Novel insights into atherosclerosis: from pathology to invasive imaging

Dr. med. Philipp Nicol
Deutsches Herzzentrum München
MAC - Munich Vascular Conference 2017
I do not have any potential conflict of interest
Agenda

1. Insights into atherosclerosis and plaque vulnerability from histopathology

2. Invasive imaging for atherosclerosis
   - Overview of current techniques
   - Detection of progressive CAD and vulnerable lesions

3. Innovative imaging
   - Overview of current techniques
   - Preclinical and clinical application

4. Summary
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1. Insights into atherosclerosis and plaque vulnerability from histopathology
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3. Summary
Development of atherosclerotic lesions

Early atherosclerosis can develop into high-risk lesions ("vulnerable plaques") → rupture and vessel thrombosis
Causes of coronary thrombosis

Rupture (65-70%)

Erosion (30-35%)

Calcified nodule (2-7%)

Virmani et al. ATVB 2000
Causes of coronary thrombosis

Rupture (65-70%)

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Causes of ACS
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## Overview

<table>
<thead>
<tr>
<th></th>
<th>OCT</th>
<th>IVUS</th>
<th>NIRS-IVUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode</strong></td>
<td>Infraredlight</td>
<td>Ultrasound</td>
<td>Spectroscopy</td>
</tr>
<tr>
<td><strong>Resolution</strong></td>
<td>10-15μm</td>
<td>150 – 200μm</td>
<td>150 – 200μm</td>
</tr>
<tr>
<td><strong>Depth</strong></td>
<td>2-3mm</td>
<td>10mm</td>
<td>10mm</td>
</tr>
<tr>
<td><strong>Radiation</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Contrast medium</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Detection</strong></td>
<td>Fibrotic cap, makrophages, Necrotic core, calcification</td>
<td>Remodeling, plaque burden, calcification</td>
<td>Lipidic plaque</td>
</tr>
</tbody>
</table>
IVUS vs. OCT

75 mm, 100-150 µm axial resolution, low sampling rate, 150 sec

75 mm, 15 µm axial resolution, high frequency samples, 2 sec
OCT for detection of progressive atherosclerotic lesions

FA=fibroatheroma; LP=lipid pool; NC=necrotic core; PIT=pathologic intimal thickening

Otsuka and Joner, Nat Rev Cardiol. 2014
Detection of culprit lesions in ACS by OCT

Plaque rupture (53%)

Plaque erosion (38%)

Calcified nodule (9%)

Similar incidence in histology and OCT!

Jia et al., JACC. 2013
OCT improves percutaneous angioplasty...

**DESIGN**

**CLI-OPCI**
- PCI with CAG only
- vs.
- PCI + OCT
(n=670; non-randomized)

**ILUMIEN III**
- PCI with CAG only
  - vs.
  - CAG + IVUS
  - vs.
  - CAG + OCT
(n=450, randomized)

**DOCTORS:**
- PCI for NSTEMI with CAG
  - vs.
  - CAG + OCT
(n=240, randomized)

**Results**

1) Improved outcome (less MI and cardiac deaths) in the +OCT-group
2) OCT revealed periprocedural complications

1) Enhanced stent expansion and improved procedural success with OCT
2) OCT revealed periprocedural complications

1) Significantly improved procedural success with OCT (higher FFR post-PCI)
2) OCT revealed periprocedural complications
What do we know about vulnerable lesions – PROSPECT trial

- 679 pts. with ACS underwent CAG and VH-IVUS
- FU 3,4 years
- MACE: 20,4% (culprit: 12,9%, non-culprit: 11,6%)
- Non-culprit lesions responsible for MACE were only mildly stenotic on CAG but classified as TCFA and plaque burden >70% with VH-IVUS

Intravascular imaging could be superior to CAG in detecting plaque vulnerability!
Can OCT detect vulnerable plaques?

Validation of OCT for TCFA (n=685 plaques)

<table>
<thead>
<tr>
<th></th>
<th>+TCFA histology</th>
<th>-TCFA histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>+TCFA OCT</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>-TCFA OCT</td>
<td>0</td>
<td>669</td>
</tr>
</tbody>
</table>

Sensitivity  \( \frac{12}{12+0} = 100\% \)
Specificity \( \frac{673}{17+673} = 98\% \)
PPV \( \frac{12}{12+17} = 41\% \)
NPV \( \frac{673}{673+0} = 100\% \)

Fujii et al. JACC imaging 2015

OCT is able to detect vulnerable plaques (TCFA); false positive results are due to foam cells, calcifications or thrombus obscuring the underlying pathologies!
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Concept of molecular imaging

- Novel and innovative imaging approaches are needed to detect vulnerable lesions unambiguously.
- Current imaging technologies provide information regarding the structural plaque composition but lack the ability to visualize plaque biology.
- Molecular imaging is able to detect biologically relevant features of plaque progression*, probably enabling the visualization of plaque vulnerability.

* Lauschner, F. & Nahrendorf M., Circ. 2011

- Fibrin
- Neovascularization
- Proteaseses (= cap thinning)
- Macrophages
- LDL
- Endothelial cells
- …
**Many technologies, many (dis-)advantages...**

<table>
<thead>
<tr>
<th>Imaging modalities</th>
<th>Features associated with increased plaque vulnerability</th>
<th>Fast analysis</th>
<th>Current status</th>
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<tbody>
<tr>
<td></td>
<td>Lumen dimensions</td>
<td>Plaque burden and positive remodelling</td>
<td>Lipid component</td>
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<tr>
<td>IVUS + X-ray</td>
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<td>++</td>
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<tr>
<td>IVUS-FLIIm</td>
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(++) indicates excellent performance of the modality; (+) moderate performance of the modality; (+) poor performance of the modality; (–) the modality is unable to provide this information; (NK) not known.

EES, endothelial shear stress; IVUS, intravascular ultrasound; RF-IVUS, radiofrequency analysis of the IVUS backscattered signal; OCT, optical coherence tomography; NIRS, near infrared spectroscopy; CTCA, computed tomographic coronary angiography; NIFR, near infrared fluorescence imaging; IVPA, intravascular photoacoustic imaging; FLIIm, fluorescence lifetime imaging.

Bourantas C. et al.; EHJ 2016
Combination of near-infrared fluorescence and IVUS in a dual imaging system (4F/40MHz)

The hybrid image is reconstructed by combining the structural ultrasound information with precisely co-registered NIR fluorescence emission signals.

Visualization of endothelial disintegration by injection of a fluorescent tracer (indocyanine green, ICG) in a swine iliac artery
First clinical application - autofluorescence

66-year old diabetic patient with unstable angina and moderate to severe stenosis of the LCX and moderate stenosis of the LAD

- Necrotic cores show elevated autofluorescence in the NIRF-range (NIRAF)
- Imaging with NIRF-OCT system in patients undergoing PCI for stable CAD (n=12)
- NIRAF intensity was elevated in plaques with a high-risk morphological phenotype (p < 0.05)

Plaque-related autofluorescence could be used as an endogenous imaging parameter for detection of vulnerable lesions!

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• Histopathology has showed us the progression of early atherosclerotic lesions into plaques with a high risk of rupture and vessel occlusion (vulnerable plaques)
• Intravascular imaging with OCT is able to visualize all steps of atherosclerotic development but is not able to reveal all vulnerable plaques due to technical limitations
• Molecular imaging describes a whole range of applications used to visualize processes involved in the plaque progression
• Various markers (externally and internally) can be used to visualize epitopes involved in these processes (e.g. NIRF)
• Clinical application is still limited but will hopefully increase in the future
Thank you for your attention