CORONARY PHYSIOLOGY IN THE CATHLAB:

FRACTIONAL FLOW RESERVE: CONCEPT, EXPERIMENTAL BASIS, CUT-OFF VALUES

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

Nico H. J. Pijls, MD, PhD
Catharina Hospital,
Eindhoven, The Netherlands
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
But....they were limited by

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

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

- \( f \) = friction coefficient
- \( s \) = separation coefficient

- **Moderate gradient at rest**
- **Moderate increment at hyperemia**
- **Small gradient at rest**
- **Large gradient at hyperemia**

- **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:
  → \textit{balloon catheter instead of 0.014'} wire

- inadequate hemodynamic conditions:
  → \textit{measuring at baseline instead of using maximum hyperemia}

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

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

FFR = 70 /100
= 0.70

FFR = 40 /70
= 0.58

FFR = 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
During Maximal Vasodilatation

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

MAXIMUM FLOW IN THE PRESENCE OF A STENOSIS

\[ \frac{\text{Distal coronary pressure at maximum hyperemia}}{\text{Aortic pressure}} \]
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)
FFR: experimental validation in chronic dog studies
Experimental basis of FFR

**Horizontal axis:**
FFR measured by true flow

**Vertical axis:**
FFR measured by Hyperemic pressure ratio

*Pijls et al, Circulation, 1993*
Including collaterals in the model……….
I \[ \frac{P_a - P_v}{P_w - P_v} = 1 + \frac{R_c}{R} = \text{constant} \]

IIa \[ FFR_{cor} = \frac{P_d - P_w}{P_a - P_w} = 1 - \frac{\Delta P}{P_a - P_w} \]

IIIa \[ FFR_{myo} = \frac{P_d - P_v}{P_a - P_v} = 1 - \frac{\Delta P}{P_a - P_v} \]

IVa \[ Q_c = (FFR_{myo} - FFR_{cor}) \cdot Q^N \]
I \quad \frac{P_a - P_v}{P_w - P_v} = 1 + \frac{R_c}{R} = \text{constant}

IIa \quad \text{FFR}_{\text{cor}} = \frac{P_d - P_w}{P_a - P_w} = 1 - \frac{\Delta P}{P_a - P_w}

IIIa \quad \text{FFR}_{\text{myo}} = \frac{P_d - P_v}{P_a - P_v} = 1 - \frac{\Delta P}{P_a - P_v}

IVa \quad Q_c = \left( \text{FFR}_{\text{myo}} - \text{FFR}_{\text{cor}} \right) \cdot Q^N
I \quad \frac{P_a - P_v}{P_w - P_v} = 1 + \frac{R_c}{R} = \text{constant}

IIa \quad FFR_{cor} = \frac{P_d - P_w}{P_a - P_w} = 1 - \frac{\Delta P}{P_a - P_w}

IIIa \quad FFR_{myo} = \frac{P_d - P_v}{P_a - P_v} = 1 - \frac{\Delta P}{P_a - P_v}

IVa \quad Q_c = (FFR_{myo} - FFR_{cor}) \cdot Q^N
I \[ \frac{P_a - P_v}{P_w - P_v} = 1 + \frac{R_c}{R} = \text{constant} \]

IIa \[ \text{FFR}_{\text{cor}} = \frac{P_d - P_w}{P_a - P_w} = 1 - \frac{\Delta P}{P_a - P_w} \]

IIIa \[ \text{FFR}_{\text{myo}} = \frac{P_d - P_v}{P_a - P_v} = 1 - \frac{\Delta P}{P_a - P_v} \]

IVa \[ Q_c = (\text{FFR}_{\text{myo}} - \text{FFR}_{\text{cor}}) \cdot Q^N \]
Experimental basis of FFR

