THEORY AND PRACTICAL SET-UP OF FFR

Educational Training Program ESC
European Heart House
april 23rd -25th 2015

Nico H. J. Pijls, MD, PhD
Catharina Hospital,
Eindhoven, The Netherlands
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

\[ \text{FFR}_{\text{myo}} = \frac{P_d}{P_a} = 0.70 \]
\[ \text{FFR}_{\text{myo}} = \frac{P_d}{P_a} \]

\( P_a \) = mean aortic pressure at maximum hyperemia

\( P_d \) = 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 catherization laboratory

pressure wire + hyperemetic stimulus = FFRmyo
0.014 sensor-tipped PTCA guidewire (electronic or fiberoptic)
CLINICAL PRACTICE:

Mr van Z.  
77 years, 
stable ang 2-3 posit ET
Fractional Flow Reserve in Clinical Practice

REST

HYPEREMIA

Crossing the lesion

FFR = 58/112 = 0.52
A Few Words About Hyperemia: (next speaker, Dr De Bruyne)

- intravenous infusion of adenosine or ATP
- intracoronary injection of adenosine
- single intravenous bolus of regadenoson

If used according to the guidelines, full and reliable hyperemia is obtained in close to 100% of patients.

(key papers: De Bruyne, Circulation 2003;107:1877-1883
McGeoch, CCI 2008;71:198-204
FAME studies, VERIFY study
Fearon & Johnson, LBT PCR 2015)
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)

Adenosine I.V.

- 50 kg = 210 ml/hr
- 60 kg = 252 ml/hr
- 70 kg = 294 ml/hr
- 80 kg = 336 ml/hr
- 90 kg = 378 ml/hr
- 100 kg = 420 ml/hr
Adenosine infusion pump

- 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
FAME studies, VERIFY study
Fearon & Johnson, LBT PCR 2015)
Is it necessary to use hyperemia?

• For practical reasons, it is advocated presently by some investigators to skip hyperemia \((iFR, \frac{Pd}{Pa}_{\text{resting}})\) with cut-off of 0.90 or to use a hybrid approach, but in exchange diagnostic accuracy decreases to 80%.

• Semi-hyperemic stimulus: single shot of contrast \(\frac{Pd}{Pa}_{\text{contrast}}\) (called \(cFFR\)).

→ Some pilot studies: cut-off point around 0.85 with accuracy of 90% compared to FFR cut-off point of 0.80.

(Dr Ribichini, N. Johnson, Friday afternoon; LBT at PCR 2015)
Correct Classification of Ischemic Stenosis

FFR
resting Pd/Pa, iFR, bSVr
angiography

100 % certainty (holy grail)
95 %
80 %
70 %

hyperemia
Pd/Pa contrast
resting indexes
angio

the pyramid of diagnostic accuracy
Correct Classification of Ischemic Stenosis

Simple paradigm: “the more hyperemia, the higher the accuracy”

FFR
resting Pd/Pa, iFR, bSVr
angiography

100 % certainty (holy grail)
95 %
80 %
70 %

hyperemia
resting indexes
angio

Pd/Pa
contrast
cFFR
Before going to clinical practice, 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
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
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

**CFR = 4.15**

**FFR = 0.98**

**CFR = 4.7**

**adenosine**
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?

Mostly seen (as also for all other physiologic indices:)

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

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

*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 =

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

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 in 5 large centers)

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.

Adapted from Petrarco et al, Eurointervention 2013
Probability that treatment decision will change if the respective index measurement is repeated.

Classification certainty of single measurement.

Pd/Pa_{rest}

Adapted from Petrarco et al, Eurointervention 2013.
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
As in any intracoronary manipulation, before entering the coronary circulation, administer 200-300 µg NTG i.c.
200 – 300 µg NTG i.c.
Ready to measure:

- Pressure Wire
- Interface

St Jude Medical, Philips/Volcano, Opsens, Acist

Saturday morning session
users friendly, “quiet” interface
Ready to go!

Completely interactive preparation of signals and pressure wire, guided by interface takes < 30 seconds
zeroing and displaying Pa on interface
zeroing and displaying Pa on interface
Unpacking of the Pressure Wire
Flushing the Pressure Wire
Green light indicates that pressure wire is ready
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
Signals have been equalized
record
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
Introduction of a “thin needle” into the valve of the ‘y’ connector

Introduction of a “large needle” in the valve of the ‘y’ connector

Introducer effect (mistake in live case in PCR 2010)
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..........
Wire disconnected → indicator orange
first stent in LCX (3.0x22)
LCX after first stent
LCX after second stent
For post-stent FFR → simply connect the pressure wire
Re-connected → indicator light green

Note: after reconnecting it can take 15-20 Seconds for signal to stabilize
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
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
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:
  
  *often moderate gradient at rest with little increase at hyperemia*

- large perfusion territory, proximal stenosis, young patient, short severe lesion, large artery, intact microvasculature:
  
  *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* → *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) next speaker

- non-hyperemic or semi-hyperemic indices and even non-invasive FFR by CT (*friday afternoon session*)

- development of fiberoptic wires and a monorail hypotube (*Opsens, BostonSc, Acist; saturday morning*)
In many complex angiographic conditions, FFR can be assessed as regular:

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

*the hyperemic pull-back recording is necessary to guide where exactly the stent(s) should be placed and to evaluate the result*

tomorrow morning
**FFR and microvascular disease**

In microvascular disease, FFR may be higher than it would be without microvascular disease

(Because FFR compares maximum myocardial flow in the presence of the stenosis with maximum flow as it would be without that stenosis, but still not normal because of the microvascular disease)

But it still indicates exactly to what degree maximum blood flow can be improved by stenting an epicardial coronary stenosis!
**10 – Procedural aspects of PCI**

Table 28: Specific PCI devices and pharmacotherapy

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>DES* are recommended for reduction of restenosis/reocclusion, if no contraindication to extended DAPT</td>
<td>I</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>
</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>
</tr>
</tbody>
</table>
Finally, a few practical tips.....
**Guiding or diagnostic catheter? 6F or smaller?**

- FFR has been measured by 5F diagnostic catheters
- but: - *more difficult steering/wire manipulation* (because diagnostic catheter lacks inner coating)
  - *damping of aortic pressure signal* due to smaller lumen

→ *I advice to use guiding catheter* (changing catheter is less cumbersome than long manipulation with wire or suboptimum signal)
How to prepare and manipulate the pressure wire

• short curve of 45-60 degree

• use the pressure wire with a torquer (cf Sion wire), i.e. true steering
OPTIMUM FFR TECHNIQUE: decrease of drift

How to decrease (apparent) drift

• after equalization (sensor at the tip of the guiding catheter), wait for 20-30 seconds for stabilization (small airbubbles in sensor cavity are flushed away)

• realize that more often as you believe, there is no drift but an inaccuracy with the guiding catheter signal (dynamic pressure; capillary forces; you forgot about the introducer)
Capillary forces in guiding catheter

Sometimes capillary forces result in misregistration of pressure by the guiding up to 10 mm Hg.

In procedures without pressure wire, this remains unnoticed.

Vigorous manual flushing of the guiding with 5-10 cc of saline, might restore true aortic pressure.
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 (also in tight stenosis) during 1 or 2 weeks and try out several hyperemic stimuli
HOW TO START A FFR PROGRAM IN YOUR CATH-LAB

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.
Practical logistics in the cath lab: *Keep it simple*
Catharina Hospital, Eindhoven, NL

1600 FFR cases per year

“It is a pleasure to measure pressure”
EINDE