CORONARY PHYSIOLOGY IN THE CATHLAB:

STRUCTURE AND FUNCTION OF THE CORONARY CIRCULATION

Educational Training Program ESC
European Heart House
April 25th - 27th 2013

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Disclosures:

Dr Pijls receives institutional research grants from St Jude Medical, and Maquet

Dr Pijls is consultant to St Jude Medical, and to Heartflow
ISSUES TO BE DISCUSSED

- structure of the coronary circulation
- relation between vessel size and perfusion area
- endothelium and development of atherosclerosis
- the 2 or 3 compartment model of the coronary circulation
- collaterals
- why functional testing / FFR?
- which lesions should be treated
Let’s have a closer look at the coronary tree…..
Fractal structure of the coronary circulation (Gould, Finet)
epicardial compartment (> 400 µm) traditionally visible by angiography and more recently by many invasive and non-invasive imaging methods
Regulation of coronary blood flow by arteriolar sphincters

normaal

F

R

reserve \approx \text{factor 5}

1/5 R

RUST

MAX. VASODILATATIE
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Relationship between vessel size and myocardial mass

Cross Sectional Area (~ flow)

Vessel Diameter (mm)

Regional Myocardial Mass

Regional Myocardial Mass (Grams)

Normal FFR = 1.0 irrespective Where it is measured

<table>
<thead>
<tr>
<th>Pressure (P_d) (mm Hg)</th>
<th>Flow (Q) (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
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<tr>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>100</td>
<td>25</td>
</tr>
</tbody>
</table>

IVUS-CSA

9 mm²
7 mm²
5 mm²
3 mm²
SIZE of the person

$FFR = 0.68$ means exactly the same in both persons.

$CSA\text{ by IVUS} = 3.3\ mm^2$ has a completely different meaning in both persons.
Value of ANY morphologic methodology (QCA, IVUS, OCT) to assess functional significance of a stenosis is limited by definition because there is simply no normal reference value.
We cannot understand the physiologic significance of a stenosis without taking into account the extent of the distal perfusion territory

…….especially not under pathologic conditions, when the “physiologic match” between vessel size and perfusion area has been lost
With permission of Dr Haitma Amin, Bahrain
similar stenosis but different extent of perfusion area

4 mm² is too small

QCA, IVUS identical CSA
4 mm²

4 mm² is sufficient

identical CSA, but different significance of stenosis
FFR accounts for the extent of the perfusion area:

Anatomic stenosis severity by IVUS or QCA is identical but physiologic severity has decreased.

→ FFR accounts for these changes !!!
Disconnect between Anatomy and Physiology

50% Stenosis       FFR=0.85

Collaterals

Myocardium

Collateral-Supplied Myocardium

Vessel-Supplied Myocardium

50% Stenosis

FFR=0.73

During Maximal Hyperemia
FFR in the distal **LAD** before and After recanalization of the **RCA**

**Before**
- RCA recanalisation
- FFR in distal LAD: 0.73

**After**
- RCA recanalisation
- FFR in distal LAD: 0.82
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DEVELOPMENT OF ATHEROSCLEROSIS

Normal
↓
Endothelial dysfunction
↓
First stages of atherosclerosis:
↓
*IVUS, OCT, FFR (abnormal pressure decline)*

Macroscopic atherosclerotic disease:
*angio,*
*non-invasive imaging (CT, MRI)*
The earliest phase of atherosclerotic coronary disease, is **endothelial dysfunction**.

This is **un**visible by any imaging method, but can be demonstrated by **functional testing**.
35-y-old male, hypertension, heavy smoker, chest pain at exercise and positive ET
Physiologic and pathologic vasomotion in 35-year old male, heavy smoker, and chest pain at exercise
tip of infusion catheter, administration of papaverin

pressure guidewire
1 papaverine induced vasodilation
2 flow-induced vasodilation
3 flow-induced paradoxical vasoconstriction
early stage of atherosclerosis

Male, 41-year-old

21-03-2006
diffuse atherosclerosis, early stage
Different stages of gross coronary atherosclerosis, easily visible on angiogram and by several non-invasive methods

