Mechanisms of Plaque destabilization Pathologic Observations

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American College of Cardiology

Renu Virmani, MD
CVPath Institute Inc.,
Gaithersburg, Maryland, USA

Conflict: Nothing to declare
Branch points are the sites of atherosclerosis and occur in areas of low shear.
Progression of Human Coronary Atherosclerosis

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

- Rupture
- Erosion
- Calcified nodule
- Healed Rupture

NC: Nucleus Caudatus
Th: Thickening
EL: Elastic Layer
FC: Fibrocellular Cap
Ca^2+: Calcium
Causes of Coronary Thrombosis

Do thin cap fibroatheromas (vulnerable plaques) go on and Rupture?

**Thin cap fibroatheroma**
- Necrotic core (21.6±23.7%)
- Thin fibrous cap (< 65 µm)
- Cap infiltrated by macrophages and lymphocytes
- Cap composition – type 1 collagen with few or absent smooth muscle cells

**Plaque Rupture**
- Discontinuous fibrous cap (23±19 µm)
- Underlying necrotic core (29.0±19.0%)
- Luminal thrombus
Thin cap Fibroatheroma (Vulnerable Plaque)
Coronary Artery

Movat

nc

nc

Fibrous cap

CD68

nc

CD68

vWF

2.0 mm

200 µm

100 µm

100 µm
Plaque rupture with mild non occlusive thrombus: mechanism by which plaques progress (asymptomatic)
Silent Ruptures and Erosions lead to Plaque Progression

Movat pentachrome

Sirius red

Sirius red with polarized light
Mean % stenosis increases with number of prior rupture sites

A

Number of prior ruptures, healed rupture sites

B

Number of prior ruptures, acute ruptures sites

11% of plaque rupture are virgin

Prevalence of Older Thrombus is an Independent Predictor of Long-Term Mortality In Patients with STEMI

Kramer MCA, et al
Circulation 2008: 118;1810-1816
## Patient Data, by Culprit Plaque

<table>
<thead>
<tr>
<th>Culprit Lesion</th>
<th>Patient age (years)</th>
<th>Male Gender</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rupture (n=65)</td>
<td>52 ± 10</td>
<td>58 (89%)</td>
<td>7 (11)</td>
<td>15 (23)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Erosion (n=50)</td>
<td>43 ± 9</td>
<td>37 (74%)</td>
<td>6 (12)</td>
<td>6 (12)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>0.03</td>
<td>0.67</td>
<td>0.84</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean± SD
Plaque Rupture

Early (< 1 day)                  Lytic (1-3 days)              Infiltrating (4-7 days)            Healing (> 7 days)

A  NC                  Th

B  NC                  Th

C  NC                  Th

D  NC                  Th

E  NC                  Th

F  NC                  Th

G  NC                  Th

H  NC                  Th

I  NC                  Th

J  NC                  Th

K  NC                  Th

L  NC                  Th

Th Th Th Th

50.0 μm

1.0 mm
Plaque Erosion

Early (< 1 day)                  Lytic (1-3 days)               Infiltrating (4-7 days)            Healing (> 7 days)

A  D  G  J

CFI L

EB KH

NC NC

NC NC

LP LP

Th Th

Th Th

Th Th

1.0 mm 1.0 mm 1.0 mm 1.0 mm

50.0 μm 50.0 μm 50.0 μm 50.0 μm

Kramer MCA, et al Submitted
Organizing Thrombus

Rupture
Infiltrating thrombus (4-7 days)

Erosion
Healing thrombus (> 7 days)

Figure 2

Kramer MCA, et al Submitted
Thrombus Age

- Rupture
- Erosion

P < 0.0001

Kramer MCA, et al Submitted
Location of Coronary Ruptures and Erosions and % Fresh and Healing Thrombi

Total lesions = 65
- Fresh thrombus (≤ 1 day)
- Healing thrombus (> 1 day)

Total lesions = 50
- Fresh thrombus (≤ 1 day)
- Healing thrombus (> 1 day)

Kramer MCA, et al Submitted
Plaque Characteristics

IEL Area $\text{mm}^2$, Plaque Area $\text{mm}^2$, Percent Stenosis, % Necrotic core, Macrophage %

Kramer MCA, et al Submitted
## Characteristics of Thrombi, and underlying x-sectional area narrowing

