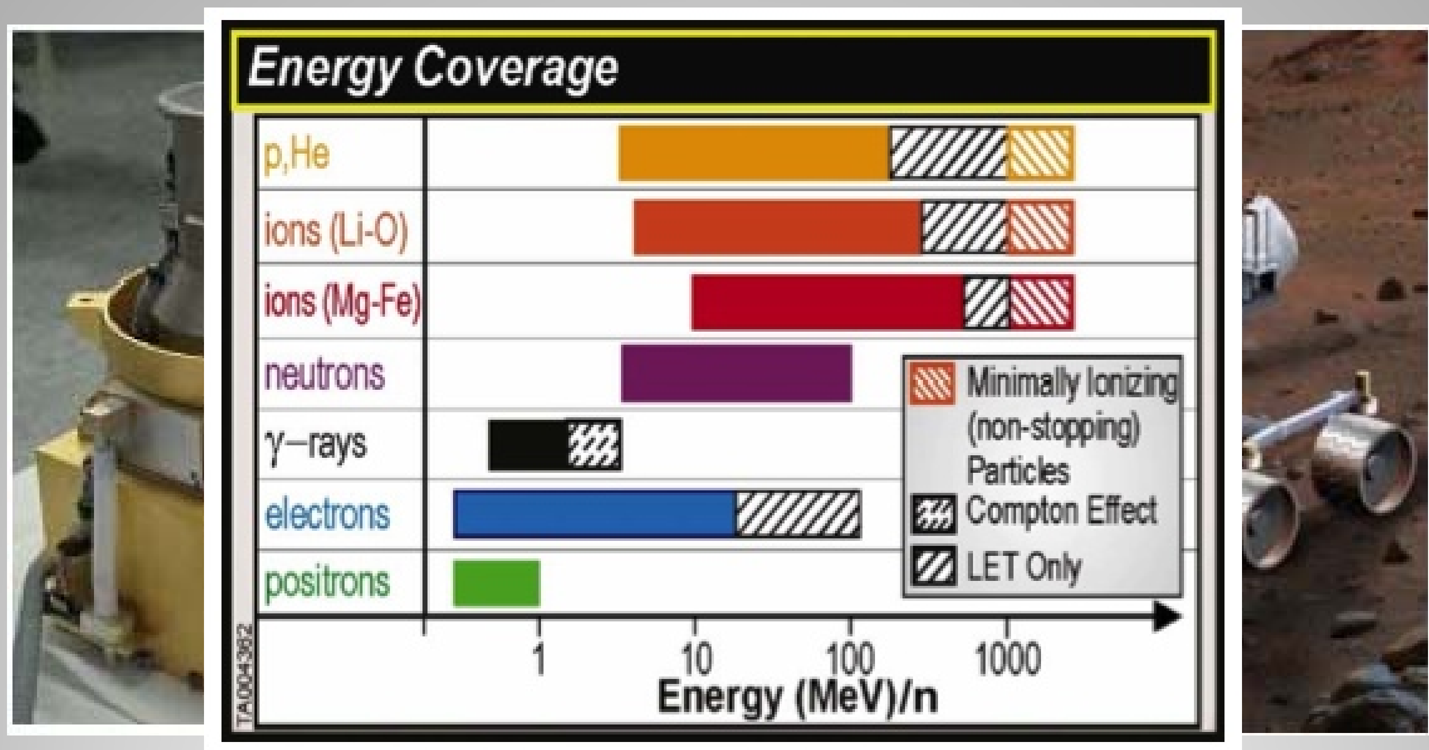

Space Radiation

Ion Species



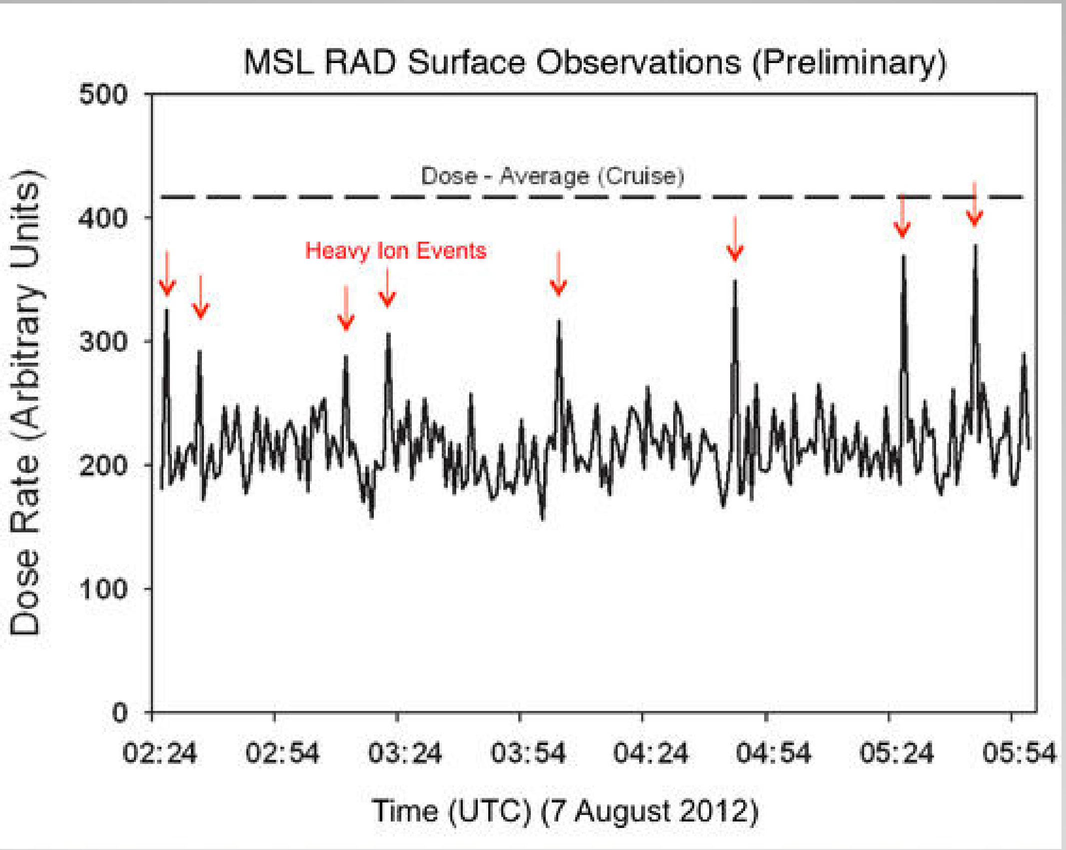
Flux
Dose
Dose equivalent
Relative Contribution
1.0E+00
1.0E-01
1.0E-02
1.0E-03
1.0E-04
1.0E-05
1.0E-06
1
3
5
7
9
11
13
15
17
19
21
23
25
27
Nuclear Charge