**Horizontal axis:**
$\text{FFR}_{\text{cor}}$ measured by true flow

**Vertical axis:**
$\text{FFR}_{\text{myo}}$ and $\text{FFR}_{\text{coll}}$
measured by Hyperemic pressure ratio

$Q_c = (\text{FFR}_{\text{myo}} - \text{FFR}_{\text{cor}}) \cdot Q^N$

Pijls et al, Circulation, 1993
Experimental Basis of Determining Maximum Coronary, Myocardial, and Collateral Blood Flow by Pressure Measurements for Assessing Functional Stenosis Severity Before and After Percutaneous Transluminal Coronary Angioplasty

Nico H.J. Pijls, MD; Jacques A.M. van Son, MD; Richard L. Kirkeeide, PhD; Bernard De Bruyne, MD; and K. Lance Gould, MD

*first full paper in Circulation: may 1993*
Description of the Model

The purpose of this model was to derive equations relating pressures to the regional distribution of maximum perfusion. Maximum flow through a stenotic artery is compared with what maximum flow would be in that same artery in the absence of that stenosis. Consequently, we express coronary flow reserve for a stenotic artery as a fraction of its normal expected value in that same artery in the absence of a stenosis. We therefore use the term “fractional flow reserve” (FFR). In the literature, the term “relative flow” reserve is used in the sense of a flow reserve relative to an adjacent normal coronary artery. However, a unique strength of the model described here is the theoretical capacity...
Description of the Model

The purpose of this model was to derive equations relating pressures to the regional distribution of maximum perfusion. Maximum flow through a stenotic artery is compared with what maximum flow would be in that same artery in the absence of that stenosis. Consequently, we express coronary flow reserve for a stenotic artery as a fraction of its normal expected value in that same artery in the absence of a stenosis. We therefore use the term “fractional flow reserve” (FFR).
Do we have to bother about $P_v$?

Only in case of studies to collateral Function, or severely elevated $P_v$

$$FFR_{coll} = \frac{P_w - P_v}{P_a - P_v}$$

$$\frac{75 - 5}{100 - 5} = 0.74 \quad \frac{75}{100} = 0.75 \quad \frac{20-5}{100-5}$$
Volumetric coronary blood flow

$Q_{phasic}$

$Q_{mean}$

200 ml/min

20 sec occlusion
Highest flow achieved at rest in any part of the heart cycle is far below average hyperemic coronary flow in all dogs.
minimal myocardial resistance during any period in diastole at rest, is ~ 250 % higher than average myocardial resistance at maximum hyperemia in all dogs.
Influence of Zero-flow pressure on FFR??
At maximum hyperemia, zero-flow pressure is close to zero (<< 15 mmHg) and has negligible influence on FFR measurement.
Influence of Zero-flow pressure on FFR ??

At rest, zero-flow pressure can be as high as 30 mmHg and influences pressure-flow relations and derived resting indexes.

At maximum hyperemia, zero-flow pressure approximates venous pressure and has negligible influence on FFR calculation.
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
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 truly 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
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
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*
Creating a gold standard by Prospective Multitesting 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)*

\textbf{ALL} studies ever performed in a wide variety of clinical & angiographic conditions, found threshold between 0.75 and 0.80

\textbf{Diagnostic accuracy} \ (> 93\%)


\textit{Oldroyd et al, Circulation 2010}
normal  $\rightarrow$ increasing stenosis  $\rightarrow$ total occlusion

$\uparrow$  $\uparrow$  100  100

$\uparrow$  $\uparrow$  100  70

$\uparrow$  $\uparrow$  100  25  (P$_{\text{wedge}}$)

**Maximum myocardial perfusion:**

$100\%$  $\rightarrow$  $70\%$  $\rightarrow$  $25\%$

**FFR:**

$1.0$  $\rightarrow$  $0.7$  $\rightarrow$  $0.25$

*In other words: FFR is linearly related to maximum achievable blood flow*
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

There is not any other index in physiology so reproducible as FFR.

VERIFY study, Berry et al, JACC 2013 (published February 2013)
At 1200 consecutive in-duplo measurements of FFR, there was NOT ANY cross-over across the gray zone.
SUMMARY (1):

• The concept of Fractional Flow Reserve has a sound scientific basis and all its aspects have been extensively validated in experimental studies in dogs and swines.