Fibrous cap atheroma with hemorrhage

Thin fibrous cap atheroma

Fibrocalcific plaque

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epicardial compartment ( > 400 µm)

microvascular compartment

traditionally visible by angiography and more recently by many invasive and non-invasive imaging methods

Black box (until recently)
The coronary microcirculation:

Still a black box ??
IMAGING OF THE EPICARDIAL COMPARTMENT

- non-invasively by CT, MRI
- invasively by angio, IVUS, OCT, and some newer techniques

FUNCTIONAL ASSESSMENT OF THE EPICARDIAL COMPARTMENT

- coronary pressure & FFR

FUNCTIONAL ASSESSMENT OF THE MICROCIRCULATION:

- IMR (Bill Fearon, Bernard De Bruyne)
- absolute flow & resistance (Gabor Toth, Inge wijnbergen)
The third compartment focal and diffuse epicardial disease hard to distinguish by traditional methods, but easily assessed and quantified by FFR (hyperemic pullback recording)
The 3rd compartment:

Diffuse epicardial coronary disease, whether or not with super-imposed focal disease

(Nils Witt, tomorrow)
How to assess the functional significance of diffuse disease, whether or not with super-imposed focal lesions?

**Which is more significant?**

- CCTA, Angiography, IVUS, or OCT

**Impossible by anatomic methods**
The 3rd compartment:

Diffuse epicardial coronary disease (Nils Witt)

easily evaluable by FFR (pressure pull-back recording)

important consequence for treatment (interventional or medical)
Male 58-y-old

Typical chest pain; positive MIBI-Spect inferior wall
Typical chest pain; positive MIBI-Spect inferior wall
Typical chest pain; positive MIBI-Spect inferior wall
Distal stenosis

Mid in-stent restenosis

Dist. stenose

Prox. stenose

Hyperemia: Pull back recording

FFR = 0.65
Hyperemic pull-back recording along the RCA
FFR: The Pressure Pull-back Curve

*Pressure pull-back curve at maximum hyperemia:*

- place sensor in distal coronary artery
- induce sustained maximum hyperemia by i.v. adenosine, or i.c. papaverine
- pull back the sensor slowly under fluoroscopy
- the individual contribution of every segment and spot to the extent of disease can be studied in this way

*Coronary pressure is unique in this respect and such detailed spatial information cannot be obtained by any other invasive or non-invasive method*
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Quantitative assessment of the contribution of coronary arterial and collateral flow to total myocardial flow is possible by coronary pressure measurements, but not trivial.

\[ Q_{myo} = Q_{cor. artery} + Q_{collateral} \]
Fractional collateral flow (also called CFI\(\rho\)) =

\[
\text{FFR}_{\text{coll}} = \frac{P_w - P_v}{P_a - P_v}
\]

Venous pressure not negligible anymore!
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next 2 days
In patients with coronary artery disease, the most important factor with respect to both

- functional class *(symptoms)*
- and prognosis *(outcome)*

Is the *presence and extent of inducible ischemia*

→ knowledge if and which lesion(s) is / are responsible for inducible ischemia, is paramount for adequate treatment in the cath.lab

→ *FRACTIONAL FLOW RESERVE*
IN SUMMARY:

• There is complex interrelation between the structure and function of the coronary circulation, not only under physiologic circumstances in healthy persons *(vessel size/perfusion area relation, endothelium, regulation of coronary blood flow)*, but also under pathologic circumstances *(atherosclerosis, plaques, stenosis, vulnerability, and ischemia)*.

• Understanding this relation is paramount to treat our patients in the cathlab in the best possible way.

• Hopefully, this course will contribute both to that *understanding* and to its translation into *practical skills*.
EINDE
EVIDENCE-BASED MEDICINE:

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

• PCI of non-ischemic lesions has no benefit, is no evidence-based medicine, is potentially harmful, and unnecessary expensive.