RAD on Curiosity



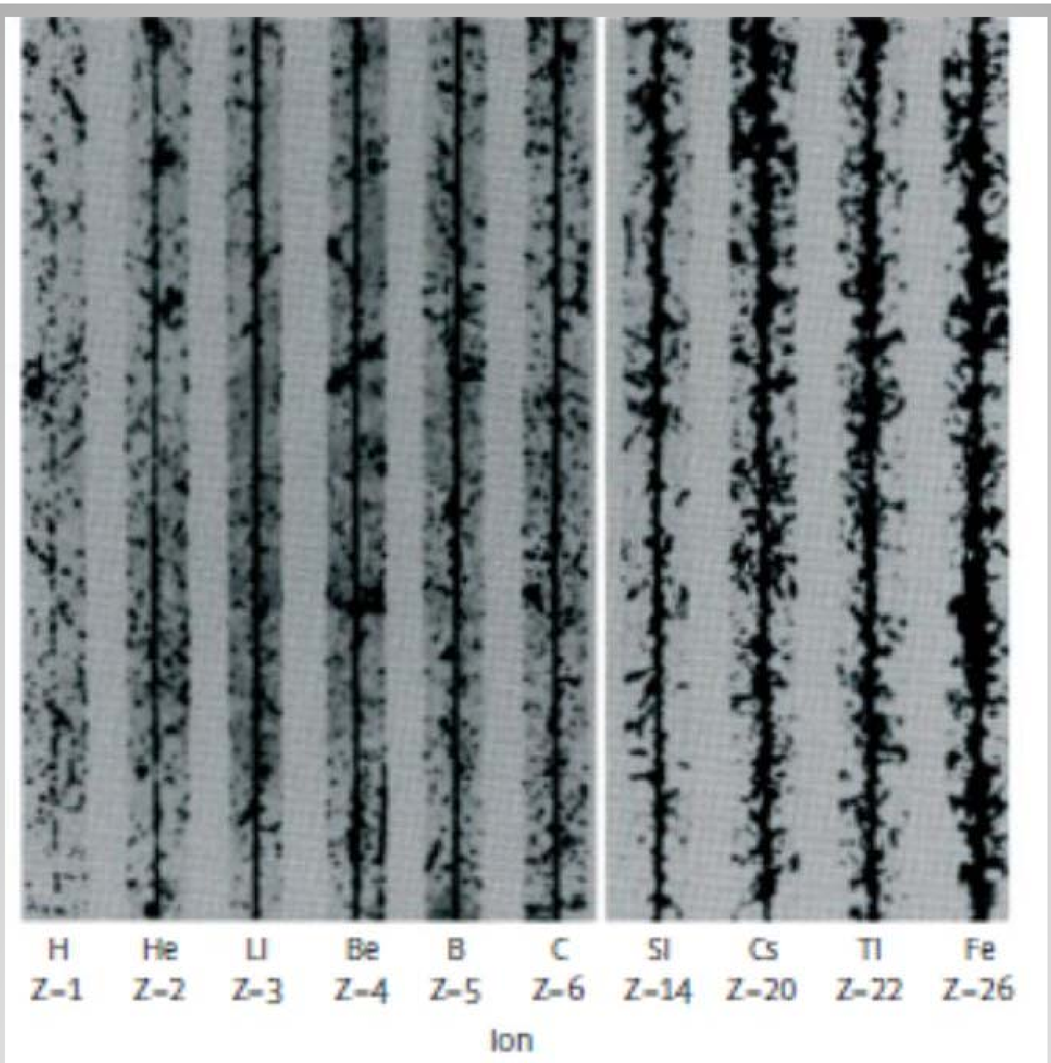
http://msl-scicorner.jpl.nasa.gov/Instruments/RAD

