CORONARY PHYSIOLOGY IN THE CATHLAB:

THEORY AND PRACTICAL SET-UP OF FFR

Educational Training Program ESC
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Gruentzig and other early investigators, intuitively noticed the importance of coronary pressure measurement.
But....they were limited by

- inadequate equipment to measure pressure: *(no Pressure Wire)*
- inadequate hemodynamic measuring conditions *(no hyperemia)*
- inadequate interpretation of pressures *(no FFR)*
But....they were limited by

- inadequate equipment to measure pressure: ➡️ balloon catheter instead of 0.014’ wire (overestimation of gradients)
But....they were limited by

- inadequate equipment to measure pressure: 
  \(\rightarrow\) *balloon catheter instead of 0.014’ wire*

- inadequate hemodynamic conditions: 
  \(\rightarrow\) *measurements at baseline instead of using maximum hyperemia*
\[ \Delta P = f.Q + s.Q^2 \]

- \( f = \text{friction coefficient} \)
- \( s = \text{separation coefficient} \)

70% long prox LAD stenosis
50% ostial left main stenosis

resting gradient cannot predict hyperemic gradient
“The resting gradient is far from enough but unfortunately, it’s all I have now”.
But....they were limited by

- inadequate equipment to measure pressure:
  → *balloon catheter instead of 0.014’ wire*

- inadequate hemodynamic conditions:
  → *measuring at baseline instead of using maximum hyperemia*

- inadequate interpretation:
  → *transstenotic gradients instead of Fractional Flow Reserve*
2 different patients with each hyperemic trans-stenotic gradient of 30 mmHg:

\[ \Delta P = 30 \text{ mmHg} \]

- **Top Diagram**
  - Pressure before stenosis: 100 mmHg
  - Pressure after stenosis: 70 mmHg
  - FFR = \( \frac{70}{100} = 0.70 \)

- **Middle Diagram**
  - Pressure before stenosis: 70 mmHg
  - Pressure after stenosis: 40 mmHg
  - FFR = \( \frac{40}{70} = 0.58 \)

- **Bottom Diagram**
  - Pressure before stenosis: 70 mmHg
  - Pressure after stenosis: 40 mmHg
  - Pressure distal to stenosis: 15 mmHg
  - FFR = \( \frac{25}{55} = 0.45 \)
Fortunately, these 3 limitations were overcome:

• In the late eighties, 0.014” pressure guide wires became available, enabling reliable distal coronary pressure (Tenerz, 1988)

• Safe and reproducible hyperemic drugs were validated for use in the human coronary circulation (Wilson, 1985)

• And it was recognized that not gradients in itself are important, but the ratio of perfusion pressures at hyperemia (Pijls & De Bruyne, 1991)
FRACTIONAL FLOW RESERVE:

The index FFR (Fractional Flow Reserve) is based upon the two following principles:

• It is not resting flow, but maximum achievable flow which determines the functional capacity (exercise tolerance) of a patient.

• At maximum vasodilation (corresponding with maximum hyperemia or with maximum exercise), blood flow to the myocardium is proportional to myocardial perfusion pressure (~hyperemic distal coronary pressure).
During Maximal Vasodilatation

\[ FFR_{myo} = \frac{P_d}{P_a} = 0.70 \]
\[ FFR_{myo} = \frac{P_d}{P_a} \]

\[ P_a = \text{mean aortic pressure at maximum hyperemia} \]

\[ P_d = \text{mean distal coronary pressure pressure at maximum hyperemia} \]
**FFR = 0.6 means:**

“Due to this particular stenosis, maximum achievable blood flow to the myocardium supplied by this artery, is only 60% of what it would be if this coronary artery were completely normal”

**If, after PCI, FFR increases to 0.9, this means:**

“Maximum achievable flow (and therefore maximum oxygen supply) has increased by 50% and is 90% now of the value achievable if the artery were completely normal”
Application in catheterization laboratory

Pressure wire + hyperemic stimulus = FFRmyo
0.014 sensor-tipped PTCA guidewire (St Jude Medical & Volcano)
Mr van Z. 77 years, stable ang 2-3 posit ET
Fractional Flow Reserve in Clinical Practice

Fractional Flow Reserve (FFR) is a non-invasive measure used to assess the severity of coronary artery narrowing. It is calculated by comparing the distal coronary pressure at rest and during hyperemia.

