Cardiovascular Alterations Team

The Multi-System Effect of Exercise Training/Nutritional Support During Prolonged Bed Rest Deconditioning: An Integrated Approach to Countermeasure Development for the Heart, Lung, Muscle and Bones
PI: Benjamin D. Levine, M.D.
Institute for Exercise and Environmental Medicine, UT Southwestern

Critical environmental limits to heat balance during extravehicular activity
PI: James A. Pawelczyk, Ph.D.
Pennsylvania State University

Radiation, Endothelial Cell Senescence, Accelerated Aging, and Atherosclerosis
PI: Art Shoukas, Ph.D.
Johns Hopkins University

Effect of high energy particle irradiation on adhesiveness of vascular endothelium and its consequences for atherosclerosis
PI: Dennis Kucik, M.D.
The University of Alabama at Birmingham
The C.A.R.D.I.A.C. Study: E 377
PIs: Benjamin D. Levine, M.D. and Michael W. Bungo, M.D.
Doug Hamilton, Smith Johnston
Consultants: Rick Page, Richard Verrier, Todd Schlegel

Cardiac Abnormalities in Rhythm and Diastolic function due to Inactivity, Atrophy and Confinement
2014 Mars Design Reference Mission Scenario (typical)

**Flight Profile**
- Transit out: 161 days
- Mars surface stay: 573 days
- Return: 154 days

**Grounded Trajectories**
- Stay on Mars Surface

**Mission Timeline**
- **Earth Departure**: Jan. 20, 2014
- **Mars Arrival**: June 30, 2014
- **Mars Departure**: Jan. 24, 2016
- **Earth Arrival**: June 26, 2016
- **Mars Perihelion**: January 22, 2013
  - December 10, 2014
Death in Space

• To date, all mortality in spaceflight due to equipment failure:
  – Apollo 1 fire 1967
  – Soyuz 1 landing 1967
  – Soyuz 11 decompression 1971
  – STS-25 Challenger explosion 1986
  – STS-107 Columbia re-entry disintegration 2003

• Just like test pilot work, or expeditions into demanding environments (Everest, Antarctica) the task itself is the main risk.
BIOLOGICAL MODEL OF SUDDEN CARDIAC DEATH

Structure
- Myocardial Infarction
  - Acute
  - Chronic
- Cardiomyopathy
  - Hypertrophic
  - Dilated
- Electrical Abnormality

Function
- Ischemia or Reperfusion
- Systemic Factors
- Neurohumoral Effects

As Adapted from Am J Cardiology 89 Myerburg et al
Causes of Sudden Death in Athletes

< 35 Years Old

1. HCM (48%)
2. Idiopathic LVH (18%)
3. Coronary Anomalies (14%)

≥ 35 Years Old

1. Coronary Disease (80%)
2. HCM (5%)
3. MVP (5%)

"autopsy negative" SCD -- ? role of genetic screening
Causes of Sudden Death in Athletes

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“autopsy negative” SCD -- ? role of genetic screening

As adapted from Barry J. Maron 1983
**Angiographic View** *(Diameter)*

100% → 50% → 25%

**Histologic View** *(Diameter)*

Normal

Glagov effect “normal lumen”

50% ↓ Diam.

75% ↓ X-Sec. Area

75% ↓ Diam.

95% ↓ X-Sect. Area
The majority of plaques that rupture are **NOT** severely narrowed and do not cause ischemia.
From Church, Levine et al, Atherosclerosis 2007
Retired NFL Football Players (N=100) with ACLS (N=40,000)

CAC score

90th% 75th% 50th% 25th%

0 <35 35-39 40-44 45-49 50-54 55-59 60-64 65-89 70-74 75-79 80+

30 35 40 45 50 55 60 65 70 75 80 85

From Church, Levine et al, Atherosclerosis 2007

All CHD Events (n=72)

Events per 1000 person-yrs

0 5 10 15 20 25 30 35

<10% 21.9

>10% 28.3

N= 1645 626 327 248 319 454

Chang et al, Am J Cardiol 2009
Can risk be mitigated by high degree of fitness?