First Look on Mars

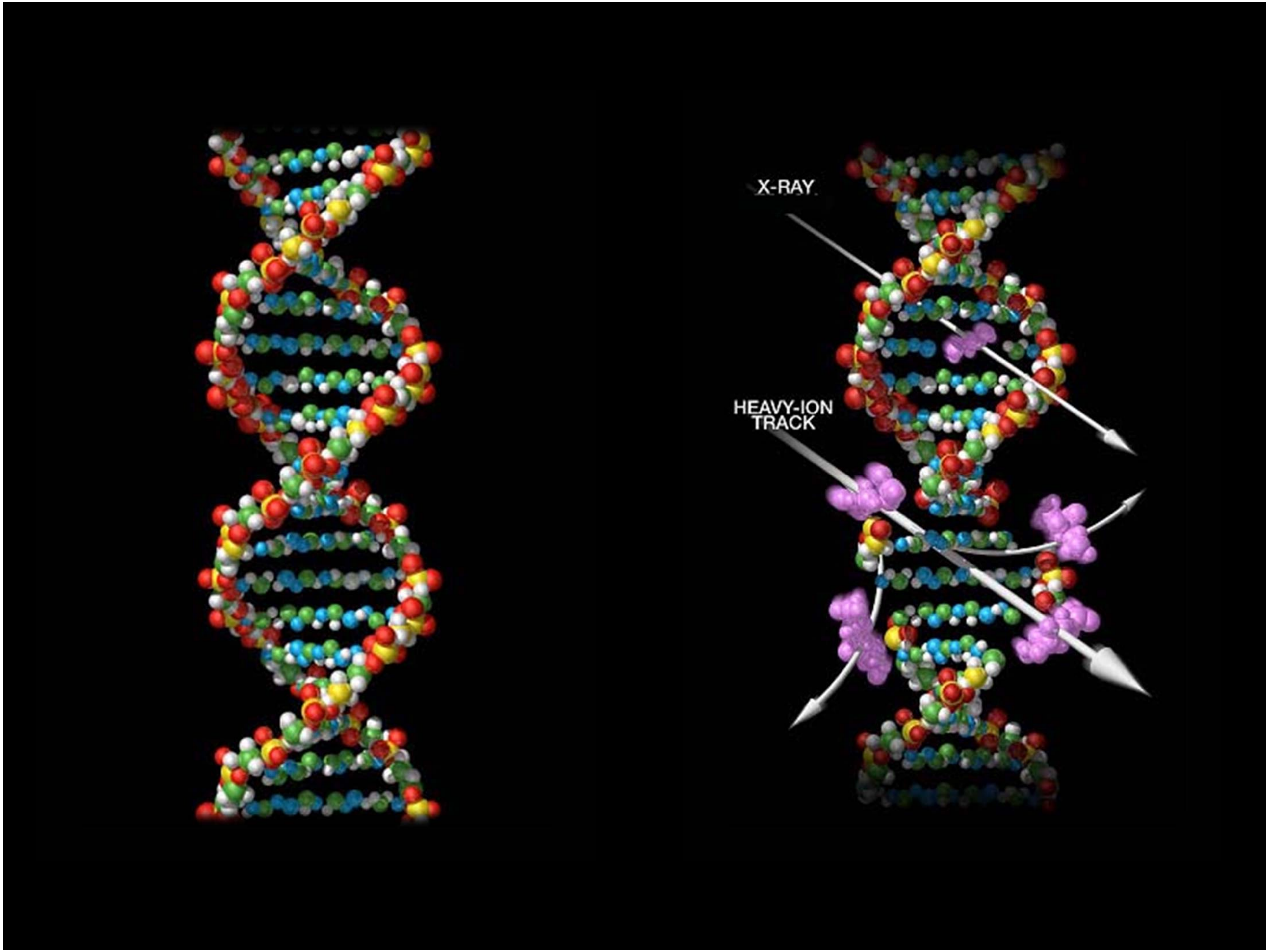


http://mars.jpl.nasa.gov/msl/mission/instruments/radiationdetectors/rad

Ion Particle Tracks

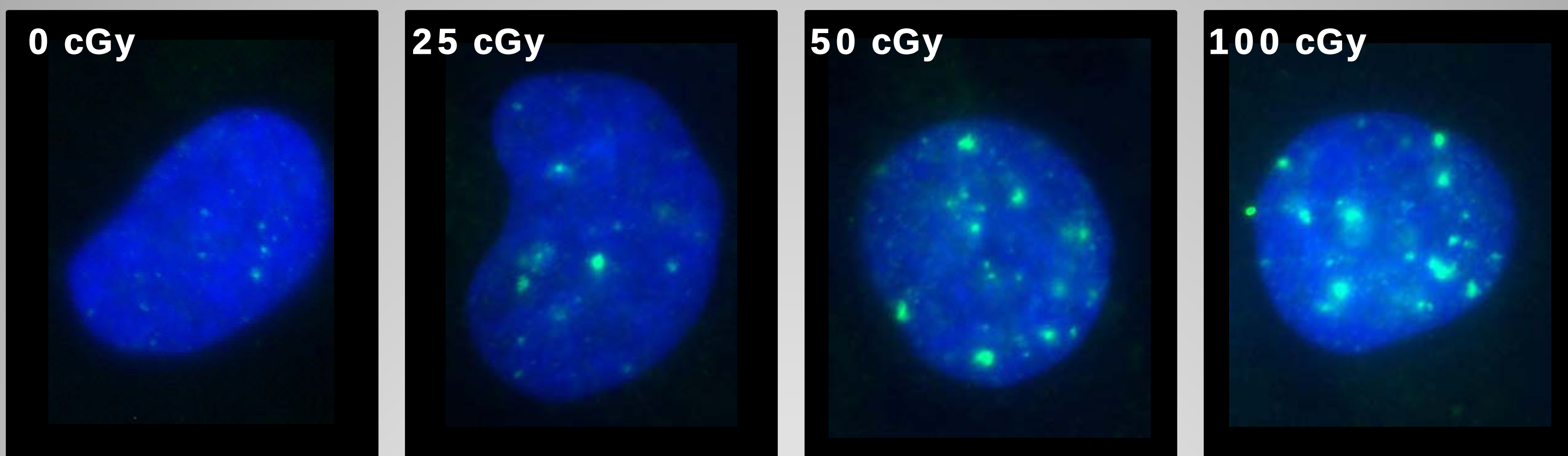


Cucinotta and Durante 2006


X-RAY
HEAVY-ION TRACK

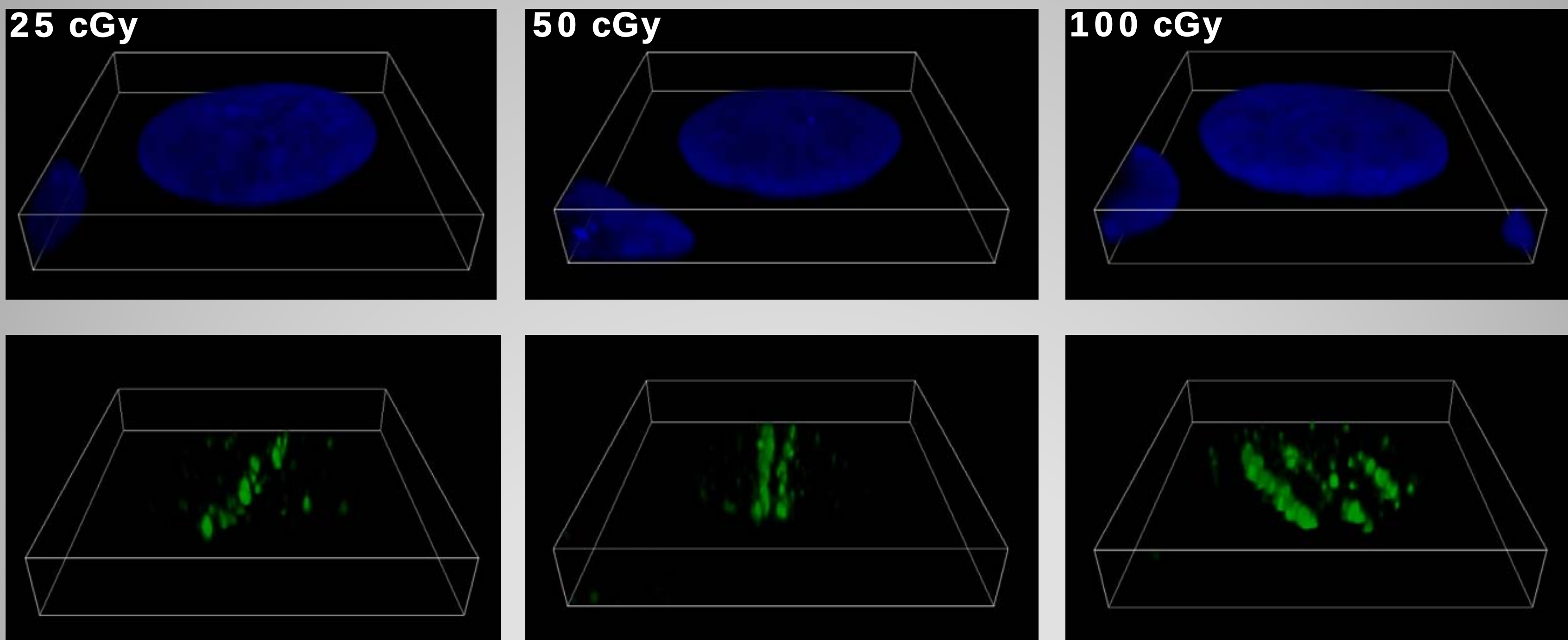
DNA Repair

^{56}Fe [600 MeV/u]

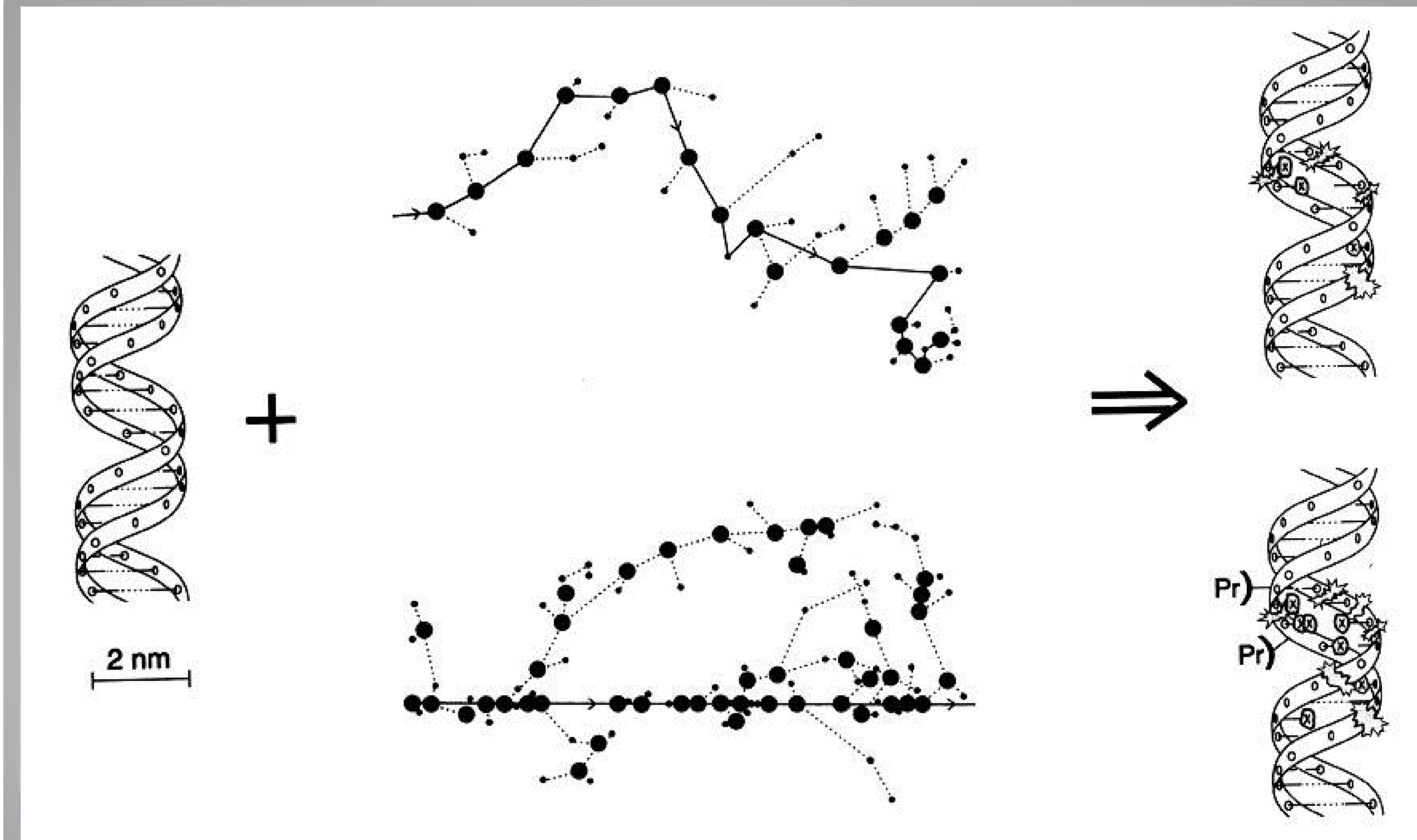


Track Structure

^{56}Fe [600 MeV/u]

