THE COMPLEX RELATION BETWEEN VULNERABILITY AND ISCHEMIA

a paradigm shift

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Paradox or antithesis?

Two apparently contradictory concepts:

1. *The most important prognostic factor in coronary artery disease, is the presence and extent of inducible ischemia:*
   - ischemic lesions → *poor prognosis*
   - non-ischemic lesions → *excellent outcome with medical treatment*

   versus

2. *concept of vulnerable plaque:*
   - plaque rupture occurs on non-significant lesions and is unpredictable
Incidence of coronary artery disease in asymptomatic, apparently healthy persons

> 50 years old : 25%
> 60 years old : 40%

Sims et al, Am Heart J 1983
Maseri, Ischemic Heart Disease 1995

What about the prognosis of these patients?

→ Related to inducibility of ischemia
Prognostic significance of reversible ischemia at MIBI-Spec

Average % Hard Events per year

12000 Patients

7.4

risk of death or AMI from an ischemic stenosis is 20 x higher than from a non-ischemic stenosis of similar angiographic severity !!!!!

iskander S, Iskandrian A E  JACC 1998
DEFER study (N=325):
Cardiac death and Acute MI after 5 years

- FFR > 0.75: 3.3%
- FFR < 0.75: 15.7%

P < 0.03

- non-ischemic stenosis, treated medically
- ischemic stenosis, treatment by PCI

Ischemic lesion is much more dangerous than non-ischemic lesion

JACC 2007; 49: 2105-2111
PCI OF ISCHEMIC LESION IMPROVES OUTCOME!

558 patients, functionally significant stenosis without symptoms: randomization in 3 treatments strategies

Davies et al, Circulation, 1997

Cumulative Mortality

- No treatment
- Medical treatment
- Revascularization

Cumulative Mortality

0% 4% 8% 12% 16% 20% 24%

P < 0.05
EVIDENCE-BASED MEDICINE:

• prognosis is related to inducibility of ischemia

• PCI of “ischemic” lesions (lesions associated with reversible ischemia) makes sense and improves symptoms and outcome

• PCI non-ischemic lesions is questionable and not better than medical treatment
BUT......

HOW DOES THIS RELATE TO THE CONCEPT OF

“MILD BUT DANGEROUS VULNERABLE PLAQUE”

?
Plaque Rupture

TCFA

Renu virmani, ETP course 2005
Let’s be a little bit more critical now ........
and distinguish facts and fiction....
FACTS:
• plaques are very common
• majority of plaques has an excellent prognosis with medical treatment
• only few plaques are vulnerable
• strongest indicator with respect to prognosis is associated ischemia

FICTION:
• every plaque is vulnerable
• every vulnerable plaque leads to ACS
• most ACS occurs in mild plaques
• screening of vulnerability can be done by imaging
Screening for vulnerable plaque? How to start?

• Suppose you have a method (whether invasive or not) with a sensitivity and specificity of 95% (*utopic*, but let’s assume).

• In the city of Eindhoven (250,000 citizens), the total number of citizens with hidden or overt CAD is at least 25,000, corresponding with at least 100,000 non-significant plaques.

• In the next 3 month, only 300 patients will develop ACS

**Suppose you screen all patients with plaques for “vulnerability”:**

285 will be discovered correctly (true positives)
5000 will be “false” positive

→ **predictive value is 5%!!**

you will place 20 unnecessary stents to prevent 1 ACS
The majority of ACS occur at the site of mild lesions. 

The mythe of the “dangerous” plaque
Underlying Stenosis Severity of Abrupt Total Occlusions

"Acute Coronary Syndromes most often occur at the site of mild stenoses"
Do Myocardial Infarctions Evolve from Mild Stenoses?

