<table>
<thead>
<tr>
<th>1. AGENCY USE ONLY (Leave blank)</th>
<th>2. REPORT DATE</th>
<th>3. REPORT TYPE AND DATES COVERED</th>
<th>4. TITLE AND SUBTITLE</th>
<th>5. FUNDING NUMBERS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5. Sep. 02</td>
<td>MAJOR REPORT</td>
<td>AHEROGENESIS 2002, NEW CONCEPTS IN PLAQUE VULNERABILITY AND C REACTIVE PROTEIN</td>
<td></td>
</tr>
<tr>
<td>6. AUTHOR(S)</td>
<td></td>
<td></td>
<td>MJ DE JONG MARLA J</td>
<td></td>
</tr>
<tr>
<td>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</td>
<td></td>
<td></td>
<td>UNIVERSITY OF KENTUCKY LEXINGTON</td>
<td></td>
</tr>
<tr>
<td>8. PERFORMING ORGANIZATION REPORT NUMBER</td>
<td></td>
<td></td>
<td>CI02-513</td>
<td></td>
</tr>
<tr>
<td>9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)</td>
<td></td>
<td></td>
<td>THE DEPARTMENT OF THE AIR FORCE</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AFIT/CIA, BLDG 125</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2950 P STREET</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WPAFB OH 45433</td>
<td></td>
</tr>
<tr>
<td>10. SPONSORING/MONITORING AGENCY REPORT NUMBER</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. SUPPLEMENTARY NOTES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12a. DISTRIBUTION AVAILABILITY STATEMENT</td>
<td></td>
<td></td>
<td>Unlimited distribution</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In Accordance With AFI 35-205/AFIT Sup 1</td>
<td></td>
</tr>
<tr>
<td>12b. DISTRIBUTION CODE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. ABSTRACT (Maximum 200 words)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. SUBJECT TERMS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. NUMBER OF PAGES</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. PRICE CODE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. SECURITY CLASSIFICATION OF REPORT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. SECURITY CLASSIFICATION OF THIS PAGE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. SECURITY CLASSIFICATION OF ABSTRACT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. LIMITATION OF ABSTRACT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Atherogenesis 2002

New Concepts In Plaque Vulnerability and C Reactive Protein

Marla J. De Jong, RN, MS, CCNS, CCRN, CEN, Major

Objectives

- Discuss history of traditional thoughts on atherogenesis and how they have changed
- Discuss basic science of atherogenesis
- Discuss concept of plaque vulnerability
- Discuss concept of inflammation and C-reactive protein and fibrinogen in atherogenesis

Atherogenesis – Past and Present

History of Atherogenesis

- Inevitable degenerative process
- Lipid storage disease
- Arteries viewed as inanimate tubes
- Plaque rupture
- Occlusive thrombus

Atherogenesis Today

- Inflammatory process
- Endothelial dysfunction
- Neurohormonal factors
- Vessel narrowing vs. dilation

Process of Atherogenesis
Arterial Anatomy
- Intimal layer
- Medial layer
- Adventitial layer

Lesion Initiation
- Endothelial damage
- Adhesion and chemoattractant molecules
  - Inflammatory leukocytes recruited
  - Extracellular lipid accumulates
- Fatty streaks

Fibrofatty stage
- Monocytes become macrophages
- Macrophages express scavenger receptors
- Macrophages ingest oxidized lipoproteins
- Lipid-laden foam cells arise

Extracellular Lipid Pools
- Foam cell necrosis
- Small lipid pools
- Smooth muscle cell proliferation/migration
- Compensatory vessel wall dilation

Glagov's Coronary Remodeling Concept
Progression
- Compensatory expansion maintains constant lumen
- Expansion overcome: lumen narrows

Core of Extracellular Lipid
- Lipid core forms
- Lesion expands
- Necrotic fatty core develops
- Fibrosis
- Effects of inflammatory mediators
Lesion Progression

- Fibrous cap forms
- Lumen narrows
- Plaque may calcify

Figure: The Heart Pathology Laboratory for Medical Education

Metalloproteinases (MMPs)

- Source
- Actions
- Regulation

Fibrous Cap Rupture

- Coagulation factors contact lipid core
- Thrombosis on nonocclusive plaque

Figure by M. Henry Giller

Endothelial Erosion

- Intimal erosion
- Blood & platelets exposed to subendothelial matrix
- Proteinases are expressed
- Mural thrombus

