“Erosion, Intraplaque hemorrhage: The other Face of Vulnerability”

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Lesions with Thrombi

• *Plaque Rupture*
• *Plaque Erosion*
• *Calcified Nodule*
Causes of Coronary Thrombosis

Development of Human Coronary Atherosclerosis

- Intimal thickening
- Intimal xanthoma
- Pathologic intimal thickening
- Fibrous cap atheroma
- Thin-cap Fibroatheroma

- Smooth muscle cells
- Macrophage foam cells
- Extracellular lipid
- Cholesterol clefts
- Necrotic core
- Calcified plaque
- Hemorrhage
- Thrombus
- Healed thrombus
- Collagen

Fibrous cap atheroma with hemorrhage

Thin fibrous cap atheroma

Fibrocalcific plaque

The Endothelium in Fatal Plaque Erosion

A

B

IEL

vWF

a

b

Th

vWF

C

vWF
Coronary Thrombosis: Plaque Erosion

→: Occlusive thrombus

↓: Left anterior descending artery

↓: Eroded intima with thrombus

Fig. 4-2
Serial Sections of Plaque Erosion in a 38-Year-Old Female Sudden Coronary Death Victim

PROXIMAL LEFT ANTERIOR DESCENDING

Fig. 4-3
Clinical and Morphologic Difference in Plaques Associated with Luminal Thrombi

Plaque Rupture

45-55% thrombi in SCD
M>F, Older, Ca**
Eccentric = concentric,
↑ Hemorrhage
Greater % stenosis
Macs, T cells, HLA-Dr

Plaque Erosion

35-40% thrombi in SCD
M=F, younger
Usually eccentric
Lesser % stenosis
SMC rich,
proteoglycans (versican)
& hyaluronan

Fig. 4-4
51 Women with Severe Coronary Atherosclerosis

P=0.007

P=0.001

P=0.01
Frequency Distribution of Percent Cross-sectional Area Stenosis by Plaque in Coronary Thrombosis

<table>
<thead>
<tr>
<th>% Stenosis</th>
<th>Mean Age</th>
<th>All Cases</th>
<th>Plaque Rupture</th>
<th>Plaque Erosion</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>42±5</td>
<td>4(8%)</td>
<td>1(4%)</td>
<td>3(14%)</td>
</tr>
<tr>
<td>60-69</td>
<td>46±7</td>
<td>9(18%)</td>
<td>4(14%)</td>
<td>5(23%)</td>
</tr>
<tr>
<td>70-79</td>
<td>49±10</td>
<td>21(42%)</td>
<td>11(39%)</td>
<td>10(45%)</td>
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<tr>
<td>80-89</td>
<td>50±5</td>
<td>8(16%)</td>
<td>5(18%)</td>
<td>3(14%)</td>
</tr>
<tr>
<td>90-99</td>
<td>52±16</td>
<td>8(16%)</td>
<td>7(25%)</td>
<td>1(5%)</td>
</tr>
<tr>
<td>Total</td>
<td>49±10</td>
<td>50(100%)</td>
<td>28(100%)</td>
<td>22(100%)</td>
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</tbody>
</table>
Plaque Erosions in Men and Women Stratified by Age

Men

<table>
<thead>
<tr>
<th>Decade</th>
<th>30s</th>
<th>40s</th>
<th>50s</th>
<th>60s</th>
<th>70s</th>
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<tr>
<td>30s</td>
<td>45</td>
<td>40</td>
<td>35</td>
<td>30</td>
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<td>35</td>
<td>30</td>
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<td>20</td>
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</tr>
<tr>
<td>50s</td>
<td>25</td>
<td>20</td>
<td>15</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>60s</td>
<td>15</td>
<td>10</td>
<td>7</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>70s</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Women

<table>
<thead>
<tr>
<th>Decade</th>
<th>30s</th>
<th>40s</th>
<th>50s</th>
<th>60s</th>
<th>70s</th>
</tr>
</thead>
<tbody>
<tr>
<td>30s</td>
<td>50</td>
<td>45</td>
<td>40</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>40s</td>
<td>45</td>
<td>40</td>
<td>35</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>50s</td>
<td>40</td>
<td>35</td>
<td>30</td>
<td>25</td>
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<tr>
<td>60s</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>70s</td>
<td>30</td>
<td>25</td>
<td>20</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

*P=0.01, †P=0.02, ¥p=0.01, ^P=0.03

All P > 0.05
Plaque Erosion and Inflammation
SCD victims <40 yrs in age

- Of 23 cases of plaque erosion, 5 occurred on a fibrous plaque without lipid deposits, 17 had pathologic intimal thickening, and 1 had a fibroatheroma.
- Organizing thrombus in 11, and organized at the base in 12. Severe inflammation observed in 2 cases.

