Cardiovascular Markers and HIV

“Yep, son, we have met the enemy and he is us!”
Pogo to Porky (as written by Walt Kelly), 1971

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CVD, Inflammation, and Aging

General issues concerning age-related decline in function

How long should we live?
Forces that have shaped our genetic architecture


Atherosclerosis as a Model for Age-Related Functional Decline: Key aspects

<table>
<thead>
<tr>
<th>Process</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Translocation to media</td>
<td>Driven at least in part by Mass Action; mechanism(s) uncertain</td>
</tr>
<tr>
<td>Lipid retention</td>
<td>Driven at least in part by GAGs;</td>
</tr>
<tr>
<td>Lipid modification</td>
<td>Driven at least in part by oxidative stress;</td>
</tr>
<tr>
<td>Activation of innate immunity</td>
<td>System in balance?</td>
</tr>
</tbody>
</table>

Yes: no atherosclerosis
No: progression to activation of adaptive immunity and atherosclerosis

Very rapid: explosive development of atheroma → vulnerable plaque & MI
More slowly: chronic development of sclerosis → heart failure

The interplay of atherothrombosis and plasma risk markers

Association of Markers of Inflammation With Chronic Disease

The “Inflammation Hypothesis” of Chronic Disease and Aging

1. In providing a necessary “interface” to the environment, “inflammation” can result in damage.
2. The better our responses and/or the more environmental stress to which we respond, the more damage we do.
3. We trade short-term benefit for long-term damage; a good trade from an evolutionary standpoint
Humans as integrated organisms: a decline in one system affects all
Is vascular decline of particular importance?

"Longevity is a vascular question, which has been well expressed in the axiom: 'a man is as old as his arteries.' William Osler, 1892.

**HEALTH**

**VASCULATURE**
- Provision of Nutrients
- Removal of Waste
- Pump function (arterial emptying)

**HEART**
- Pump function (arterial filling)

**LUNG**
- Provision of key nutrient: O2
- Elimination of CO2 waste

**KIDNEY**
- Elimination of waste
- RAS function
- Fluidic control

**BRAIN**
- Cognitive function
- Endocrine function

**SKELETON**
- Structure
- Hematopoiesis
- Source of pain

**PANCREAS**
- Digestive function
- Key endocrine function

**THYROID**
- Metabolic regulation

**LIVER**
- Coagulation
- Detoxification

**ADIPOSE TISSUE**
- Energy storage
- Endocrine function

**THYMUS**
- Immune Function

There's a lot of vascular disease in the elderly

<table>
<thead>
<tr>
<th>Controls</th>
<th>Incident Angina</th>
<th>Incident MI</th>
<th>Incident Stroke</th>
<th>CVD-free</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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Increased Inflammation in the Elderly:
Are Diseases of Older Age the Cause?

Is Vascular Disease Particularly Important?

Four Levels of “Inflammation” Affecting Circulating Biomarkers and Mediators

1. Remodeling Associated With Growth / Aging: Initially improved organ function, but in older age decreased organ function; cause?

2. Physiology-Enabled: adiposity, insulin resistance

3. Wound Repair: decreased organ function (e.g., scar tissue)

4. Response to Chronic Pathogenic Stimulation:
   - viral infections, e.g., HIV-based lymphatic fibrosis
   - lipid infiltration, e.g., atherosclerosis
   - toxin exposure, e.g., alcoholic cirrhosis, cigarette smoke

5. Response to the Presence of Disease:
   - Atherosclerotically damaged blood vessels → inc. coagulation

Bone Remodeling: a Model for a Lifetime of Change?

- In bone remodeling, we resorb and replace ~10% of our skeleton/year;
- Other tissues are slower (brain) or faster (intestinal epithelium);
- Overall rates in all tissues: ??
- This is inflammation too....
Inflammatory Cytokines Go Up with Age

InChianti: Information on inflammatory markers, cardiovascular risk factors, and diseases was collected in 595 men and 748 women sampled from the general population (age, 20-102 years).

Figure 1: Mean values of inflammatory markers according to sex and age group, expressed as number of standard deviations from the population mean, male; female. * p <0.05, ** p <0.01, *** p <0.001. Adiposity-related proinflammatory changes in the young start at an early age.

