Morphology and Distribution of Atherosclerotic Plaque

Tokai Univ. Japan
Gaku Nakazawa, MD
Background – 1 –

• Angiographic classification of bifurcation lesions has been reported (Safian, Duke, Sanborn, Lefevre, Medina).

• However, little is know about pathophysiology and nature of bifurcation lesions (sites)
• High procedural complication and restenosis rates have been reported in patients after bifurcation stenting in BMS era.

• DES reduced restenosis rates after percutaneous coronary intervention for bifurcation lesions. In addition, technical improvements provide a wide therapeutic window.

• However, no report has described pathology of bifurcation stenting.
Intervention for Bifurcation lesion

BMS ¹) 6 months DES ²)

62% 48% 37%

28% 19% 8%

Bifurcation lesion is always one of the predictors of LST.
Why so susceptible to get diseased?

Steady Laminar Blood Flow

- Shear Stress
- NO
- PG12
- tPA
- Thrombomodulin
- Antithrombotic
- Antimigration
- Pro-survival
- NO
- Endothelium
- Smooth Muscle
- Antigrowth
- TGF-β

Flow Reversal

- Low Mean Shear
- Prothrombotic
- Promigration
- MCP-1
- VCAM-1
- Pro-apoptosis
- Endothelium
- Smooth Muscle
- Progrowth
- Ang II
- PDGF
- Endothelin-1
- Atherosclerotic Lesion

Vascular Biology

Neonatal Intima Formation in the Human Coronary Artery

Yuji Ikari, Bruce M. McManus, Jennifer Kenyon, Stephen M. Schwartz

Schematic representation of the shear stress patterns induced by the castin apoE−/− mice fed an atherogenic Western diet

Oscillatory vortices with oscillatory shear stress
≈14 N/m² (range 60 N/m²)

increased shear stress
increases from: ≈10 N/m² (upstream)
to ≈25 N/m² (downstream)

lowered shear stress
≈10 N/m²

undisturbed shear stress
≈15 N/m²

Lowered shear stress and vortices with oscillatory shear stress induce atherosclerosis in apoE−/− mice fed an atherogenic Western diet

Atherosclerosis detected by Oil Red O

Histological analyses of carotid arteries 9 weeks after cast placement in apoE−/− mice fed a Western diet

Histological analyses of carotid arteries 9 weeks after cast placement in apoE−/− mice fed a Western diet

A

macrophages  lipids  VSMC actin  collagen  MMP activity

low sh.str.  
oscill. sh.str.

B

area (% intima)  area (% intima)  area (% intima)  area (% intima)  area (% intima)

low  low  low  low  low
oscill.  oscill.  oscill.  oscill.  oscill.
macrophages  lipids  VSMCs  collagen  MMP activity

Dynamic flow alterations dictate leukocyte adhesion and response to endovascular interventions

Yoram Richter, Adam Groothuis, Philip Seifert, and Elazer R. Edelman

Vessel Geometry and Flow Pattern

Stenosis

Released

Flow divider

Lateral wall

Impact of Flow Pattern on Neointimal Formation

SPECIFIC AIMS

• To determine the location and extent of atherosclerosis in areas of bifurcation

• To explore the pathologic findings and differences between BMS and DES implanted in bifurcation lesions
Non-stented atherosclerotic lesion

From CVPath sudden coronary death registry, coronary artery bifurcation sites that had been longitudinally cut were examined.

<table>
<thead>
<tr>
<th>Examined bifurcation (N= 26)</th>
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</thead>
<tbody>
<tr>
<td>LM/ LAD/ LCX</td>
<td>5</td>
</tr>
<tr>
<td>LAD/ LD</td>
<td>14</td>
</tr>
<tr>
<td>LCX/ OM</td>
<td>5</td>
</tr>
<tr>
<td>LCX/ PDA</td>
<td>1</td>
</tr>
<tr>
<td>RCA/ PDA</td>
<td>1</td>
</tr>
</tbody>
</table>
Atherosclerotic plaque formation at bifurcation lesion
Plaque Formation