→ knowledge if and which lesion(s) is / are responsible for inducible ischemia, is paramount for adequate treatment in the cath.lab

→ FRACTIONAL FLOW RESERVE
THE CORONARY ANGIOGRAM IS ONLY A CRUDE TOOL TO PREDICT IF A STENOSIS CAUSES ISCHEMIA:

- shortcomings of imaging itself

- discrepancy between structure and function (especially under pathologic conditions)

- very hard to predict functional severity of disease from structural abnormalities

- complex influence of pathologic structure on blood flow
similar stenosis but different extent of perfusion area

4 mm$^2$ is too small

QCA, IVUS
identical CSA
4 mm$^2$

4 mm$^2$ is sufficient

identical CSA, but different significance of stenosis
\[ \Delta P = \frac{k \rho (v_2^2 - v_0^2)}{2} = \frac{k \rho Q}{2} \left( \frac{1}{a_s^2} - \frac{1}{a_0^2} \right) \]
Even in the geometrically most “ideal” stenosis, it is impossible to predict the functional severity and influence on blood flow from hydraulic theory.
In summary: EVIDENCE-BASED MEDICINE:

knowledge if and which lesion(s) is / are responsible for inducible ischemia, is paramount for adequate treatment in the cath.lab

The angiogram (and IVUS!) have fundamental Shortcomings to indicate ischemia correctly

Rationale of Fractional Flow Reserve
Whatever the stenosis might look like..., whatever the pressure/flow relations across the stenosis might be....,

To understand the meaning of the stenosis for the patient, the MOST important number to know is the resulting distal perfusion pressure at hyperemia, as a fraction of normal perfusion pressure ( = aortic pressure)

This ratio determines completely the physiologic significance of the stenosis and its consequences for the patient!!

It is called FFR
einde
During Maximal Vasodilatation

\[ FFR_{myo} = \frac{P_d}{P_a} = 0.70 \]
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• collaterals
• why functional testing / FFR ?
• which lesions should be treated
  ——→ those causing ischemia
• *ischemia & vulnerability: paradox or antithesis* ?
  *(Bernard De Bruyne, later today)*
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  \( \rightarrow \text{those causing ischemia} \)
• ischemia & vulnerability: paradox or antithesis ?
Paradox or antithesis?

Excellent outcome of medical treatment in non-ischemic stenosis (DEFER study, many non-invasive studies)

versus

concept of vulnerable plaque
today  ?  tomorrow

TCFA

Plaque Rupture

Renu virmani, ETP course 2005
Let’s look a little bit more critical to such “plaques”....
What are the facts ?? What is the fiction ??
(Vulnerable) Plaque: 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
• vulnerability can be assessed by imaging
Underlying Stenosis Severity of Abrupt Total Occlusions

Falk, Shah and Fuster, Circulation 1995

"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 Angiography-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><strong>A few days to 11 years (average 3.9 years)</strong></td>
</tr>
</tbody>
</table>

(average 3.9 years)
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” catheterization 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

Adapted from Alderman et al. J Am Coll Cardiol 1993
DEFER study (N=325) :
Cardiac death and Acute MI after 5 years

- ischemic lesion is much more dangerous than non-ischemic lesion
- risk of individual non-ischemic lesion to cause death or AMI, is very small and < 1 % per year !!

JACC 2007; 49: 2105-2111
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_
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
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• vulnerable plaques: facts & fiction
• ischemia & vulnerability: paradox or antithesis?
“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
TLR2 stimulation (Pam3Cys)

Versteeg et al, Heart 2007
Concept of Yesterday:

Pro-inflammatory cytokines, activated monocytes, etc

Vulnerability ("out of the blue")
Concept of Tomorrow:

ischemic episodes

Pro-inflammatory cytokines, activated monocytes, etc

Vulnerability
by the way: 70% area
Stenosis !!

