STRUCTURE OF THE CORONARY CIRCULATION

Educational Training Program ESC
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• *Dr Pijls received institutional research grants from St Jude Medical and Pharma Solutions*

• *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 *(to be discussed tomorrow)*
03 cc/schema Braunwald
Let’s have a closer look at the coronary tree…..
Fractale structure of the coronary circulation (Gould, Finet)
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)
Regulation of coronary blood flow by arteriolar sphincters

To be further discussed by Dirk Duncker
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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)

AORTA 100 mmHg

pressure \((P_d)\) (mm Hg)

flow \((Q)\) (ml/min)

IVUS-CSA

9 mm\(^2\)

7 mm\(^2\)

5 mm\(^2\)

3 mm\(^2\)
Normal FFR = 1.0 irrespective where it is measured.
**SIZE of the person (importance of perfusion territory)**

Suppose both of these 2 persons have a proximal LAD stenosis.

- **FFR = 0.68**
  - means exactly the same in both persons.

- **CSA by IVUS = 3.3 mm²**
  - has a completely different meaning in both persons.

- **LAD blood flow = 100 ml/min**
  - 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 mm$^2$ is too small
QCA, IVUS
identical CSA
4 mm$^2$

4 mm$^2$ 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

50% Stenosis

Collateral-Supplied Myocardium

Vessel-Supplied Myocardium

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

Normal
↓
Endothelial dysfunction
↓
First stages of atherosclerosis:
   \textit{IVUS, OCT, FFR (abnormal pressure decline)}
↓
Macroscopic atherosclerotic disease:
   \textit{angio, non-invasive imaging (CT, MRI)}
The earliest phase of atherosclerotic coronary disease, is **endothelial dysfunction**.

This is unvisible 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

29 cc/Achol vb (6)
Physiologic and pathologic vasomotion in 35-year old male, heavy smoker, and chest pain at exercise
1. Papaverine-induced vasodilation
2. Flow-induced vasodilation
3. Flow-induced paradoxical vasoconstriction
early stage of atherosclerosis

Male, 41-year-old

22-03-2006
diffuse atherosclerosis, early stage
hyperemic pull-back LAD

diseased segment
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

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Black box (until recently)
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
The coronary microcirculation: *Still a black box??*

**IMAGING OF THE MICROVASCULAR COMPARTMENT**

- can only be done indirectly (blush, PET, MIBI. MRI)

**FUNCTIONAL ASSESSMENT OF THE MICROCIRCULATION:**

- IMR (*Bill Fearon, Keith Oldroyd*)
- absolute flow & resistance (*Bernard De Bruyne*)

→ Saturday morning session
The third compartment **focal and diffuse** epicardial disease is microvascular compartment.

Hard to distinguish by traditional methods, but easily assessed and quantified by FFR (hyperemic pullback recording).
How to assess the functional significance of diffuse disease, whether or not with super-imposed focal lesions?

Which is more significant?

\[
\begin{align*}
\text{100} & \quad 3 \text{ mm}^2 & \quad 85 \\
\text{FFR} = 0.85
\end{align*}
\]

\[
\begin{align*}
\text{100} & \quad 5 \text{ mm}^2 & \quad 5 \text{ mm}^2 & \quad 60 \\
\text{FFR} = 0.60
\end{align*}
\]

Impossible by anatomic methods

CCTA, Angiography, IVUS, or OCT
The 3rd compartment:

Diffuse epicardial coronary disease (whether or not with superimposed focal lesions) *(Bernard De Bruyne, tomorrow morning)*

- 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
CASE # 3
Distal stenosis

Mid in-stent restenosis

Dist. stenose

Hyperemia: Pull back recording

FFR = 0.65
Hyperemic pull-back recording along the RCA
IN SUMMARY:

• Coronary anatomy is just one side of the coin.