- **REST**
  - Pressure values: 150, 100, 50, 0
  - Legend: Crossing the lesion

- **HYPEREMIA**
  - Pressure values: 112, 58
  - Legend: FFR = 58/112 = 0.52
A FEW WORDS ABOUT HYPEREMIA

(next speaker, Bernard De Bruyne)
Adenosine for i.v. infusion

(standard bag 200 mg = 100 ml)

price: Euro 2,= per bag

prepared by hospital pharmacy

manufacturing protocol available at carias@cze.nl
Infusion rate simply adjusted according to body weight ( ....kg  →  ......ml/min)
• no preparation in the lab
• no difficult calculations
• always the same dilution
• no risk of dosage error
• no loss of time
MAXIMUM HYPEREMIA IS IMPORTANT!

**NOTE:**

- sometimes, periodic fluctuations are present during i.v. adenosine induced steady state hyperemia

- this is related to the speed of metabolization of adenosine (patient-dependent) and the breathing pattern

- *always take the lowest value of FFR*

(key papers: De Bruyne, Circulation 2003;107:1877-1883  
McGeoch, CCI 2008;71:198-204)
Is it necessary to use hyperemia?

- For practical reasons, it is advocated presently by some investigators to skip hyperemia (iFR, Pd/Pa$_{\text{resting}}$) or to use a hybrid approach, but in exchange diagnostic accuracy decreases from 95% to 80%.

- Simpel intermediate solution: Pd/Pa$_{\text{contrast}}$ (called cFFR)

$\rightarrow$ cut-off point around 0.85 with accuracy $\geq$ 90% compared to FFR cut-off point of 0.80

(A.Jeremias, N. Johnson, Saturday morning)
Advantages of Pd/Pa contrast (cFFR) compared to iFR or Pd/Pa at “rest”

- no ECG needed; easier to perform
- no specific software needed, can be used with every pressure wire & interface
- no particular steady state needed (resting conditions or hyperemia)
- more accurate than those resting indexes
Correct Classification of Ischemic Stenosis

FFR

resting Pd/Pa, iFR, bSVr ("FFR-light")

angiography

100 % certainty (holy grail)

95 %

hyperemia

80 %

Pd/Pa (cFFR) contrast

70 %

resting indexes

the pyramid of diagnostic accuracy

angio
Prerequisites for a reliable index for decision making

- sound scientific basis and experimental validation
- accurate
- reproducible
- easy to perform
- predict outcome
Prerequisites for a reliable index for decision making

- sound scientific basis and experimental validation

All basic features of FFR have been thoroughly validated experimentally over more than 10 years

- 1993-2006: 5 original papers in Circulation on animal studies in dogs and swine
- 1994-2012: 64 original papers in NEJM, Circulation, JACC and EHJ in humans

> 2000 publications in PubMed
FFR: experimental validation in chronic dog studies
Prerequisites for a reliable index for decision making

• sound scientific basis and experimental validation
• *accurate, i.e. uniform normal value and clear cut-off with narrow gray zone*
• reproducible
• easy to perform
• predict outcome

} tomorrow
Fractional Flow Reserve in Normal Coronary Arteries

33 truely normal coronary arteries in patients without coronary artery disease:

$$\text{FFR} = 0.98 \pm 0.02\ (\text{range} \ 0.93 - 1.00)$$

Pijls, Circulation 1995;92: 183-193

86 apparently normal contralateral arteries in patients with coronary disease:

$$\text{FFR} = 0.87 \pm 0.09\ (\text{range} \ 0.64 - 0.97)$$

De Bruyne, Circulation 2001; 104:2401-2406
Normal Coronary Artery

FFR = 0.98

CFR = 4.7
Threshold value of FFR to detect significant stenosis in humans

How can you validate a new index if no standard exists???

prospective multitesting Bayesian approach

How to search for the threshold of a new index?