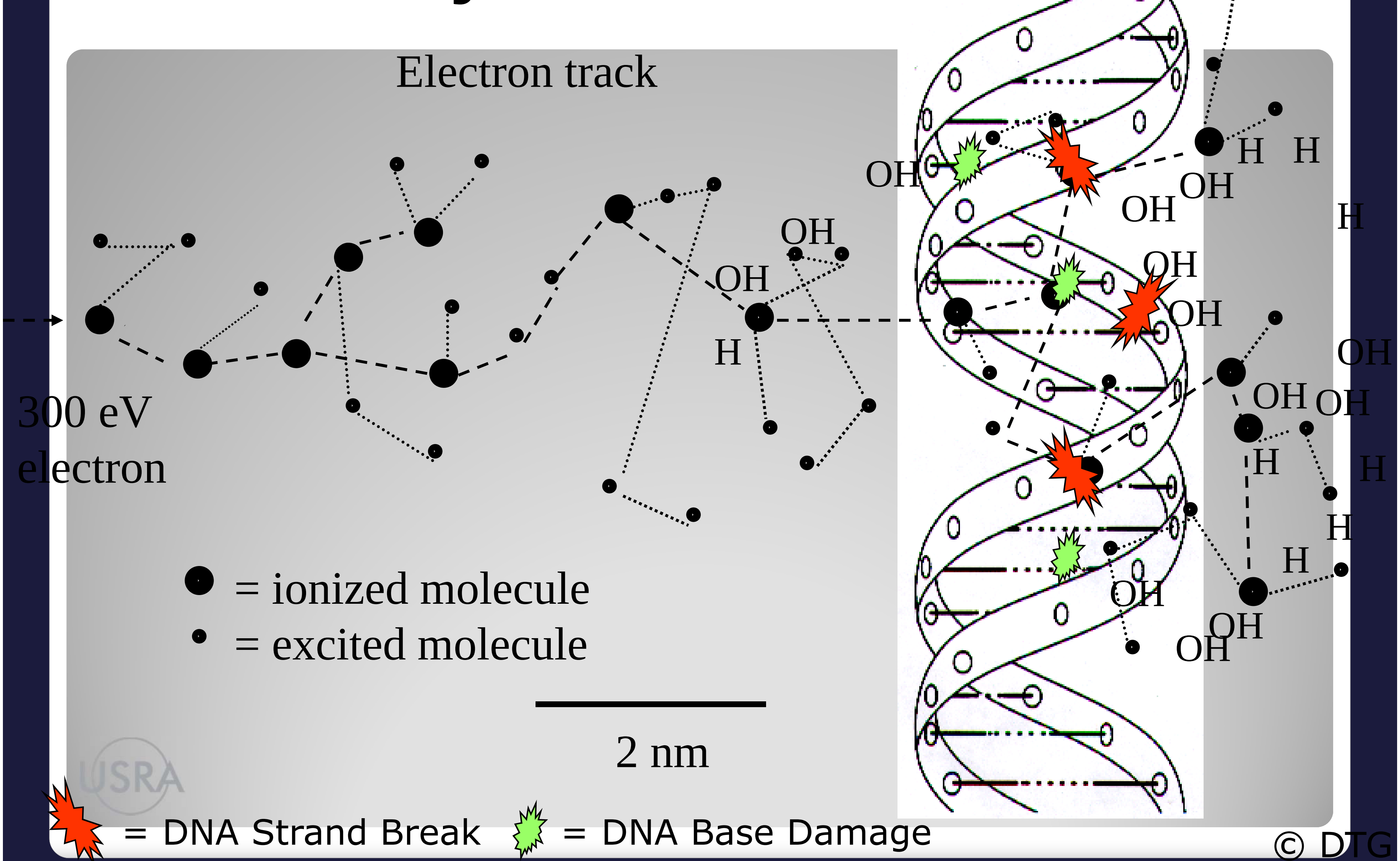


Clustered Lesions



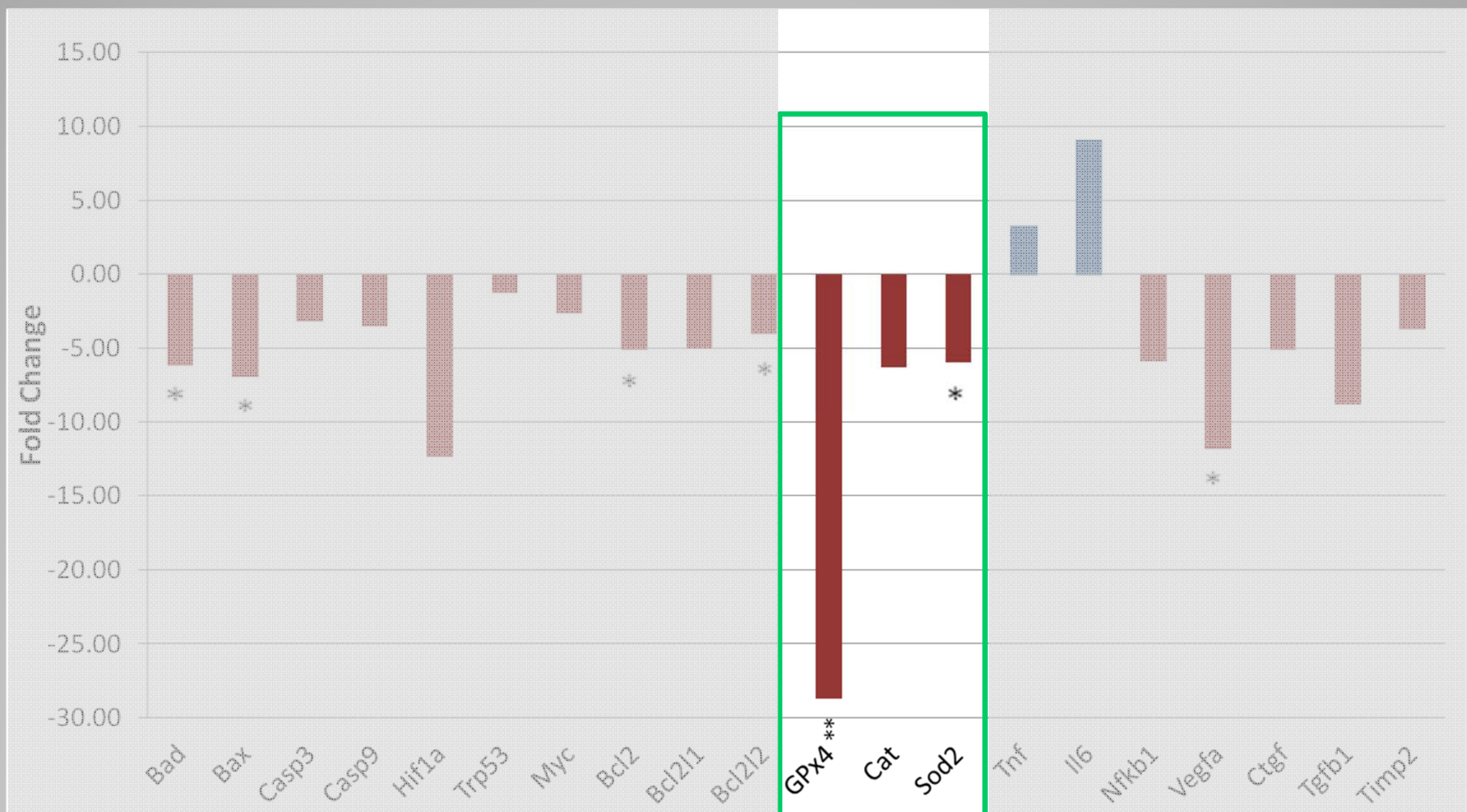
Goodhead 1994

Secondary Effects



Oxidative Mechanisms of Myocardial Tissue Remodeling in a Model of High Dietary Heme Iron Exposed to Radiation