Lamonte et al, 2006

Relative Risk of CV Event In Patients with Calcium Score >100

Exercise Capacity (METS)

Annualized Event Rate

CAC >400
CAC = 101-400
CAC = 10-100
CAC = 0-10

Can risk be mitigated by high degree of fitness?

Relative Risk of CV Event In Patients with Calcium Score >100

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<table>
<thead>
<tr>
<th>Age (5 year intervals)</th>
<th>CAC score</th>
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<tbody>
<tr>
<td>&lt;35</td>
<td>0</td>
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<tr>
<td>35-39</td>
<td>25</td>
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<td>40-44</td>
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<td>75-79</td>
<td>65</td>
</tr>
<tr>
<td>80+</td>
<td>70</td>
</tr>
</tbody>
</table>

Chang et al, Am J Cardiol 2009

From Church, Levine et al, Atherosclerosis 2007
CAC = 0 Carries **Very** Low Risk of Events (~0.5/1000 per year)

Taylor et al
JACC 2005

• Prospective
Army Coronary
Calcium (PACC)
Project
• 2,000 asx M & F
Age 40-50
• 3 yr f/u
Progression of CAC May Also Be Important

Raggi et al
Circulation 2004

- ~500 asx M & F, age 50 – 70
- two scans; 3 yr f/u
- all received a statin after 1st scan
MDCT Can Detect Features of Vulnerable Plaque

Motoyama et al, JACC 2007
Problems with Multi-Detector CT Angiography

1. Requires slow heart rate (often give β-blockers);
2. High radiation doses (prospective ECG gating may help);
3. Requires large dose of contrast (nothing will help);
4. Difficult to quantify/no prospective data;
5. Expense!
   • what are the cutpoints for treatment? (size of plaque and necrotic core, thinness of cap, amount of remodeling, etc.)
   • where to look in the coronary tree?
   • when is invasive therapy indicated (in asx patient)?
37 yo woman
11 years after XRT
For Hodgkin's Disease
Summary: Iron ion and proton irradiation of vascular endothelium affects subsequent adhesion of monocytic cells

Dennis F. Kucik, MD, Ph.D, et al.
University of Alabama at Birmingham and Birmingham Veterans Administration Medical Center

- Radiation causes inflammation, and chronic, low-level vascular inflammation is a risk factor for atherosclerosis.
  - Consistent with increased risk of cardiovascular disease among radiation-therapy patients, atomic bomb survivors, and early radiation techs (prior to 1950)

- At least part of the inflammatory response to radiation is a change in the adhesiveness of the endothelial cells that line the blood vessels
  - This triggers inappropriate accumulation of white blood cells, which can set off an inflammatory cascade

**Hypothesis:** Radiation of the type encountered on deep space missions alters the adhesive properties of vascular endothelium, and resultant vascular inflammation accelerates atherosclerosis.

**Approach:**
- Irradiate endothelial cell monolayers to determine the effect of radiation on cell adhesion
- Irradiate mouse aortic arches and carotids to determine the effect of radiation on development of atherosclerosis

**Results:**
- Both iron ion and proton irradiation of aortic endothelial cells
  - Increases surface expression of specific adhesion molecules
  - Increases endothelial cell adhesiveness for monocytic cells
    - Greatest effect is not at the highest radiation dose
      - Suggests mechanism other than simple cell surface damage
- Experiments with whole mice are underway to determine whether development of atherosclerosis is accelerated

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**Figure 1:**
- Total adhesion of monocytes to proton-irradiated endothelial cells
- Control, 0.50 Gy, 2 Gy

- Total adhesion of monocytes to \(^{56}\text{Fe}\)-irradiated endothelial cells
- Control, 2 Gy, 5 Gy
RESULTS: The DHE fluorescence rate in the aorta segments of rats exposed to 1 Gy was significantly greater than that of control rats (8.45e-5±0.733e-5 sec^{-1} versus 4.84e-5±1.29e-5 sec^{-1}, p<0.05). Furthermore, 30 minutes of Oxp incubation significantly attenuated the DHE response in irradiated aorta.