In most studies:

Analysis of **ROC curve** in a particular population and "cherry-picking" the best value

(e.g. all resting indexes like Pd/Pa at rest, iFR, bSVR but also some hyperemic indexes like hSVR)

Such studies are often called "*prospective*" but in fact are based upon a *retrospective* analysis of data (that is inherent to ROC analysis)

But……in another population, another ROC and another "best cut-off point" and "accuracy" will be found !!!
<table>
<thead>
<tr>
<th>Author</th>
<th>Meeting or Citation</th>
<th>Date</th>
<th>N</th>
<th>iFR cutoff*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies</td>
<td>TCT</td>
<td>2011 November</td>
<td>157</td>
<td>none**</td>
</tr>
<tr>
<td>Sen</td>
<td>JACC 59:1392</td>
<td>2011 December</td>
<td>157</td>
<td>0.83</td>
</tr>
<tr>
<td>Park</td>
<td>EuroPCR</td>
<td>2012 May</td>
<td>238</td>
<td>0.89</td>
</tr>
<tr>
<td>Petraco</td>
<td>EuroIntervention</td>
<td>2012 August</td>
<td>339</td>
<td>0.89</td>
</tr>
<tr>
<td>Jeremias</td>
<td>TCT</td>
<td>2012 October</td>
<td>1548</td>
<td>0.90</td>
</tr>
<tr>
<td>Indolfi</td>
<td>TCT</td>
<td>2012 October</td>
<td>71</td>
<td>0.93</td>
</tr>
<tr>
<td>Johnson</td>
<td>JACC 61:1428</td>
<td>2013 February</td>
<td>1129</td>
<td>0.89</td>
</tr>
<tr>
<td>Sen</td>
<td>JACC 61:1409</td>
<td>2013 April</td>
<td>51</td>
<td>0.86</td>
</tr>
</tbody>
</table>

*Value of iFR best corresponding to FFR of 0.80 varies from 0.83 - 0.93*
How to search for a threshold that can be truly used as gold standard?

The right way to go is a 2-step approach:

1. **Exploration** of range where a true threshold is expected: *in a population in whom you can definitely conclude if there is disease or not*

2. Truly **prospective** validation *of that particular threshold* in an arbitrary population, using a combined gold standard *(prospective multitesting Bayesian approach; NEJM 1996; 334:1703-08)*

→ **Fractional Flow reserve**
Proper validation of any index needs **2 steps:**

1. **Searching for the threshold value in a selected population** 
   (sens, specif, NPV, PPV, ROC analysis)

2. Prospective validation in a population with unknown characteristics

Pijls et al, Circulation 1995
De Bruyne, Circulation 1996
Proper validation of any index needs **2 steps:**

1. Searching for the threshold value in a selected population
   (sens, specif, NPV, PPV, ROC analysis)

2. Prospective validation in a population with unknown characteristics

**Validation of FFR in humans (step 1)**

Pijls et al, Circulation 1995
De Bruyne, Circulation 1996
Creating a gold standard by Prospective Multitest Sequential Bayesian Approach:

- Exerc testing = electrical index of ischemia
- MIBISpect = perfusion index of ischemia
- Dobutrex Echo = contractile index of ischemia
- reversal from positive before to negative after intervention, proves true positivity before and true negativity after test

Diagnostic accuracy of FFR =

\[
\left(1-0.75\right) \times \left(1-0.8\right) \times \left(1-0.8\right)^{-1} = 99 \%
\]

3 unclassifiable patients (no intervention)  
→ worst case scenario for FFR  → 93 %

Pijls et al, NEJM 1996
FFR is the only functional index which has ever been validated versus a true gold standard. (Prospective multi-testing Bayesian methodology)

All studies ever performed in a wide variety of clinical & angiographic conditions, found threshold between 0.75 and 0.80

Diagnostic accuracy ≥ 93%

Oldroyd et al, Circulation 2010
Let’s have a closer look to FFR

Prerequisites for a reliable index for decision making

• sound scientific basis and experimental validation
• accurate
• *reproducible*
• easy to perform
• predict outcome

{tomorrow}
Reproducibility of FFR

VERIFY study, Berry et al, JACC 2013 (published februari 2013)

(all-comers during one month)