Serial Angiographic (Retrospective) Studies in Patients with MI and a Prior Coronary Angiogram

No QCA, No IVUS but unblinded “eyebolling”

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Delay Angio-MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambrose et al, JACC 1988</td>
<td>23</td>
<td>1 month to 7 years</td>
</tr>
<tr>
<td>Little et al, Circulation 1988</td>
<td>42</td>
<td>4 days to 6.3 years</td>
</tr>
<tr>
<td>Giroud et al, AJC 1992</td>
<td>92</td>
<td>1 month to 11 years</td>
</tr>
<tr>
<td>Moise et al, AJC 1984</td>
<td>116</td>
<td>39 months</td>
</tr>
<tr>
<td>Webster et al, JACC 1990</td>
<td>30</td>
<td>55 months</td>
</tr>
<tr>
<td>Hackett et al, AJC 1989</td>
<td>10</td>
<td>21 months</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>313</strong></td>
<td></td>
</tr>
</tbody>
</table>

A few days to 11 years (average 3.9 years !!!)
THE MYTHE OF
THE “DANGEROUS” PLAQUE

The hypothesis of the occurrence of acute MI on such previously non-significant plaque is based upon

- 6 small retrospective studies
- with a total of 313 patients
- in whom the “index” catherization was performed an average of 3.9 years before the acute event

All other literature (21 “meta-analyses” and hundreds of references), refer to these 6 studies !!!
Coronary Occlusion at 5 Years as a Function of Stenosis Severity

Coronary Segments (n)

<table>
<thead>
<tr>
<th>% Occlusion at 5 Year</th>
<th>Stenosis Severity at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>0-49%</td>
<td>1%</td>
</tr>
<tr>
<td>50-80%</td>
<td>2%</td>
</tr>
<tr>
<td>81-95%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Adapted from Alderman et al. J Am Coll Cardiol 1993
IVUS Examination: Clinical Outcome after Deferred Interventions

- 300 pts; 13 mos F-U
- CSA = only independent predictor of events
- Independent predictors of TLR: diabetes, min CSA, AS
- When CSA > 4 mm$^2$:  
  - event rate: 4%
  - TLR: 2.8%

Abizaid AS et al. Circulation, 1999
Severity of Coronary Atherosclerosis at Sites of Plaque Rupture with Occlusive Thrombosis

Area Stenosis = \( \frac{\text{Vessel area} - \text{lumen area}}{\text{Vessel area}} \)

Mean = 91 % Area Stenosis
\( \approx 68 \% \) Diameter Stenosis

\( \frac{\text{Total Number (n=182) of Stenoses}}{\text{Area Stenosis (\%)}} \)

\( \begin{align*}
\text{67-75\%} & : 0 \\
\text{76-80\%} & : 0 \\
\text{81-90\%} & : 20 \\
\text{>90\%} & : 62 \\
\end{align*} \)

Qiao J-H et al. JACC 1991
Stenosis Severity at Primary PCI in AMI

- 156 stenoses with distal flow enabling accurate QCA out of 250 consecutive Acute MI’s
- In 92%, underlying stenosis was > 50%
- In 71%, underlying stenosis was > 70%

Frobert et al CCI, 2007, 70: 958-965
250 consecutive patients with ST-elevation MI in the Catharina Hospital:

- underlying stenosis angiographically significant in 92% of the cases

- At meticulous anamnesis, 80% of patients had recurrent chest pain in the year before the acute myocardial infarction occurred!!

_Frobert et al CCI, 2007, 70: 958-965_
The fact that acute coronary syndromes “sometimes” occur in relation to a previously insignificant plaque, does not mean that a plaque is more dangerous than a severe stenosis, because:

**Non-significant “plaques”:**

Are 20 x more frequent than severe lesions. So, even if 50% of ACS would be related to such plaque, its individual risk is 20 times lower than the risk of a severe stenosis

**Non-significant “plaques”:**

Are often not giving complaints and therefore not treated in a similar way as a physiologically significant stenosis *(aspirin, statines, stenting)*
Paradox or antithesis?