Concept of today:

ischemic episodes

Pro-inflammatory cytokines etc

Vulnerability
new paradigm:

Plaque / stenosis
\[\rightarrow\]
Ischemic episodes
\[\rightarrow\]
production of remodelling-promoting substances

- successful remodelling, decrease of ischemia
- overshoot, plaque rupture

Searching for vulnerability starts with searching for ischemia
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!”
FUNCTIONAL ASSESSMENT OF BOTH COMPARTMENTS TOGETHER:

• non-invasively
  (exercise testing, stress echo, Mibi)

• invasively: intracoronary Doppler, absolute flow

FUNCTIONAL ASSESSMENT OF THE MICROCIRCULATION:

• Index of Microcirculatory Resistance (IMR)
The coronary microcirculation:

Still a black box ??
focal and diffuse
Epicardial disease

microvascular compartment

Invasive indexes *(saturday morning)*:
IMR *(Bill Fearon)*
absolute resistance *(Nico Pijls)*
We cannot understand the physiologic significance of a stenosis without taking into account the distal perfusion territory.
majority of resistance located in arterioles (100-400 µm)
Death & MI during 5 years of follow-up after PCI vs Medical Treatment in ISCHEMIC stenosis.

Kaplan-Meier plots of Landmark Analysis of

**Death or MI**

- **≤7 days:** HR 7.99 (0.99-64.6); p=0.038
- **> 8 days:** HR 0.42 (0.17-1.04); p=0.053
- **p-interaction:** p=0.003

---

**FAME 2: FFR-Guided PCI versus Medical Therapy in Stable CAD**
Kaplan-Meier plots of Landmark Analysis of **Death or MI**

- **≤7 days:** HR 7.99 (0.99-64.6); *p*=0.038
- **> 8 days:** HR 0.42 (0.17-1.04); *p*=0.053

*p*-interaction: *p*=0.003

**FAME 2: FFR-Guided PCI versus Medical Therapy in Stable CAD**
Patients with proven ischemia

freedom from angina after stenting ischemic stenosis

DEFER-study, JACC 2007; 49 : 2105-2111
Death & MI 5 during 5 years of follow-up after PCI vs Medical Treatment in **NON-ischemic** stenosis

Pijls et al
JACC 2007
Is it important to detect ischemia?

Log hazard ratio for revascularization (Revasc) vs medical therapy (Medical Rx) as a function of % myocardium ischemic based on final Cox proportional hazards model.

Above 10% ischemic myocardium, the survival benefit from revascularisation increases with the extent of ischemia.

The risk for death or acute myocardial infarction in the next five years is 20 times higher for an ischemic lesion compared to a non-ischemic lesion !!!

12000 Patients (2 x 6000) similar stenosis severity by coronary angio

% death or Acute MI/year

no ischemia         ischemia

0.6                  7.4

Iskander S, Iskandrian A E JACC 1998
Risk to die or experience myocardial infarction in the next 5 years related to a coronary stenosis:

- **non-ischemic stenosis**: $< 1\% \text{ per year} \quad (*)$
  (NUCLEAR studies, PET, MRI, DEFER, FAME)

- **ischemic stenosis, if left untreated**: $5-10\% \text{ per year}$
  (Many historical registries, nuclear studies, ACIP, CCTA, MRI, FFR)

- **stented stenosis**: $2-3\% \text{ per year}$
  (e.g. DEFER, FAME, SYNTAX, many large studies and registries)
HIER HOREN OOK ERGENS 1 of 2 DIas
UIT FAME 1 en FAME 2
Uit Fame 2 is er al
Uit Fame 1 de dia met het lage aantal infarcten
En dood (0,2%)
THE KEY ISSUE IN INTERVENTIONAL CARDIOLOGY IS TO DISCRIMINATE THOSE LESIONS RESPONSIBLE FOR INDUCIBLE ISCHEMIA

Fractional Flow Reserve
THE EPICARDIAL COMPARTMENT IS RATHER EASY TO ASSESS:

**IMAGING OF THE EPICARDIAL COMPARTMENT**

- non-invasively by CT, MRI
- invasively by angio, IVUS, OCT, and some newer techniques

**FUNCTIONAL ASSESSMENT OF THE EPICARDIAL COMPARTMENT**

- coronary pressure & FFR
focal and diffuse Epicardial disease

microvascular compartment

Invasive indexes:
IMR (*Bill Fearon, Bernard De Bruyne*)

absolute flow & resistance (*Gabor Toth, Inge wijnbergen*)

FFR

Specific indexes ??