There is not any other index in physiology so reproducible as FFR
Probability that treatment decision will change if the respective index measurement is repeated

Classification certainty of single measurement

2.4% of patients go from green to gray or v.v. and 2.4% from red to gray. Almost nobody ever crosses from red to green or v.v.
Probability that treatment decision will change if the respective index measurement is repeated

Classification certainty of single measurement

Pd/Pa_{rest}

iFR

40%

FFR

5%

FFR, VERIFY study

iFR, ADVISE study

Pd/Pa_{rest} VERIFY study
At 1200 consecutive in-duplo measurements of FFR, there was NOT ANY cross-over across the gray zone.
Let’s have a closer look to FFR

Prerequisites for a reliable index for decision making

- sound scientific basis and experimental validation
- accurate
- reproducible
- *easy to perform*
- predict outcome
PRACTICAL PERFORMANCE OF FFR - MEASUREMENT
Mr R, born 22-01-1968 (46-year-old

- admission on Jan 25th, 2014 with acute lateral wall MI
- PPCI of occluded diagonal branch

- Concomittant 3-vessel disease:
  - LAD: 50%
  - LCX: long tandem lesion 50-70% + 70-90%
  - RCA: 50-70%

- Syntax score: 22

- Heartteam: CABG or FFR-guided MVD PCI

choice for FFR guided PCI, as pilot for FAME-3
70% RCA
50% LAD
90% long LCX
Note!

As in any intracoronary manipulation, before entering the coronary circulation, administer **200-300 µg NTG i.c.**
200 – 300 µg NTG i.c.
Unpacking of the Pressure Wire
Flushing the Pressure Wire
Connecting the Pressure Wire to Analyzer
Calibrating Pressure Wire
Pressure Wire Calibrated: Ok
Pressure Wire introduced into Y-connector
Shaping of the tip of the PW
Introducing the PW into the Guiding Catheter
start with verification of equal signals when sensor is located at tip of the guiding catheter and equalize
NOTE:

introducer needle in or out !?!

doesn’t matter as long as you realize what you are doing

1. Know your needle

2. Realize that some apparent “drift” at the end is not drift per se but can be caused by the presence of the introducer when doing the initial measurement and absence of the (removed) introducer at the end
Introducer effect  *(mistake in live case in PCR 2010)*

Introduction of a “thin needle” into the valve of the ‘y’ connector

Introduction of a “large needle” in the valve of the ‘y’ connector
70% RCA
50% LAD
90% long LCX
equalization before entering LCA
PressureWire in LAD
resting hyperemia

LAD

adenosine i.v.
PressureWire in LCX
resting hyperemia

LCX Pull-back
Because sensor is 3 cm from tip, easily **pull-back and push-up for exact spatial information.**

**Pull-back recording** for detailed spatial information about distribution of lesions along the complete artery.
If you need to treat, disconnect pressure wire
disconnecting the pressure wire...........
first stent in LCX (3.0x22)
LCX after first stent
LCX after second stent
For post-stent FFR → simply connect the pressure wire
LCX after 2 stents

resting  hyperemia

adenosine

Post-stent FFR measurement to evaluate result
Verification of equal pressures when back at guiding.
equalization before entering RCA
PressureWire in RCA
resting → hyperemia (i.v. adenosine)

RCA

pullback - advance - etc
resting

hyperemia (i.v. adenosine)

pullback - advance - etc
resting

hyperemia

Pd/Pa = 0.99
iFR = 1.00
FFR = 0.54

pullback
Stent in RCA (3.5x 18)
RCA after stenting
RCA after stenting

resting

hyperemia

(adenosine)
verification of equal pressures when back at guiding

Total time for all measurements in 3 arteries (with central i.v. adenosine) and 3 stents in 2 arteries: 31 minutes
It is often mandatory to use some kind of hyperemia to unmask the true severity of a coronary stenosis!!
In general:

• small perfusion territory, distal stenosis, older patient, moderate long lesion, small artery, microvascular disease:
  \[ \text{often moderate gradient at rest with little increase at hyperemia} \]