• The concept comprises not only maximum myocardial perfusion (most important from clinical point of view), but also coronary and collateral flow and describes the complete coronary circulation in terms of pressures.
SUMMARY (2):

- There is a sharp cut-off value between ischemic and non-ischemic values with a narrow “gray zone”. And FFR is the only physiologic index for which this has been prospectively validated versus a true gold standard.

- The reproducibility of FFR is unsurpassed by any other index.
Doppler flow velocity recording in a human coronary artery

resting

hyperemia (adenosine)
FFR(A+B) = \frac{P_d}{P_a}
FFR(A)_{app} = \frac{P_m}{P_a}
FFR(B)_{app} = \frac{P_d}{P_m}

proximal stenosis first treated (n=19)

distal stenosis first treated (n=13)

\text{FFR(B)}_{true} = \frac{P_m'}{P_a'} \approx \frac{P_d'}{P_a'}
\text{FFR(A)}_{true} = \frac{P_m'}{P_a'} \approx \frac{P_d'}{P_a'}

\text{ECG}
Flow Velocity

P_a \quad \text{(mean aortic pressure, by guiding catheter)}
\text{ } P_m \quad \text{(pressure wire #1)}
\text{ } P_d \quad \text{(pressure wire #2)}

\Delta P(A)
\text{apparent FFRmyo (A) = } \frac{69}{100} = 0.69
\text{true FFRmyo (A) = } \frac{63}{98} = 0.64
\text{(by the equation)}

\Delta P(B)

\Delta P(A)

release of stenosis A

\text{FFRmyo (B) = } \frac{39}{49} = 0.79
\text{FFRmyo (B) = } \frac{68}{87} = 0.78
Animal study: instrumentation
Average myocardial resistance with increasing stenosis severity

- **Mild Stenosis**
- **Moderate Stenosis**
- **Severe Stenosis**

- Not taking into account collateral flow
- Taking into account collateral flow
normal $\rightarrow$ increasing stenosis $\rightarrow$ total occlusion

\[ Q_{myo} = Q_{cor} \]

\[ Q_{myo} = Q_{cor} + Q_{collat} \]

\[ Q_{myo} = Q_{collat} \]

\[ Q_{cor} = 0 \]

True microcirculatory resistance: \( R_{myo} = \frac{P_d}{Q_{myo}} \)

<table>
<thead>
<tr>
<th>( P_d / Q_{cor} )</th>
<th>( P_d / Q_{cor} )</th>
<th>( P_d / Q_{cor} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>= ( R_{myo} )</td>
<td>&gt; ( R_{myo} )</td>
<td>= ( \infty )</td>
</tr>
</tbody>
</table>
Severe stenosis

After stenting

After stenting: ballon size 1mm smaller than stent

Empty balloon: ≈10% area stenosis
FFR ≈ 0.85

4 atmospheres: ≈50% area stenosis
FFR ≈ 0.70

12 atmospheres: ≈75% area stenosis
FFR ≈ 0.55

30 patients

Aarnoudse et al, Circulation 2004
**Apparent** myocardial resistance with increasing stenosis severity

Apparent microvascular resistance calculated as $P_{\text{distal}} / Q_{\text{coronary}}$

(artificial increase due to using $Q_{\text{cor}}$ instead of $Q_{\text{myo}}$!!)
Coronary flow ≠ Myocardial flow

How to solve this problem ??

Coronary wedge pressure (P_w) mandatory

Once Pw is known, the relative distribution of myocardial, coronary, and collateral flow is known

(se seminal paper on the introduction of FFR, Circulation 1993)
**True** microcirculatory resistance can be represented by:

\[
IMR = Pa \cdot Tmn \cdot \frac{(Pd - Pw)}{(Pa - Pw)}
\]

wedge pressure necessary to calculate microcirculatory resistance, unless epicardial artery is “normal” (FFR = 1.0)

Similarly, if Doppler is used:

\[
H-MRv \ “true” = \frac{Pa}{Vmax} \cdot \frac{(Pd - Pw)}{(Pa - Pw)}
\]

validation in in-vitro model (CCI 2004;62:56-63)
validation in animals (Circulation 2004;109:2269-2272)
validation in humans (Circulation 2004;110:2137-2142)
Severe stenosis