Figure by M. Henry Giller

Plaque Healing

- Fibrinolysis
- Smooth muscle cell proliferation
- Increase in plaque size

Figure by M. Henry Giller
Arteries at Risk

- Shape of arteries
- Areas with preexisting intimal thickening

Plaque Vulnerability Defined

- Asymptomatic atherosclerotic lesions with a tendency to rupture
- High risk for luminal thrombosis

Plaque Vulnerability

Characteristics of Stable Lesions

- Many smooth muscle cells
- Thick fibrotic caps
- Limited amount of lipid
- A small, noninflamed lipid core

Characteristics of Unstable Lesions

- Mechanical factors
  - Vasospasm
  - Turbulent blood flow
  - Large liquid lipid core
  - Plaque flexion
  - Thin fibrous cap

Characteristics of Unstable Lesions

- Fibrous cap
  - Decreased collagen synthesis
  - Collagen degradation
  - Smooth muscle cell loss
  - Increased cytokines

Liao, JC, 1998
Characteristics of Unstable Lesions
- Plaque constituents
  - Increased esterified cholesterol
  - Decreased extracellular matrix
  - Increased metalloproteinases
  - Increased T cells and macrophages
  - Warmer plaque temperature

Other Triggers of Plaque Disruption
- Circadian variation
- Seasonal variation
- Physical exertion
- Emotional stress

Inflammation and Atherogenesis

Triggers for Inflammation
- Oxidized lipoproteins
- Dyslipidemia
- Hypertension
- Diabetes
- Obesity
- Infection

Consequences of Inflammation
- Endothelial inflammation
- Leukocyte recruitment & adhesion
- Local inflammatory response
- Atheroma thrombotic complications
- Acute coronary syndromes

Markers of Inflammation
C-Reactive Protein (CRP)
C-Reactive Protein

- Acute-phase marker
- Easily measured
- hs-CRP
- Levels > 2 μg/ml indicate high risk
- Significance

Functions of CRP

- Induces expression of adhesion molecules
- Mediates LDL update
- Induces monocyte recruitment into artery wall
- Enhances production of MCP-1

Research Related to CRP

- CARE Trial
- Physician’s Health Study
- Women’s Health Study
- PRINCE Trial
- AFCAPS/TexCAPS Study

Other Inflammatory Markers

Fibrinogen

- Major coagulation factor
- Acute phase reactant
- Increases during inflammation
- May promote smooth muscle cell growth
- May attract WBCs
- May promote platelet aggregation
- May inhibit fibrinolysis

Interleukin 6

- Cytokine
- Affects platelet production
- Induces synthesis of acute phase proteins
- Predictor for CAD
- Levels > 5 ng/L → increased mortality
Myeloperoxidase (MPO)
- A leukocyte enzyme
- Promotes oxidation of lipoproteins
- May activate latent MMPs
- May cause plaque destabilization
- May cause endothelial dysfunction
- Levels correlate with CAD

Cellular Adhesion Molecules
- Selectins
- B2 integrins
- Immunoglobins

B-Type Natriuretic Peptide
- Reflects neurohormonal activity
- Prognostic marker for ACS & CHF
- Increases with transient ischemia
- Threshold level 80 pg/mL

Pregnancy-Associated Plasma Protein A (PAPP-A)
- A potentially proatherosclerotic MMP
- Present in unstable plaques
- Levels > 10 mIU associated with ACS
- Higher in pts with USA/AMI than in controls

Diagnostic Tools for Inflammation
- Angioscopy
- Thermal imaging
- Lasers
- High resolution IVUS
- Light-tipped catheters
- MRI
- Raman spectroscopy
- Magnetic resonance coronary angiography
- Electron beam computed tomography
- PET scanning
- Optical coherence tomography
- Intravascular shear stress imaging
- Microbubble contrast echocardiographic imaging
- Many others
Is There Any Hope?

Risk Factors for Atherosclerosis
- Smoking
- Hypertension
- Hypercholesterolemia
- Infections
- Diabetes
- Hypoxia
- Oxidants
- Turbulent Flow

Risk Reduction
- Cholesterol reduction
- ACE inhibitors
- Clopidogrel
- Aspirin
- Glucose control
- Smoking cessation
- Exercise

Unanswered Questions

- Do measurements of inflammation identify pts at risk, and do these independently predict risk beyond currently used tools?
- Are specific therapies available to reduce serum levels of markers of inflammation?
- Do therapies that lower serum levels of inflammatory markers reduce CV risk?
- Which is the optimal test for prognostic evaluation?
- Which pt population should be targeted for testing?
- What is the role of endothelial dysfunction compared to other new risk assessment strategies?
References