• large perfusion territory, proximal stenosis, young patient, short severe lesion, large artery, intact microvasculature:
  \[ \text{often minimal gradient at rest with large increase at hyperemia} \]
Let’s have a closer look to FFR

**Prerequisites for a reliable index for decision making**

- sound scientific basis and experimental validation
- accurate
- reproducible
- easy to perform
- *predict outcome* \( \longrightarrow \) tomorrow
Recent developments:

- wireless connections (*Aeris Wire, SJM*)

- Complete Integration of FFR Measurement in the Regular Environment of the Cathlab (*General Electric*)

- new hyperemic stimuli (single peripheral injection of Regadenoson)

- non-hyperemic or semi-hyperemic indices and even non-invasive FFR by CT

  *saturday morning session*
In many complex angiographic conditions, FFR can be assessed as regular:

- ostial lesions
- MVD
- left main lesions
- tandem lesions
- diffuse disease

Full hyperemia (and particularly the hyperemic pull-back recording) is necessary to guide where exactly the stent(s) should be placed

tomorrow morning
# 10 – Procedural aspects of PCI

**Table 28: Specific PCI devices and pharmacotherapy**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR-guided PCI is recommended for detection of ischemia-related lesion(s) when objective evidence of vessel-related ischemia is not available</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>DES* are recommended for reduction of restenosis/reocclusion, if no contraindication to extended DAPT</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Distal embolic protection is recommended during PCI of SVG disease to avoid distal embolisation of debris and prevent MI</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Rotablation is recommended for preparation of heavily calcified or severely fibrotic lesions that cannot be crossed by a balloon or adequately dilated before planned stenting</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
Starting – up FFR measurements in your Lab:

• study the principles and understand the concept

• be prepared to rely upon your brains, rather than on the angio: what you measure is more reliable than what you see

• involve your nurses/technicians/residents and convince your fellow staff members

• do not just an occasional patient with a mild stenosis once in a week, but use the PW consistently in 10 or 20 consecutive cases during 1 or 2 weeks
If you decide to measure FFR, *do it always in the same way and be consistent in your decision:* 

- **FFR > 0.80** → no stent indicated, medical treatment 
- **FFR < 0.75** → stent, if technically feasible 

Measuring FFR of > 0.80 and placing a stent as yet, is *NONSENSE*

If you are not prepared to believe your measurement, You can better not do it

“FFR never lies” 

cooperation of your nurses is of paramount importance!

- preparing the equipment, cables, pressure wire
- taking care of hyperemic stimulus *(keep it simple)*
- anticipate to the procedure, remind you to measure
- willingness to spend some extra time, if needed

therefore, train your nurses and make them understand the principles, practice, and great advantages of FFR

Similar for fellows and colleagues!
....and last but not least:

**EASY to use** means **READY to use**: 

Design the configuration in your cath.lab in an optimum way to enable instantaneous use of the PressureWire if the case demands it.
Catharina Hospital, Eindhoven, NL

1800 FFR cases per year
EINDE
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 or peripheral bolus of regadenoson
• 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
pressure pullback recording at hyperemia
Male 58-y-old

Typical chest pain; positive MIBI-Spect inferior wall
Typical chest pain; positive MIPI-Spect inferior wall
Very obese male, typical chest pain; positive MIBI-Spect inferior wall
roughly identical MIBI in all 3 patients: reversible defect inferior wall
pull-back  advance
Hyperemia: Pull back recording

FFR = 0.65
Hyperemic pull-back recording along the RCA
Hyperaemia: sensor in PLRCA

FFR = 70/118 = 0.61
Dist. stenose

Mid in-stent restenose

Dist. stenose

Hyperemia: Pull back recording

FFR = 0.65
Dist. Stenosis after treatment

Prox. stenosis after treatment

Hyperaemie: sensor in PLRCA

FFR = 116/118 = 0.98
A few final issues:

- pressure pullback recording
- *always necessary to induce hyperemia?*
- regadenoson
A bunch of older and newer resting indexes: *Pd/Pa at rest, diastolic Pd/Pa, iFR, i-iFR, bSRv, (“FFR-light”)*, which have in common that they all avoid hyperemia and only have a moderate accuracy (70% -80%)
**necessity of hyperemia**

- If Pd/Pa at rest (or comparable indices, like iFR) is $< 0.80$, as a matter of fact FFR will also be $< 0.80$ and hyperemia in itself is not strictly mandatory to decide upon inducible ischemia.