LM + LAD severe stenosis

LM
PLAD
PLCx

C

2.0 mm

D

200 µm

E

200 µm
Plaque Formation in Bifurcation

**Plaque thickness**

- **Main Vessel proximal**
  - High shear
  - Low shear

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6</td>
<td>1.2</td>
<td>1.4</td>
<td>1.6</td>
</tr>
</tbody>
</table>

- **Main Vessel distal**
  - High shear
  - Low shear

<table>
<thead>
<tr>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6</td>
<td>0.8</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Necrotic core thickness**

- **Main Vessel proximal**
  - High shear
  - Low shear

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
</tbody>
</table>

- **Main Vessel distal**
  - High shear
  - Low shear

<table>
<thead>
<tr>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>0.4</td>
<td>0.4</td>
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</tbody>
</table>

IVUS classification for LMCA bifurcation plaque distribution

Pathology of Bifurcation Stenting

Comparison between DES & BMS
## DES implantation in Bifurcation Lesion

<table>
<thead>
<tr>
<th></th>
<th>DES (n=19)</th>
<th>BMS (n=21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>61 ± 16</td>
<td>58 ± 17</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Male Gender (%)</strong></td>
<td>15 (79)</td>
<td>13 (62)</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Mean duration (day)</strong></td>
<td>330 [188, 680]</td>
<td>150 [54, 540]</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>&gt;30 days (%)</strong></td>
<td>12 (63)</td>
<td>14 (67)</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Technique</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 stent</td>
<td>10</td>
<td>9</td>
<td>0.38</td>
</tr>
<tr>
<td>2 stent, T/ V/ Crush</td>
<td>5/ 2/ 2</td>
<td>9/ 3/ 0</td>
<td></td>
</tr>
<tr>
<td><strong>Number of stents</strong></td>
<td>1.9 ± 0.8</td>
<td>1.8 ± 0.8</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Restenosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV (%)</td>
<td>1 (6)</td>
<td>7 (33)</td>
<td>0.03</td>
</tr>
<tr>
<td>SB (%)</td>
<td>3 (16)</td>
<td>6 (29)</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Thrombosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV (%)</td>
<td>3 (43)</td>
<td>3 (43)</td>
<td>0.33</td>
</tr>
<tr>
<td>SB (%)</td>
<td>3 (43)</td>
<td>4 (57)</td>
<td>0.73</td>
</tr>
<tr>
<td>&gt; 30 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV (%)</td>
<td>9 (75)</td>
<td>5 (36)</td>
<td>0.04</td>
</tr>
<tr>
<td>SB (%)</td>
<td>5 (42)</td>
<td>2 (14)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Timing of thrombus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>270 [195, 585]</td>
<td>60 [35, 105]</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Morphometric Analysis

### Morphometric Analysis

<table>
<thead>
<tr>
<th></th>
<th>BMS</th>
<th>DES</th>
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<tbody>
<tr>
<td></td>
<td>Flow divider</td>
<td>Lateral wall</td>
</tr>
<tr>
<td>Neointimal thickness (mm)</td>
<td>0.42 ± 0.35</td>
<td>0.50 ± 0.34</td>
</tr>
<tr>
<td>Struts with fibrin (%)</td>
<td>24 ± 30</td>
<td>20 ± 30</td>
</tr>
</tbody>
</table>
| Uncovered Strut (%)        | 17 ± 31      | 5 ± 10        | 0.08     | 48 ± 33      | 13 ± 24       | <0.0001  

*Delayed arterial healing in flow divider site in DES.*

DES implantation in Bifurcation Lesion

55M died suddenly 2 years after PCI, Taxus stents implantation in the distal LM (LAD/CX)

Flow disturbance induced by stent

Conclusions

- Coronary plaque in bifurcation lesions forms predominantly in the low shear zone.
- DES induce delayed healing especially in the region of the flow divider because of flow disturbance at bifurcations. Thrombus is predominantly initiated in areas of uncovered struts at flow divider regions.
- Bench testing of bifurcation lesion showed exaggerated flow disturbance by stenting.