Radiation, Oxidation, & Cardiac Myocyte

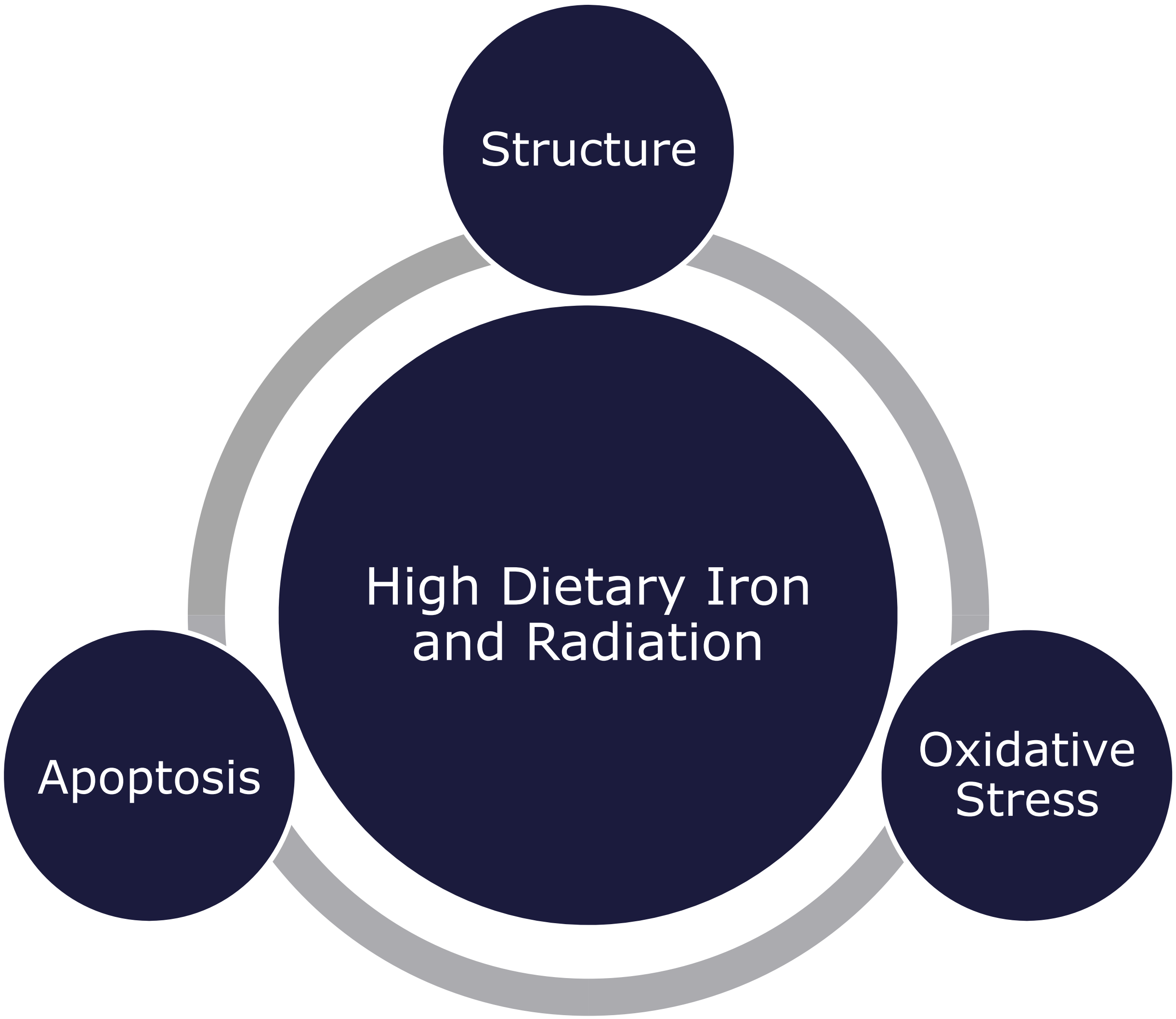


Gene expression in mice 4hr after irradiation with ^{137}Cs.
6 Gy compared to sham.

Cardiac Specific Aims

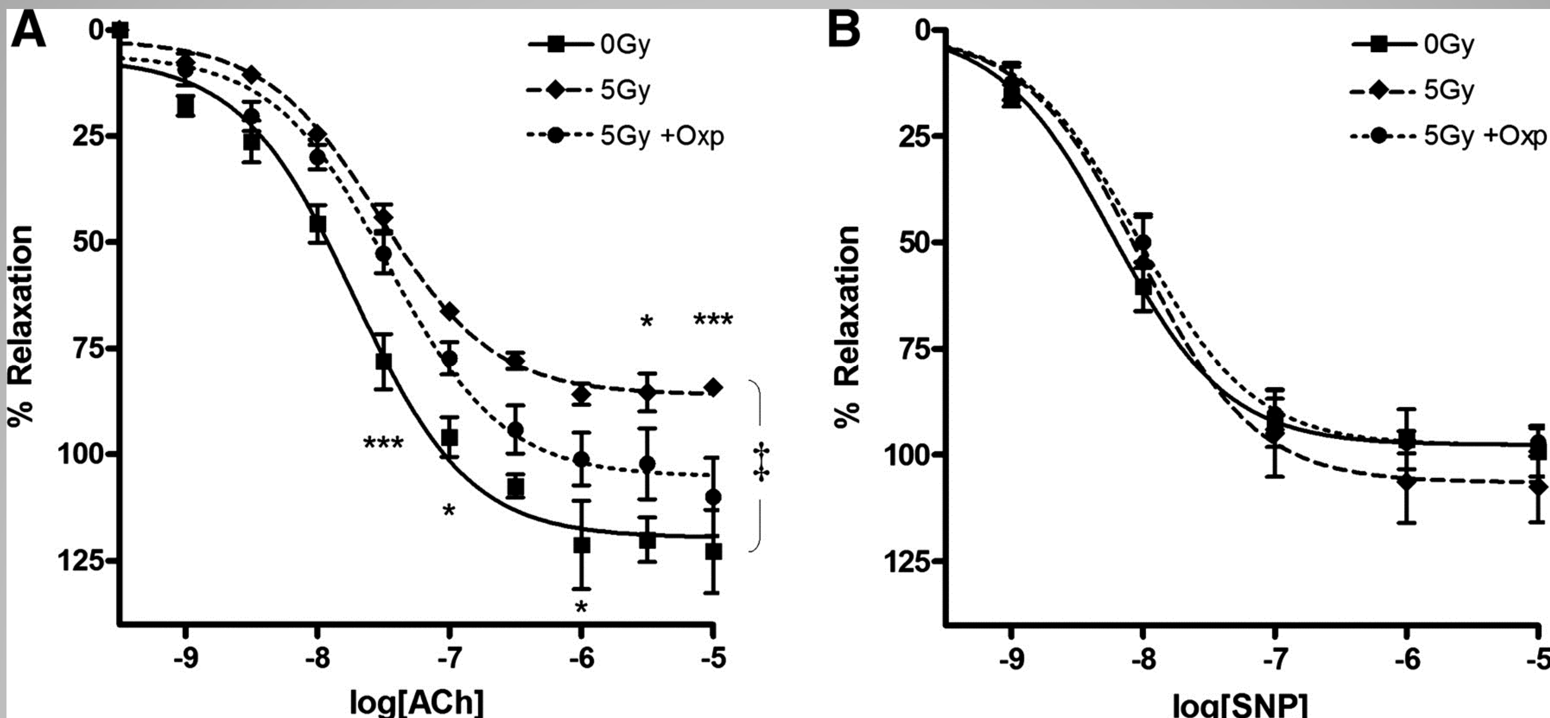
- **Aim 1:** To determine the short-term consequences of the independent and combined effects of gamma radiation and elevated body iron stores on measures of cardiac structure.

- **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.


Structure
High Dietary Iron and Radiation
Apoptosis
Oxidative Stress

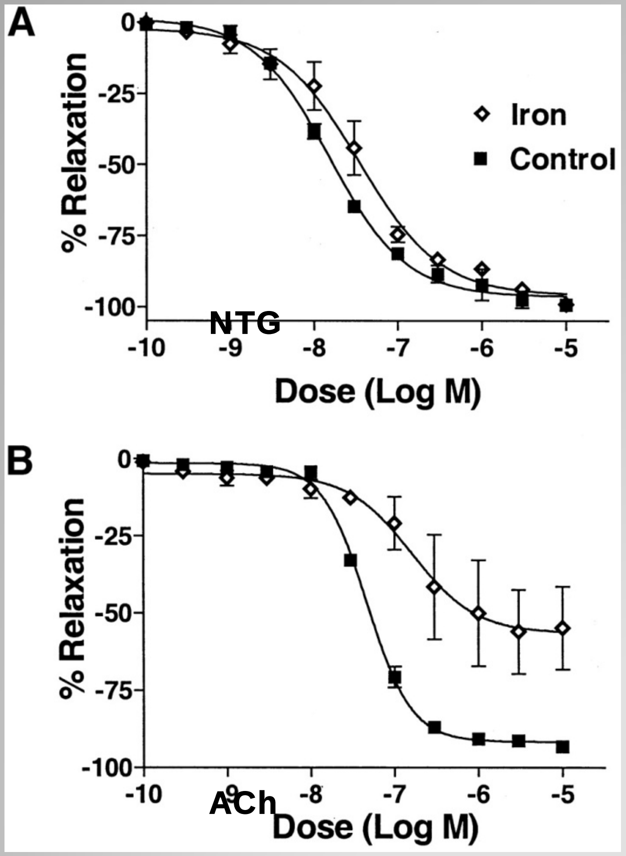
High Dietary Heme Iron Combined with Irradiation Promotes a Proatherogenic Endothelial Cell Phenotype due to Increased Oxidative Stress

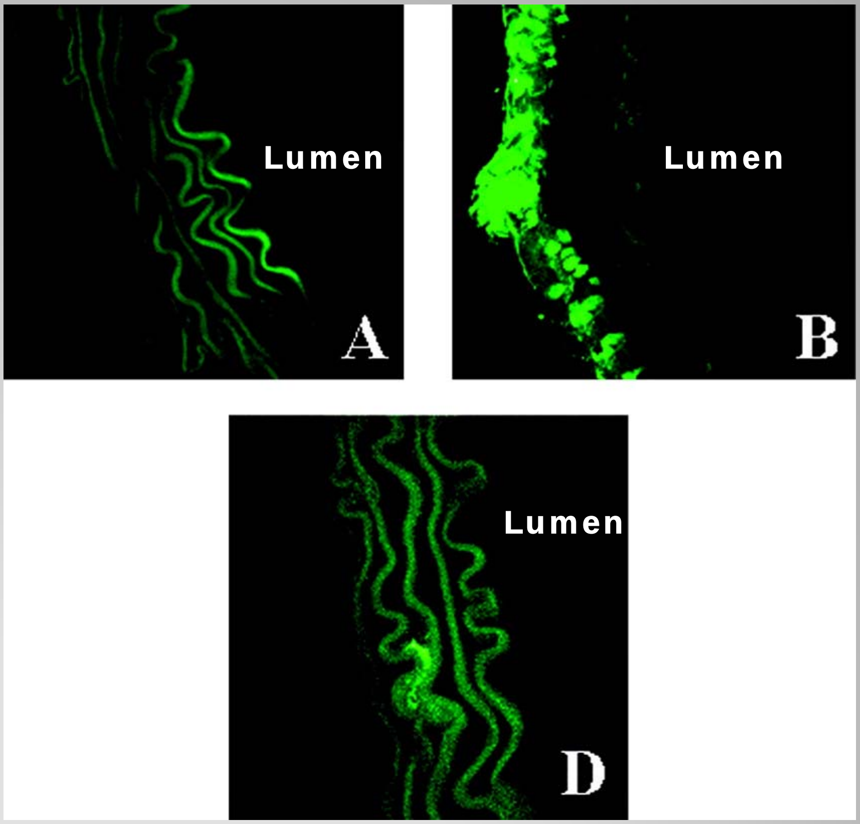
Radiation, Endothelial Dysfunction, and Oxidative Stress



Soucy K G et al. J Appl Physiol 2010;108:1250-1258

High Iron, Endothelial Dysfunction, and Oxidative Stress





Day S M et al. Circulation **2003;107:2601-2606**

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.