- But without hyperemia, you cannot make a meaningful pull-back recording and you are losing a lot of valuable information.

- And without hyperemia and FFR, you cannot judge how much a patient improved by stenting: you don’t know where you came from ("did FFR go from 0.78 to 0.91 or from 0.65 to 0.91?"), and no resting conditions exist after PCI (paradoxical deterioration of resting indexes).
<table>
<thead>
<tr>
<th>Patient scheduled for diagnostic FFR/FFR-guided PCI (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
</tr>
<tr>
<td>First vessel scheduled for FFR-measurement (Study artery)</td>
</tr>
<tr>
<td>Start of procedure</td>
</tr>
<tr>
<td>Equilibration (resting conditions)</td>
</tr>
<tr>
<td>IV Adenosine measurement 1</td>
</tr>
<tr>
<td>Regadenoson measurement 1 *</td>
</tr>
<tr>
<td>IV Adenosine measurement 2</td>
</tr>
<tr>
<td>Regadenoson measurement 2 *</td>
</tr>
</tbody>
</table>
Adenosine (central venous infusion) vs Regadenoson for maximum hyperemia

- 100 arbitrary patients admitted for FFR measurement
- central venous line (femoral sheath) and peripheral line
- adenosine 140 µg/kg/min as central venous infusion vs single bolus of 400 µg regadenoson in central or peripheral vein
- adenosine #1, regadenoson #1, adenosine#2, regadenoson #2
- randomization with respect to regadenoson:
  
  \[
  \begin{align*}
  \text{central/central} & \quad (N=25) \\
  \text{peripheral/central} & \quad (N=25) \\
  \text{central/peripheral} & \quad (N=25) \\
  \text{peripheral/peripheral} & \quad (N=25)
  \end{align*}
  \]
Adenosine (central venous infusion) vs Regadenoson for maximum hyperemia

ss hyp + “baseline” 10 min ss hyp + 0.5 “1½ baseline” 10 min

adenosine #1 regadenoson #1 (centr or periph)

adenosine #2 regadenoson #2 (periph or central)
Adenosine (central venous infusion) vs Regadenoson (central venous single bolus injection 400 µg)

N=30
courtesy of Dr Lokien van Nunen
Adenosine (central venous infusion) vs Regadenoson (peripheral venous single bolus injection 400 µg)

N=30
courtesy of Dr Lokien van Nunen
Regadenoson
(central venous single bolus injection 400 µg vs peripheral single bolus 400 µg)

N=20
courtesy of Dr Lokien van Nunen
**Results of first 47 Patients**

- Maximum hyperemia achieved by regadenoson in ALL patients (difference compared to central venous adenosine 0.00 +/- 0.02)

- No difference between central and peripheral regadenoson

- Hyperemic plateau reached ≤ 40 sec in all patients both for central and peripheral regadenoson

- Duration of hyperemic plateau varied from 75 sec to 9 minutes (sufficient for pull-back recording in all patients)

- Zero complications or side-effects both for adenosine (*94 runs*) or (repeated) regadenoson (*94 injections*), except the well-known and innocent chest discomfort (graded 6/10 vs 5/10, respectively) and a few skipped beats in 2 patients (adeno) without necessity to interrupt administration
Adenosine (Central Venous Infusion) \textit{versus} Single Bolus Injection of Regadenoson For Maximum Hyperemia
Aims of this study:

• To investigate if the hyperemic effect of **single bolus regadenoson injection** is equal to the present gold standard i.e. **central venous adenosine infusion**

• To determine **time intervals** to onset of maximum hyperemia and the **duration of steady state hyperemia** if present

• To compare **central venous vs peripheral venous administration of regadenoson**

• To investigate **side-effects** as well as **safety of repeated regadenoson injections**, if desired
Conclusions (halfway this study)

• Regadenoson as a single bolus injection of 400 µg, is an excellent alternative for central venous adenosine infusion to induce maximum hyperemia.