RESULTS: Following 10^{-5}M ACh administration, aortas of 0Gy rats demonstrated a 25% fluorescent rate increase from baseline slope (125±8.42%), while aortas of the 1Gy-irradiated rats have a negligible response (97.0±6.22%). Dietary XO inhibition elevated this response significantly, compared to untreated, 1Gy irradiated rats (159±19.4%, *P<0.05). The SNP response between groups is similar, implying that DAF-FM loading is consistent and sufficient.

RESULTS: In the study of chronic XO inhibition, rats exposed to 100cGy radiation possessed a significantly elevated PWV (4.45±0.244 m/sec, n=8) from 0cGy-exposed rats (n=10, P<0.01) and 100cGy Oxp-diet rats (n=6, P<0.05). The PWV measurements in 0cGy and 100cGy+Oxp rats are not statistically different.

RESULTS: Sham irradiated rats (n=8) produced maximal relaxations of 86.7±2.40%. Rats receiving Oxp drinking water demonstrated a vasorelaxation improvement (93.1±6.71%, n=6) from sham rats and 100cGy-exposed rats (79.0±3.00%, n=8). These data were fit with sigmoidal dose-response equation. Comparing the fits with F test analysis indicates that the maximal responses and fitted curves are statistically different between treatment groups (P<0.05).
RESULTS: The aorta of 5Gy irradiated rats demonstrate a significantly elevated XO activity from controls (*\(P<0.05\), unpaired Student \(t\) test). Remarkably, this activation is abolished by Oxp dietary inhibition (**\(P<0.01\), unpaired Student \(t\) test), endothelium removal (#\(P<0.05\), paired Student \(t\) test), and allopurinol treatment (‡\(P<0.001\), paired Student \(t\) test). Total XO+XDH activity was not significantly affected by radiation or Oxp diet. As a result, the aortic XO:XDH activity ratio was increased by 5Gy-radiation, whereas Oxp treatment significantly reduced the ratio (***\(P<0.001\), unpaired Student \(t\) test).
1. Spaceflight is a risky business - but if the astronaut's environment is secure, coronary disease is the biggest lifethreatening medical risk;

2. Current screening strategies make the risk of flying an astronaut with subclinical disease small;

3. Space radiation exposure may inflame the coronary arteries, potentially accelerating atherosclerosis;

4. We are working on strategies to quantify this risk, and develop preventive approaches.
...And yet there is no sign of humans in this picture, not our reworking of the Earth's surface, not our machines, not ourselves. From this vantage point, our obsession with nationalism is nowhere in evidence.

The *Apollo* pictures of the whole Earth conveyed to multitudes something well known to astronomers: *On the scale of worlds--to say nothing of stars or galaxies--humans are inconsequential*, a thin film of life on an obscure and solitary lump of rock and metal.
...But for us, it's different. Look again at that dot. That's here. That's home. That's us. On it everyone you love, everyone you know, everyone you ever heard of, every human being who ever was, lived out their lives.

...The aggregate of our joy and suffering, thousands of confident religions, ideologies, and economic doctrines,... every hero and coward, ...every mother and father,... every "superstar", “supreme leader", saint and sinner in the history of our species lived there--on a mote of dust suspended in a sunbeam.
...Think of the rivers of blood spilled by all those generals and emperors so that, in glory and triumph, they could become the momentary masters of a fraction of a dot...

There is perhaps no better demonstration of the folly of human conceits than this distant image of our tiny world. To me, it underscores our responsibility to deal more kindly with one another, and to preserve and cherish the pale blue dot, the only home we've ever known