Adiposity-related proinflammatory changes in the young start at an early age

<table>
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<tr>
<th>BOYS</th>
<th>GIRLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1070.2</td>
</tr>
<tr>
<td>SBP median</td>
<td>1070.2</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>1070.2</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1070.2</td>
</tr>
<tr>
<td>Leptin</td>
<td>1070.2</td>
</tr>
<tr>
<td>HMW</td>
<td>1070.2</td>
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Correlation Coefficients Between LnCRP and CVD Risk Factors
Boys & Girls 3 to 17 Years of Age in NHANES 1999 to 2000

Ford ES. Circulation. 2003;108:1053-1058
Jarvisalo et al., ATVB 22:1323, 2002

Little/No Increase with Age After Adjusting for CVD

Age regression coefficients and their 95% CIs estimated from linear models predicting level of inflammatory markers:
• "a" estimates the crude affect of age;
• "b" is adjusted for cardiovascular risk factors;
• "c" is also adjusted for subclinical cardiovascular diseases;
• "d" is adjusted for CHD, CHF, stroke, PAD, COPD, diabetes, hypertension, osteoporosis, CFR, cancer, dementia, and depression.

R² values reported below the confidence interval are for the model used to estimate the age regression coefficients.

Ferrucci et al., Blood. 2005;105: 2294-2299

Fibrinogen and CRP are independent biomarkers of early mortality in elderly men

Cardiovascular Health Study: N ~2500 men >65 years at baseline
The outcome is CVD mortality within 3 years of baseline

Heart rate ~ 20

Hazard Ratio

Type 2 diabetes
Congestive Heart Failure
Some cancers (short “lead times”)
Cognitive decline
Frailty
All-cause and CVD Death
All chronic diseases of old age?

Association of Markers of Inflammation With CVD Risk
SMART Case – Control Study

<table>
<thead>
<tr>
<th>Sampling Point</th>
<th>Biomarker</th>
<th>Deaths, Median (25th, 75th)</th>
<th>Controls, Median (25th, 75th)</th>
<th>Difference p-Value* after Log</th>
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<tr>
<td>Week 0</td>
<td>CRP (ng/ml)</td>
<td>4.24 (2.97, 8.74)</td>
<td>3.21 (1.88, 8.18)</td>
<td>0.70 (0.70)</td>
</tr>
<tr>
<td></td>
<td>D-dimer (ug/ml)</td>
<td>3.48 (2.77, 8.30)</td>
<td>2.95 (2.14, 4.50)</td>
<td>0.53 (0.53)</td>
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<td>IL-6 (pg/ml)</td>
<td>3.40 (2.77, 8.30)</td>
<td>2.95 (2.14, 4.50)</td>
<td>0.53 (0.53)</td>
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<td>TNF-alpha (pg/ml)</td>
<td>3.40 (2.77, 8.30)</td>
<td>2.95 (2.14, 4.50)</td>
<td>0.53 (0.53)</td>
</tr>
<tr>
<td>Week 12</td>
<td>CRP (ng/ml)</td>
<td>4.24 (2.97, 8.74)</td>
<td>3.21 (1.88, 8.18)</td>
<td>0.70 (0.70)</td>
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SMART: Risk of death associated with biomarker at study entrance

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<tr>
<th>Biomarker</th>
<th>Type of Study</th>
<th>25th Percentile (Reference)</th>
<th>50th Percentile</th>
<th>75th Percentile</th>
<th>25th Percentile (Control)</th>
<th>50th Percentile</th>
<th>75th Percentile</th>
<th>OR (95% CI)</th>
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<tr>
<td>CRP</td>
<td>3.07</td>
<td>0.918</td>
<td>1.342</td>
<td>4.24</td>
<td>0.859</td>
<td>1.342</td>
<td>4.24</td>
<td>3.84 (1.85, 8.03)</td>
</tr>
<tr>
<td>D-dimer</td>
<td>0.53</td>
<td>0.289</td>
<td>0.418</td>
<td>0.70</td>
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Issues to Consider in Viral Infection

- General features of viral infection
  - Tissue damage → activation of innate immunity
- Specific features of the infection; e.g., in HIV:
  - Loss of T helper function → opportunistic infections & loss of surveillance
  - Loss of lymph node function → general loss of adaptive immunity
  - Loss of GALT function → activation of coagulation
- Common co-infections; e.g., for HIV this might be HCV:
  - HCV → decreased liver function → "aging" & altered biomarker profile
- Therapy, again in HIV:
  - ART → decreased inflammation due to control of viral load & possible proinflammatory effects (? Mechanism)