• Rapid onset (~ 30 sec) and steady state long enough (at least 75 sec) to perform pressure pullback recording.

• In case multiple arteries need to be investigated, repeated injection can be performed and is safe.

• No noticeable side effects of regadenoson or adenosine, except the harmless chest discomfort.
Correct Classification of Ischemic Stenosis

FFR

resting Pd/Pa, iFR, bSVr ("FFR-light")

angiography

100 % certainty (holy grail)

95 %

80 %

70 %

hyperemia

resting indexes

angio

the pyramid of diagnostic accuracy
FRACTIONAL FLOW RESERVE:

The index FFR (Fractional Flow Reserve) is based upon the two following principles:

- *It is not resting flow, but maximum achievable flow which determines the functional capacity (exercise tolerance) of a patient.*

- *At maximum vasodilation (corresponding with maximum hyperemia or with maximum exercise), blood flow to the myocardium is proportional to myocardial perfusion pressure* (~hyperemic distal coronary pressure)
FRACTIONAL FLOW RESERVE =

MAXIMUM FLOW IN THE PRESENCE OF A STENOSIS

\[ \frac{\text{Distal coronary pressure at maximum hyperemia}}{\text{Aortic pressure}} \]
Maximum myocardial perfusion:

100% → 70% → 25%

FFR: 1.0 → 0.7 → 0.25

In other words: FFR is linearly related to maximum achievable blood flow.
Angina Pectoris & Pos MIBI:
Typical chest pain; positive MIBI-Spect inferior wall
Hyperemic pull-back recording along the RCA
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.
to assess *collateral flow*: measurement of coronary wedge pressure during balloon inflation can be done

\[
\text{Fractional collateral flow} = \frac{(P_d - P_w)}{(P_a - P_w)}
\]
CONCLUSIONS (1):

• when interpreting (studies to) the accuracy & reproducibility of (physiologic) indexes used in the catherization lab, some critical attitude and understanding of statistics is mandatory

• simple ROC analysis is insufficient to validate any index. A two-step Bayesian approach is mandatory

• So far, such approach has only been applied to FFR

• Therefore, it is justified to use FFR as gold standard
CONCLUSIONS (2):

• newer indexes to avoid hyperemia have been introduced recently. This simplifies the procedure at the cost of diagnostic accuracy.

• of all those non-hyperemic indexes, Pd/Pa contrast (also called cFFR), is most attractive because it can be determined very easy, without ECG, without specific software, and without assuming a steady resting state. Its accuracy compared to FFR is ≥ 90%.

• In complex disease, ostial lesions, tandem stenosis, etc, the full hyperemic pull-back recording remains mandatory.
Correct Classification of Ischemic Stenosis

FFR

resting Pd/Pa, iFR, bSVr ("FFR-light")

angiography

100 % certainty (holy grail)

95 %

hyperemia

80 %

resting indexes

70 %

angio

the piramid of diagnostic accuracy
MAXIMUM VASODILATORY STIMULI

!! Maximum hyperemia is paramount to achieve optimum accuracy
(95% with hyperemia; 80% without hyperemia)

• PAPAVERINE i.c.
• ADENOSINE i.c.
• ADENOSINE i.v. \{ Well-established \}
• ATP i.c
• ATP i.v.
• *regadenoson* ? \rightarrow\ new
Hyperemia with i.v. adenosine is extremely reproducible:

**VERIFY study (N=205)**
Berry et al, JACC 2013
(all-comers during one month
Without a single exception)

**Regadenoson study (N=100)**
Van Nunen et al, 2014 (in press)
(2x adenosine and 2x regadenoson)
Mr R, born 22-01-1968 (46-year-old)

- admission on jan 25th with acute lateral wall MI
- PPCI of occluded diagonal branch

- Concomittant 3-vessel disease:
  - LAD : 50%
  - LCX : long tandem lesion 50-70% + 70-90%
  - RCA : 50-70%

- Syntax score: 22

- Heartteam: CABG or FFR-guided MVD PCI

choice for FFR guided PCI, as pilot for FAME-3
Second stent in CX (3,5x18)
Prerequisites for a reliable index for decision making

- sound scientific basis and experimental validation