<table>
<thead>
<tr>
<th>Patient /Plaque Characteristics</th>
<th>&lt;75% Stenosis (n=53)</th>
<th>P value</th>
<th>Ø75% Stenosis (n=62)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rupture (N=23)</td>
<td>Erosion (n=30)</td>
<td></td>
<td>Rupture (n=42)</td>
</tr>
<tr>
<td>Patient age</td>
<td>52 ± 12</td>
<td>43 ± 9</td>
<td>0.02</td>
<td>52 ± 9</td>
</tr>
<tr>
<td>Male Gender</td>
<td>22 (96)</td>
<td>22 (73)</td>
<td>0.02</td>
<td>36 (86)</td>
</tr>
<tr>
<td>Thrombus age</td>
<td>0.001</td>
<td></td>
<td>0.03</td>
<td>0.001</td>
</tr>
<tr>
<td>Early</td>
<td>12 (52)</td>
<td>3 (10)</td>
<td></td>
<td>18 (43)</td>
</tr>
<tr>
<td>Late</td>
<td>11 (48)</td>
<td>27 (90)</td>
<td></td>
<td>24 (57)</td>
</tr>
<tr>
<td>IEL area (mm²)</td>
<td>13.6 ± 5.2</td>
<td>9.2 ± 3.9</td>
<td>0.001</td>
<td>13.7 ± 6.5</td>
</tr>
<tr>
<td>Plaque Burden</td>
<td>217 ± 72</td>
<td>179 ± 69</td>
<td>0.08</td>
<td>237 ± 65</td>
</tr>
<tr>
<td>Necrotic core</td>
<td>23 (100)</td>
<td>14 (47%)</td>
<td>&lt;0.001</td>
<td>42 (100)</td>
</tr>
<tr>
<td>Necrotic core area mm²</td>
<td>2.99 ± 2.7</td>
<td>0.63 ± 1.1</td>
<td>&lt;0.0001</td>
<td>4.98 ± 5.0</td>
</tr>
<tr>
<td>Necrotic core area %</td>
<td>33.6 ± 23.5</td>
<td>10.4 ± 17.9</td>
<td>&lt;0.0001</td>
<td>36.8 ± 23.4</td>
</tr>
<tr>
<td>Macrophage area mm²</td>
<td>4.3 ± 2.7</td>
<td>2.2 ± 2.2</td>
<td>0.003</td>
<td>3.0 ± 2.7</td>
</tr>
</tbody>
</table>
Myocardial Infarction: Rupture vs. Erosion

Kramer MCA, et al Submitted
Myocardial Infarction: Early vs. Late and Rupture V. Erosion

- Early ≤ 1 day
- Late > 1 day
- Rupture
- Erosion

P = 0.008
P = 0.01
P = ns
P = 0.08

Percent %

No MI
Healed MI
AMI+Healing MI
AMI+Healing + healed MI

n=15, n=21
n=8, n=15
n=8, n=30
n=4, n=8

Kramer MCA, Submitted
Plaque Erosion

Stable Erosion

Different Accumulation of Proteoglycan and Hyaluronan in Different Culprit lesions

Kolodgie FD, ATVB 2002
Intramyocardial Emboli more Common in Plaque Erosion vs. Plaque Rupture

%Hearts with Intramyocardial Emboli

Erosion: 74%
Rupture: 40%
p<0.03
Intramyocardial Emboli and Myocardial Necrosis

In hearts with intramyocardial emboli:
- 57% associated with focal myocardial necrosis
  • Of these, 83% with multiple emboli (86% in vessels <120 µm in diameter)
- 24% associated with acute MI, 5% with myocardial scars (healed MI), 14% with normal myocardium
Conclusions: Healing of Ruptures vs. Erosions

- The etiology and pathologenesis of Ruptures and Erosions is significantly different regarding inflammation, remodeling, growth rate, and healing of thrombus.
- Plaque erosions are associated with late stage maturation of thrombus as compared to ruptures.
- Healing thrombi are seen in 85% of erosions versus 55% of ruptures and clinical studies have suggested that healing thrombi clinically have worse prognosis in patients presenting with STEMI (Kramer MCA, Circulation 2008).
- Plaque erosions have been associated with greater distal embolization as compared to rupture (74% vs. 38%).
- Therefore understanding erosions which are more common in women <50 years may need different modality of artery interrogation as well as treatment strategies than men.
Possibility of OCT imaging
Findings from Ex-Vivo Imaging

Thin-cap fibroatheroma

OCT images taken by Hoffmann, U & Donnelly, P. MGH
Multi-slice CT vs. Histology

Micro-calcification

Non-calcified plaque

Fibrous

Micro-calcification (dark purple)

LAD
Detecting Macrophages in Vulnerable Plaque

Thin-cap fibroatheroma

Movat Kp-1 (Macrophage)

Possibility of OCT imaging
Findings from Ex-Vivo Imaging

Fibrous plaque with calcification

Fibroatheroma

OCT images taken by Hoffmann, U & Donnelly, P. MGH