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Erosion</th>
<th>Rupture</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMC’s (cells/mm²)</td>
<td>794±334</td>
<td>164±177</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Macrophages (cells/mm²)</td>
<td>251±159</td>
<td>585±219</td>
<td>0.0007</td>
</tr>
<tr>
<td>T-cells (cells/mm²)</td>
<td>1.3±0.8</td>
<td>6.4±1.3</td>
<td>0.008</td>
</tr>
</tbody>
</table>
Acute Plaque Erosion
No Thrombus Organization

A: Th
B: SMCs
C: MΦ
D: T-cells
E: PLT
F: Fibrin
“Inflamed” Erosion

A: Th

B: Inflammatory Cells
  Fibrin

C: MΦ

D: T-cells
Plaque Erosion
Early Thrombus Organization

A
B
C
D
E
F

SMCs
PLT
Fibrin
Plaque Erosion
Organized Thrombus

A

B

C

D

E

SMCs

Residual Fibrin

Residual Fibrin

Carstair’s
Remodeling in Varying Coronary Lesion Morphologies

IEL-Expected IEL (mm²)

A.

IEL-Expected IEL (plaque area)

B.

Remodeling in Varying Coronary Lesion Morphologies
Influence of Age on Coronary Thrombosis in Men and Women

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Plaque Rupture
- Plaque erosion
- Calcified Nodule
- Stable Plaque

No. of Cases

- Females:
  - <50 years: 55 cases
  - >50 years: 41 cases
- Males:
  - <50 years: 14 cases
  - >50 years: 38 cases
**Plaque erosion and Matrix**

A. Movat stain

B. Sirius Red

C. Versican

D. bHABR

E. Biglycan

F. Decorin
Stable Plaque

A

B

C

D

E

F

Versican

bHABR

Biglycan

Decorin
Distribution of Proteoglycans in Plaque Erosion

**A**

**Versican**

- Semiquantitative Score
- P < 0.0001
- P < 0.0001

**B**

**Hyaluronan**

- Semiquantitative Score
- P < 0.0001
- P = 0.001

**C**

**Biglycan**

- Semiquantitative Score
- P = 0.009
- P = 0.0005

**D**

**Decorin**

- Semiquantitative Score

Fig. 4-12
HA: fibrin polymerization
Promotes adherence
platelets
macrophages

HA interferes with endothelial adherence

CD 44 expression in SMC, inflammatory cells, and platelets. CD44 induces SMC migration

Hyaluronan & Versican
Biglycan
Decorin

Th

Hyaluronan

vWF
CD44
CD61
Fibrin II
Role of Hyaluronan and CD44 at Sites of Plaque Erosion

- Increased hyaluronan at plaque thrombus interphase
- Hyaluronan may interfere with the integrity of normal vascular endothelium - endothelial cells from large vessels have lower potential for adherence to hyaluronan. Endothelial cells in culture demonstrate decreased cell growth and increased propensity to apoptosis.
- Hyaluronan binds to CD44 and CD44 receptors have been shown to mediate the adhesion of platelets to hyaluronan. The deendothelialized surface of erosion may expose hyaluronan, thereby promoting platelet attachment via CD44. CD44 promotes atherosclerosis by mediating inflammatory cell recruitment.
Thrombus Propagation in Plaque Rupture

A. Platelet-rich thrombus

B. Proximal fibrin-rich propagated thrombus

C. Carstairs' Platelets

D. Proximal Propagated Thrombus

Fig. 3-15
Thin-cap Fibroatheroma

Recent Intraplaque Hemorrhage is seen at Multiple sites in Patients Dying SCD

Plaque Hemorrhage

- Plaque rupture
- Plaque erosion
- Severe CAD >75%
Intraplaque Hemorrhage and Progression of Coronary Atherosclerosis

• Conversion of a stable, asymptomatic lesion to an unstable, ruptured plaque involves many processes, the most studied of which is inflammation, cellular breakdown, and expansion of the acellular, lipid rich, necrotic core.

• Commonly believed that death of macrophages and SM foam cells, in addition to the aggregation of lipoproteins, contribute to the accumulation of extracellular free cholesterol within unstable plaques.

• Contribution of intraplaque hemorrhage to the expansion of necrotic core has not been explored.

Consequence of Extravasated Erythrocytes Outside the Vasculature

- Free cholesterol content of erythrocyte membrane exceeds that of all other cells in the body, with lipid constituting 40% of the weight.
- Yeagle in 1985 showed that extravasated erythrocytes contain free cholesterol and Arbustini et al. in 2002 showed macrophage infiltration in intimal plaques in pulmonary trunk of patients with pulmonary hypertension at sites containing erythrocyte membranes.