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Aging, Endothelial Progenitor Cell Function, and HZE Radiation

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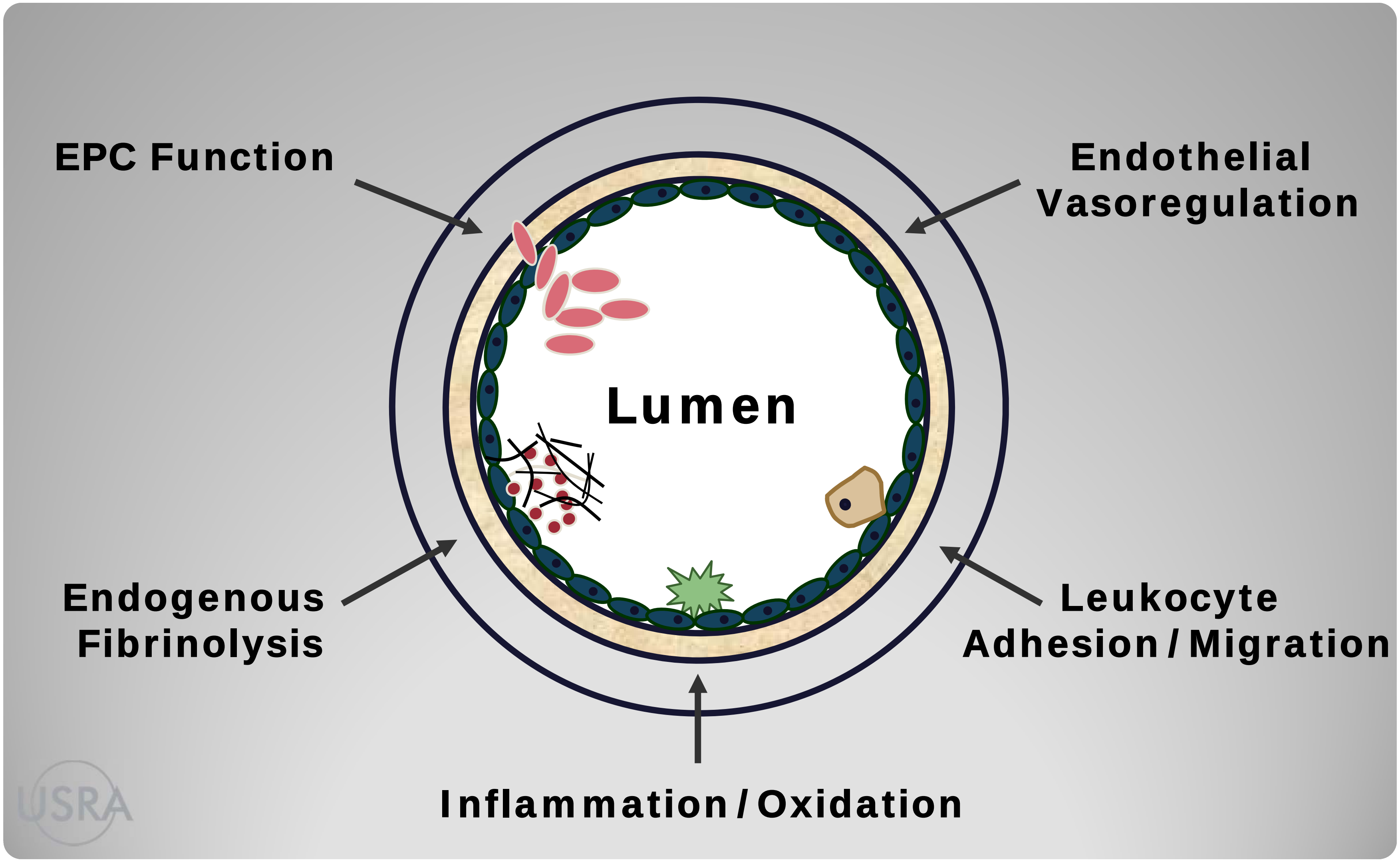
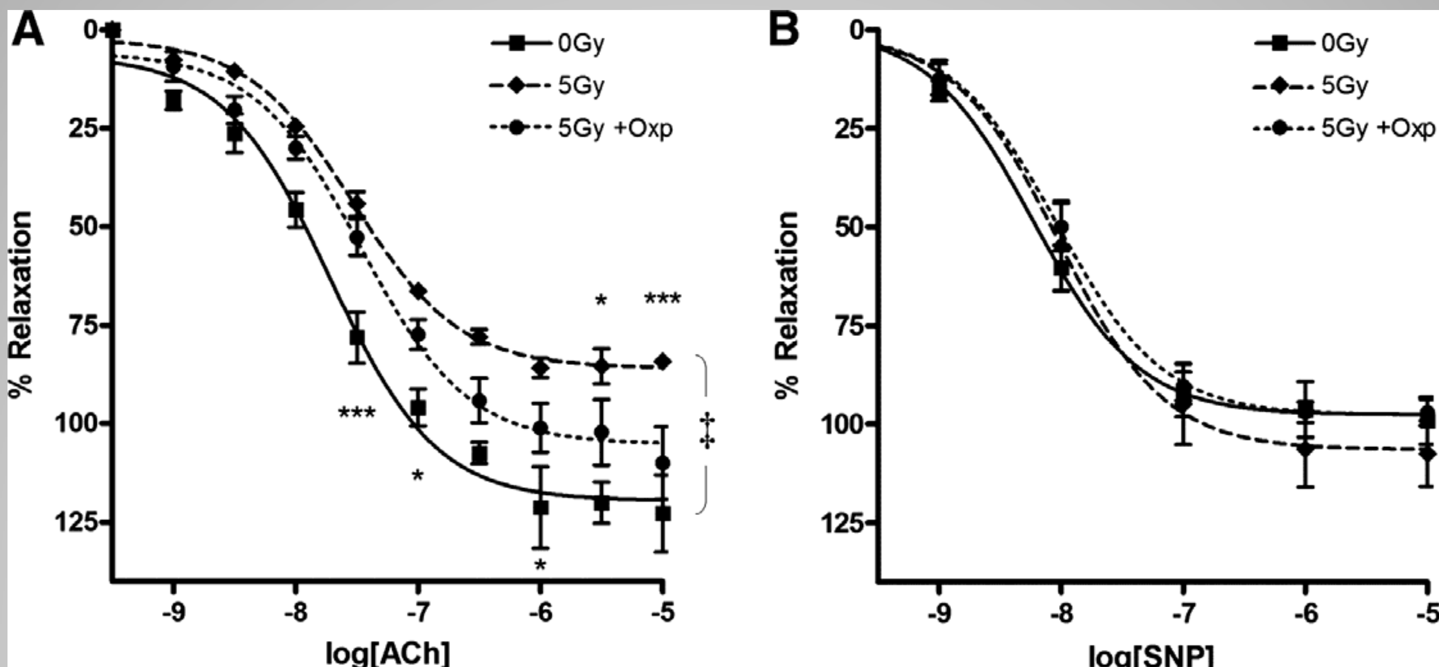

EPC Function
Endothelial Vasoregulation
Lumen
Endogenous Fibrinolysis
Leukocyte Adhesion / Migration
Inflammation / Oxidation

Radiation, Endothelial Dysfunction, and Oxidative Stress



Soucy K G et al. J Appl Physiol 2010;108:1250-1258

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.