*Ischemia-related concept of prognosis*
- Excellent outcome of medical treatment in non-ischemic stenosis
- Dangerous lesions are those associated with reversible ischemia

versus

*Concept of vulnerable plaque*

→ relation between vulnerability and ischemia !?!
This is not a mild plaque but a 70% area stenosis !!!

Low FFR

Renu Virmani, ETP course 2005
“The missing link”

Is there a link between vulnerability and ischemia?

Hypothesis:

• repetitive ischemia and
• high shear stress / pressure gradients

induce vulnerability

Supported by studies on the relation between vulnerability markers and low FFR: on-going work of Pasterkamp et.al. Heart 2007
TOLL-LIKE RECEPTORS ON LEUCOCYTES AND VULNERABILITY MARKERS

- Toll-like receptors (TLRs) are part of innate immune system

- **Activation of TLRs results in production of pro-inflammatory cytokines, TNF-α, and other markers of vulnerability**

- In animal models, **ischemia triggers TLR expression** with increased production of TNF-α and other pro-inflammatory substances

J Cereb Blood Flow Metab. 2004 Nov;24(11):1288-304*
If it is realized that also in humans

- coronary ischemia induces activation of TLRs
- ischemic coronary lesions can be detected by FFR

Is FFR related to TLR activity?
Pilot Study in 50 humans: Methods

- Patients undergoing FFR measurement included in study
- Arterial blood sample drawn immediately following sheath insertion
- Blood sample transferred to lithium-heparin tube and placed on ice to prevent preliminary TLR activation
- Samples incubated overnight with TLR ligands
- TLR2 stimulation: 500, 50 and 5 ng/ml Pam3Cys
- TLR4 stimulation: 100, 10 and 1 ng/ml lipopolysaccharide
- ELISA for TNF-α and other cytokines in stimulated samples

Steeg et al, Heart 2007
TLR2 stimulation (Pam3Cys)

Steeg et al, Heart 2007
Results of that pilot study

- TNF-α production following stimulation of TLRs in whole blood is significantly higher if FFR<0.75

- Episodes of myocardial ischemia trigger for enhanced sensibility of TLRs and production of markers of inflammation

2 running studies:

- TERMS study: Toll-like receptor expression and response in patients undergoing myocardial SPECT (100 patients, currently running)

- CTMM: Large multicenter trial to establish relation between FFR and vulnerability markers (800 patients)
Yesterday:

Pro-inflammatory cytokines etc

\[ \Rightarrow \]

Vulnerability

(“out of the blue”)
Today / Tomorrow:

Ischemic episodes → Pro-inflammatory cytokines etc → Vulnerability
Suppose aliens would visit us and would like to investigate the determinants of a fire.

Substance X, always detected when there has been a fire

Living unidentified object releasing the substance X

“Substance X (also called “water”) must be dangerous substance!”
new paradigm:

Plaque / stenosis
↓
Repetitive ischemic episodes
↓
production of remodelling-promoting substances

successful remodelling, relieve of ischemia
overshoot, plaque rupture

Searching for vulnerability starts with searching for ischemia
Screening for vulnerable plaque? How to continue?

• Strongest indicator with respect to prognosis, is inducible ischemia.

• Historical data & ACIP-trial: in asymptomatic patients with proven ischemia (ET / MIBI-Spect / FFR) but without intervention, at least 5% (50/1000) will develop ACS within the next year.

• suppose you screen 1000 patients with ischemic lesions: 45 will be discovered correctly (“true”-positives) 45 will be “false” positive

**predictive value is 50%!!**
you will place 1 unnecessary stent to prevent 1 ACS

Bayes theorem, Melin et.al, Circulation 1981
IN SUMMARY:

- There is a relation between vulnerability and ischemia, although complex and not yet completely understood.

- Vulnerability does not occur “out-of-the-blue”, but is promoted in many cases by repetitive episodes of ischemia.

- Searching for vulnerable plaques in general, is searching for the needle in the haystack.

- However, the haystack can be made much smaller (and the screening process made more effective), by first searching for ischemia!