We examined tissues from nonvascular location to determine the effect of hemorrhage:

- Pericardial hemorrhage
- Intratumor hemorrhage (atrial hemangiomas, hemorrhagic pericarditis, papillary carcinoma of kidney etc)

Intracardiac Hemangioma (A-F) and Hemorrhagic Pericarditis (G-I)

Plaque Types Studied

A. Pathologic Intima Thickening

B. Fibroatheroma ‘Early’ Core

C. Fibroatheroma ‘Late’ Core

D. Thin Cap Fibroatheroma
Extent of Glycophorin A and Iron Accumulation Relative to Necrotic Core Size

Morphometric Analysis of Hemorrhagic Events in Human Coronary Plaques from Sudden Death Victims

<table>
<thead>
<tr>
<th>Plaque Type</th>
<th>GpA Score</th>
<th>Iron</th>
<th>Necrotic Core (mm²)</th>
<th>MΦ (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIT no core</td>
<td>0.09±0.04</td>
<td>0.07±0.05</td>
<td>0.0</td>
<td>0.002±0.001</td>
</tr>
<tr>
<td>(n=129)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA early core</td>
<td>0.23±0.07</td>
<td>0.17±0.08</td>
<td>0.06±0.02</td>
<td>0.018±0.004</td>
</tr>
<tr>
<td>(n=79)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA late core</td>
<td>*0.94±0.11</td>
<td>*0.41±0.09</td>
<td>*0.84±0.08</td>
<td>*0.059±0.007</td>
</tr>
<tr>
<td>(n=105)</td>
<td></td>
<td></td>
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<tr>
<td>TCFA</td>
<td>*1.60±0.20</td>
<td>*1.24±0.24</td>
<td>*1.95±0.30</td>
<td>*0.142±0.016</td>
</tr>
<tr>
<td>(n=52)</td>
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</tbody>
</table>

Values are reported as the means±SE, *p<0.001 versus early core. The number in parenthesis represent the number of lesions examined; the total number= 365. MΦ = macrophages

Fibrous Cap Atheroma (Late Necrosis)

Thin Fibrous Cap Atheroma

Plaque hemorrhage contributes to enlargement of the necrotic core

- Importance has been shown in human plaques - red cell membrane contributes to free cholesterol and larger necrotic cores.
- Macrophage accumulation is triggered by crystallization of cholesterol from erythrocyte membrane and foreign body reaction as seen in cholesterol granulomas and e.g., receptors on erythrocytes bind a wide array of chemokines, MCP-1; lipid oxidation from senescent RBCs or iron-catalyzed reactions may liberate potent chemoattractants
Plaque Vasa Vasorum

• Plaque capillaries are observed in atherosclerotic plaques with plaque thickness > 0.5 mm, suggesting that wall ischemia may be a determinant of neovascularization.

• Heistead and Armstrong reported a 5 fold increase in intimal/medial blood flow from proliferating micro vessels in monkeys fed a high cholesterol diet for 17 months. (Ateriosclerosis 1986)

• Plaque Vv may be a potential source of inflammation within the plaque [expression of VCAM-1, ICAM-1 and E-selectin has been shown in plaque Vv (O’Brian, et al. AJP 1994).

• Inflammation and matrix composition of atherosclerotic plaques may also influence angiogenesis.
Intraplaque Vasa Vasorum in Coronary Plaques with a Necrotic Core

150 mm thick sections stained with Ulex

A

B

nc

nc
Vasa Vasorum in Plaque Rupture

A. Movat

B. NC

C. α-SMA

D. vWF

E. CD68

F. UCHL
Mechanism of coordinated angiogenesis and inflammation in the progressive enlargement of the necrotic core

$\uparrow$Macrophage via MCP=1, M-CSF within plaque - $\uparrow$

$\uparrow$VEGF = $\uparrow$angiogenesis

T-lymphocytes - $\uparrow$angiogenesis via Toll-like receptors (TLR) 2 and 4 CD40/CD40L
Erosion, and Intraplaque Hemorrhage: The other face of vulnerability

Conclusions:

• The dominant cause of coronary thrombosis is plaque rupture (commoner in men), followed by erosion (more common in women).

• Erosion lesions are rich in smooth muscle cells with paucity of macrophages, and majority do not have an underlying necrotic core. Usually seen in younger individuals and in females who often present with atypical chest pain.

• Total cholesterol and HDL are not associated with erosion.

• Underlying base of the thrombus is rich in proteoglycans and hyaluronan. It is conceivable that plaque erosion has a different etiology possibly secondary to vasospasm of the arterial wall rather than atherosclerotic.
Erosion, and Intraplaque Hemorrhage: The other face of vulnerability

Conclusions:

- Intraplaque hemorrhage is commonly seen in coronary arteries of patients dying with plaque rupture.
- Red cell membranes contribute to enlargement of the necrotic core (lipid core expansion) and an increase in macrophage content.
- Angiogenesis of atherosclerotic plaques contribute to plaque hemorrhages.
- Angiogenesis of the intima occurs at sites of medial destruction where T-lymphocytes accumulate.
- Understanding the relationship of angiogenesis, inflammation and plaque progression are key to understanding atherosclerosis and its progression.
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