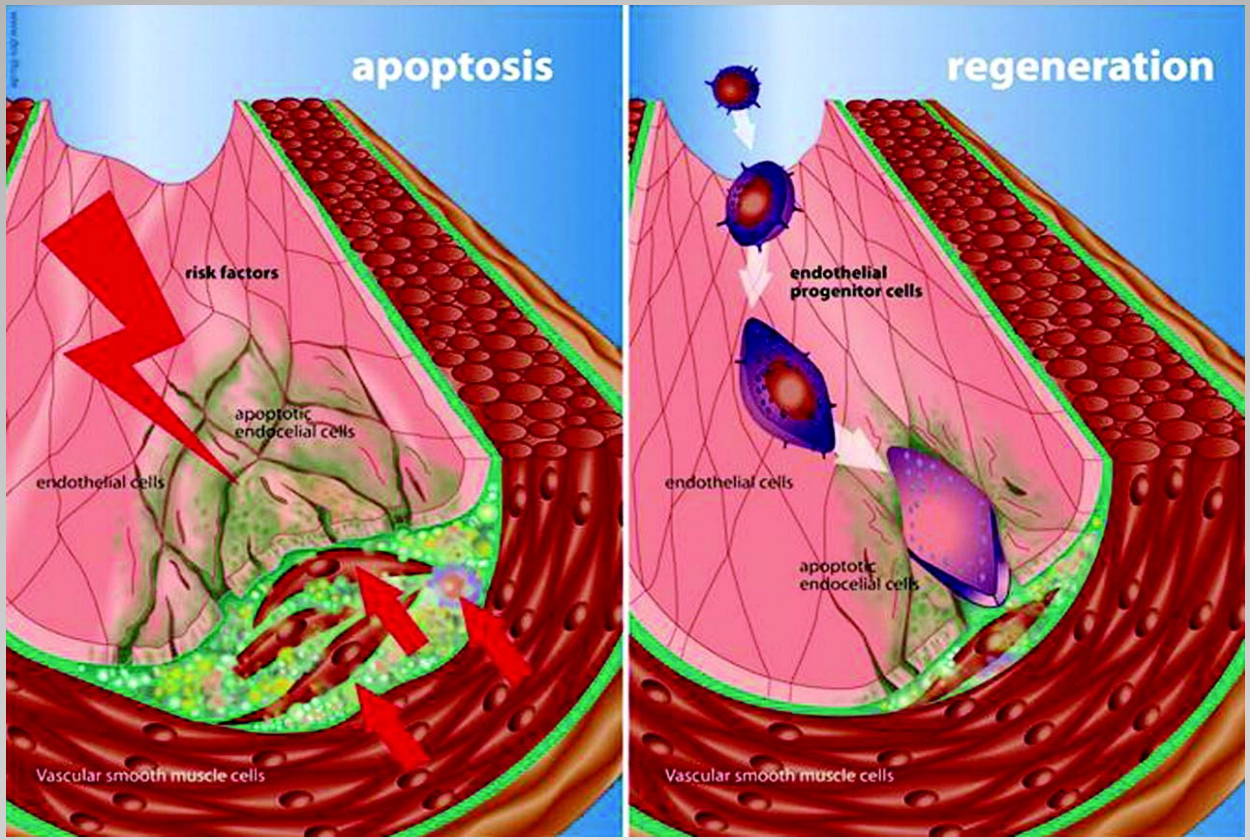
USRA

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

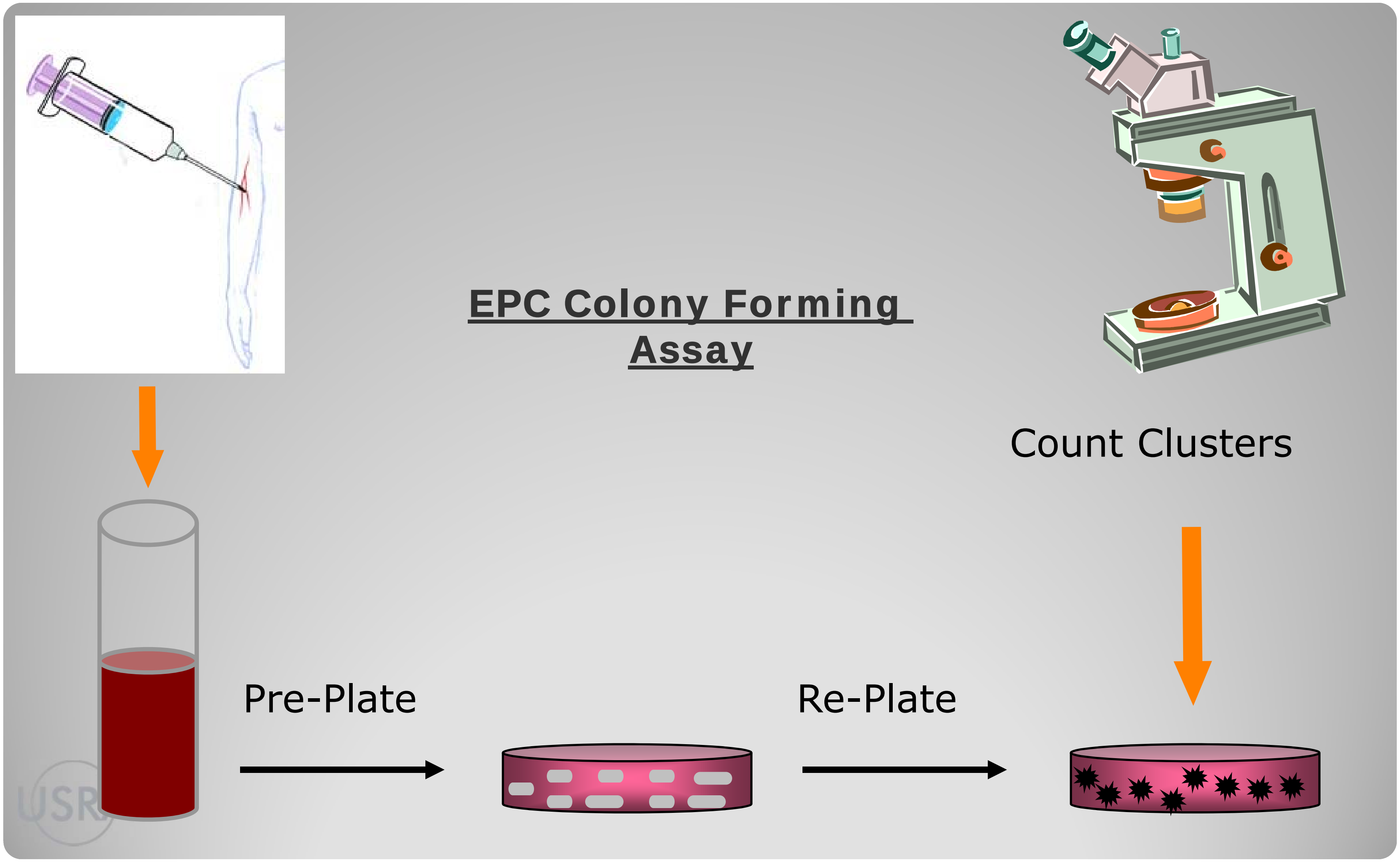


Werner, N. et al. Arterioscler Thromb Vasc Biol 2006

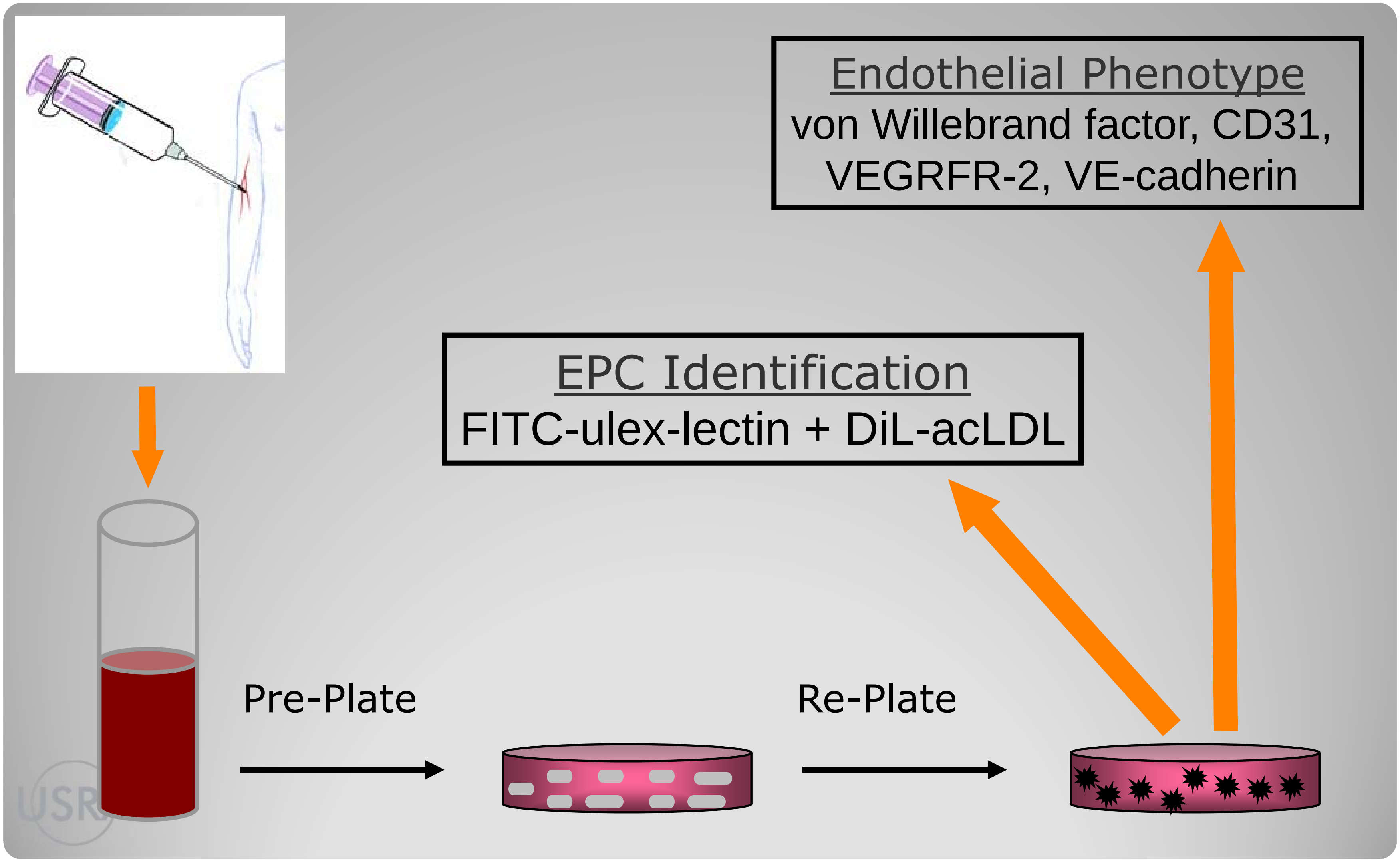
Radiation and EPC Function

- **EPC Functional Characeristics:**
  - Clonogenic Capacity
  - Migration
  - Angiogenic Growth Factor Release

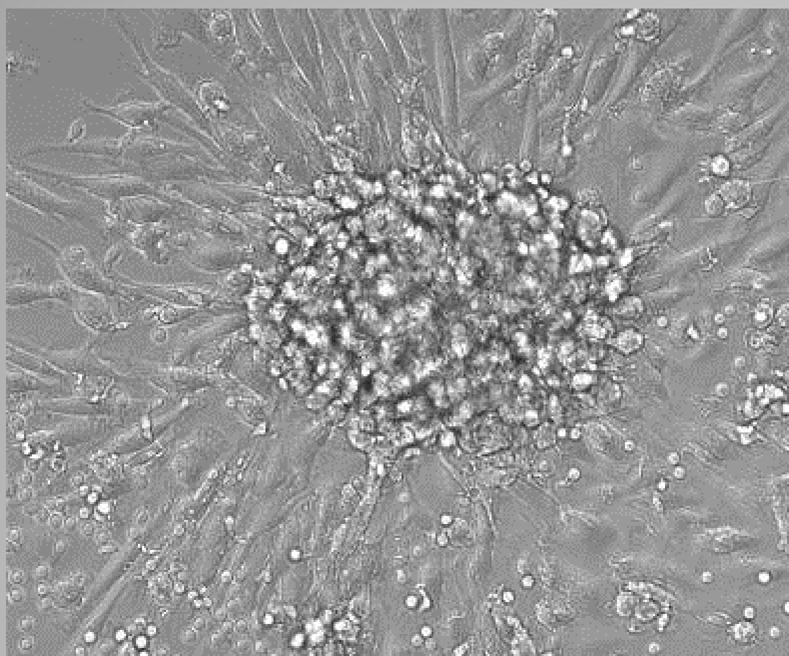
CFU Protocol



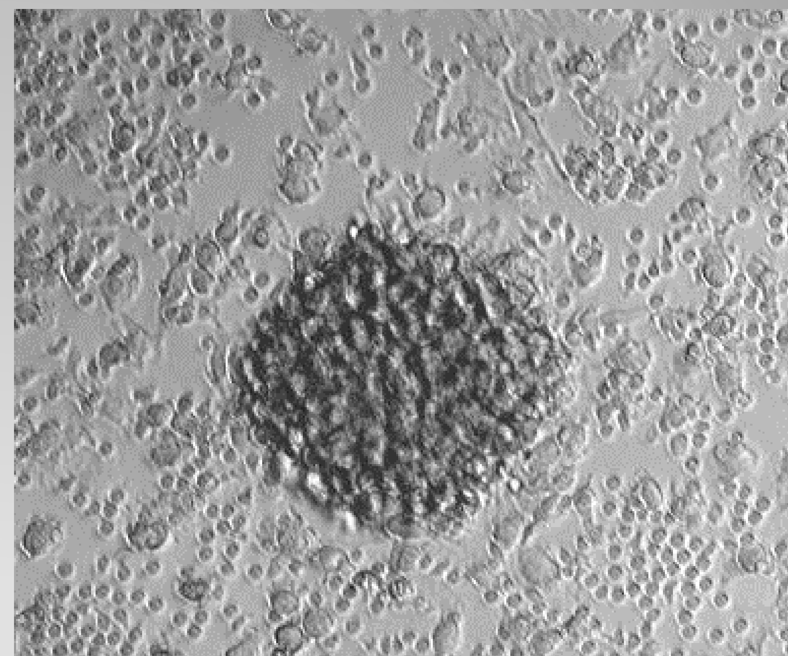
EPC Identification in Culture



Colony Examples



Counted



Not Counted

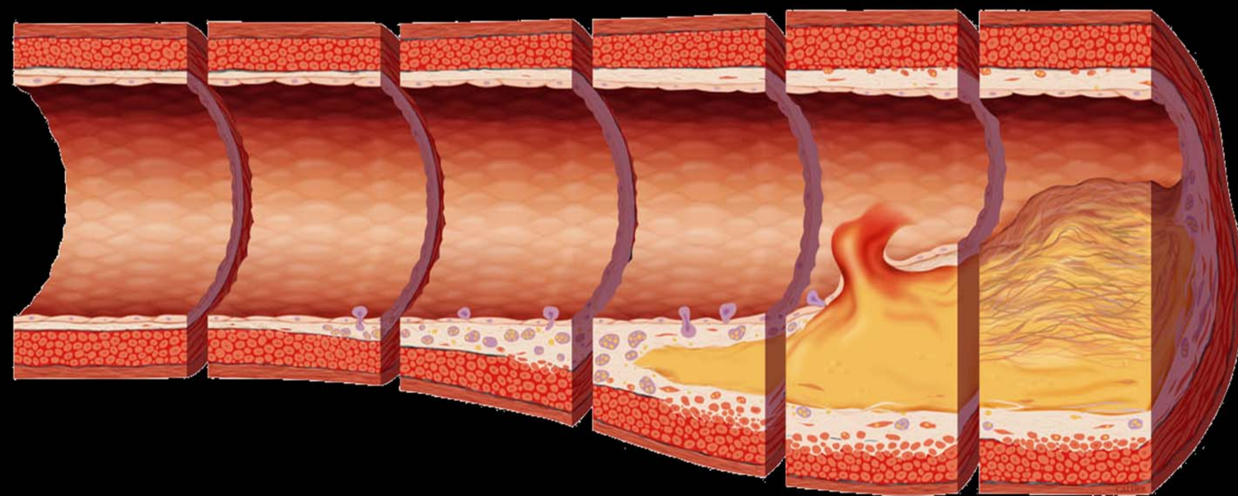
EPC Migration Protocol

Peripheral Blood Samples Collected:

Preplated for 2 days

EPC Migration: Modified Boyden Chamber

Atherosclerotic Timeline



Endothelial dysfunction →

From first decade	From third decade	From fourth decade	
Growth mainly by lipid accumulation		Thrombosis, hematoma	Smooth muscle and collagen

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

Acknowledgements

- **Cardiovascular Laboratory**
  - Sydney Stein
  - Angela Brown
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  - Sara Zwart, Ph.D.

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