• 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
The 3rd compartment:

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

(Bernard De Bruyne, tomorrow)
In patients with coronary artery disease, the most important factor with respect to both

• functional class \((\text{symptoms})\)

• and prognosis \((\text{outcome})\)

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
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
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 coron circulation
• **collaterals**
• why functional testing / FFR ?
• which lesions should be treated
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- structure of the coronary circulation
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- the 2 or 3 compartment model of the coronary circulation
- collaterals \textit{(to be discussed tomorrow)}
- which lesions should be treated?
- why functional testing / FFR?

\textit{next 2 days}
\[ Q_{\text{myo}} = Q_{\text{cor.artery}} + Q_{\text{collateral}} \]

Quantitative assessment of the contribution of coronary arterial and collateral flow to total myocardial flow is possible by coronary pressure measurements, but not trivial.

Pijls & De Bruyne: Circulation 1993
Coronary Pressure, sec edition, Kluwer 2000
Fractional collateral flow (also called CFI\(p\)) = 

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

Venous pressure not negligible anymore!
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 mm² is too small

QCA, IVUS
identical CSA
4 mm²

4 mm² is sufficient

identical CSA, but different significance of stenosis
\[ \Delta P = \frac{k \rho (v_s^2 - v_0^2)}{2} = \frac{k \rho Q}{2} \left( \frac{1}{a_s^2} - \frac{1}{a_0^2} \right) \]
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
During Maximal Vasodilatation

\[ \text{FFR}_{\text{myo}} = \frac{P_d}{P_a} = 0.70 \]
ISSUES TO BE DISCUSSED

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• the 2 or 3 compartment model of the coronary circulation
• 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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- **which lesions should be treated**
  
  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
Let’s look a little bit more critical to such “plaques”....
What are the facts ?? What is the 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 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><strong>A few days to 11 years (average 3.9 years !!!)</strong></td>
</tr>
</tbody>
</table>
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

Coronary Segments (n)

Stenosis Severity at Baseline

% Occlusion at 5 Year

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!!
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!!*
INCIDENCE OF CORONARY ARTERY DISEASE IN ASYMPTOMATIC, APPARENTLY HEALTHY PERSONS

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
• structure of the coronary circulation
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• the 2 or 3 compartment model of the coronary circulation
• collaterals
• why functional testing / FFR?
• which lesions should be treated
• vulnerable plaques: facts & fiction
• ischemia & vulnerability: paradox or antithesis?
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)

- Pam3Cys 5 ng/ml
- Pam3Cys 50 ng/ml
- Pam3Cys 500 ng/ml

Versteeg et al, Heart 2007
Pro-inflammatory cytokines, activated monocytes, etc

Vulnerability
(“out of the blue”)
Concept of Tomorrow:

Ischemic episodes

Pro-inflammatory cytokines, activated monocytes, etc

Vulnerability
Concept of today:

by the way: 70% area Stenosis !!

ischemic episodes

Pro-inflammatory cytokines etc

Vulnerability
new paradigm:

Plaque / stenosis
↓
Ischemic episodes
↓
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 (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

**Specific indexes ??**

→ **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!
The majority of resistance is located in arterioles (100-400 µm).
Death & MI during 5 years of follow-up after PCI vs Medical Treatment in ISCHEMIC stenosis

Shaw et al, Circulation 2008

PCI

MEDICAL

Rate of death or MI (%)
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
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
freedom from angina after stenting ischemic stenosis
Death & MI 5 during 5 years of follow-up after PCI vs Medical Treatment in **NON-ischemic** stenosis

- **MEDICAL**: 3.3%
- **PCI**: 7.9%

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.

*P<0.001


ETP, April 2011
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 !!!

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% per year *  
  (NUCLEAR studies, PET, MRI, DEFER, FAME)

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

- **stented stenosis:** 2-3% per year  
  (e.g DEFER, FAME, SYNTAX, many large studies and registries)
Hier horen ook gereeds 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)