After stenting

After stenting: ballon size 1mm smaller than stent

Empty balloon: ≈10% area stenosis
FFR ≈ 0.85

4 atmospheres: ≈50% area stenosis
FFR ≈ 0.70

12 atmospheres: ≈75% area stenosis
FFR ≈ 0.55

30 patients

Aarnoudse et al, Circulation 2004
Minimal myocardial resistance with increasing stenosis severity

**apparent** microvascular resistance calculated as \( \frac{P_{\text{distal}}}{Q_{\text{coronary}}} \)

**true** microvascular resistance calculated as \( \frac{P_{\text{distal}}}{Q_{\text{myocardial}}} \)

Aarnoudse et al, Circulation 2004
• Minimal microcirculatory resistance, if calculated appropriately, is independent of epicardial stenosis severity

• IMR is a specific index for the microcirculation

• Therefore, it can be used for intra-individual follow-up of minimal microcirculatory resistance within the same patient, provided that the sensor is at the same location in the artery
Some Features of Fractional Flow Reserve:

In addition to its unequaled accuracy to distinguish reversible ischemia, FFR has a number of beautiful features making it such a suitable index to obtain physiologic information about the coronary circulation....

... These have all been validated experimentally and in humans.
FEATURES OF FFR

• Normal value = 1.0 for every patient and every artery
• FFR is *not influenced by changing hemodynamic conditions* (heart rate, blood pressure, contractility)
• FFR specifically relates the influence of the epicardial stenosis to myocardial perfusion area and blood flow
• FFR accounts for collaterals
• FFR has a *circumscripct threshold value* (~ 0.75 – 0.80) to indicate ischemia
• FFR is easy to measure (success rate 99 %) and extremely *reproducible*
• Pressure measurement has un *unequaled spatial resolution*
Prerequisites for a reliable index for decision making

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

(predict outcome):

1. is it safe to DEFER FFR-negative lesions
2. better outcome by PCI of FFR-positive lesions
Influence of the “Resting Flow” on CFR

Resting flow in the cath lab is an illusion

CFR = 4.8

CFR = 2.8

10 cm.s\(^{-1}\)

48 cm.s\(^{-1}\)

56 cm.s\(^{-1}\)

20 cm.s\(^{-1}\)
Hemodynamic Variability of FFR\textsubscript{myo} and CFR

**FFR**

**CFR**

- Baseline
- Pacing
- Nitroprusside
- Dobutamine

B. De Bruyne et al Circulation 1996
The **DEFER** Study: Reproducibility of FFR

Reproducability of pressure derived FFR

\[ y = 0.9792x + 0.0139 \]

\[ R = 0.983 \]

Data 17 years old and measured by 0.018” fiberoptic catheter (with a lot of drift) in the early days of coronary pressure measurement
Reproducibility of FFR

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

There is not any other index in physiology so reproducible as FFR
Hocus-pocus with statistics (3)
About reproducibility and “wrong decisions”

Or: confusing a-priori and a-posteriori knowledge

• In Catharina Hospital, 6000 invasive procedures (diagnostics and PCI) are performed annually

• Prior to a procedure, kidney function is checked

• If GFR < 60 ml/min → prehydration

• Accuracy of GFR measurement is ≤ 3ml/min (rather good!, you don’t think so?)
Hocus-pocus with statistics (3)
About reproducibility and “wrong decisions”

Or: confusing a-priori and a-posteriori knowledge

• In the year 2012, out of the 6000 patients, GFR was between 57 and 63 ml/min in 387 of them.

• In ~50% of these 387 patients, a second measurement would have switched them from above 60 ml to below or vice versa.

• Does this mean that you could better not determine renal function prior to PCI/ CAG, because “it is wrong in the group of patients where it matters” ???
What is fundamentally wrong in this reasoning?

- confusing *a-priori* and *a-posteriori* knowledge

You do not know *beforehand* who is close to the “cut-off” value (if you would know that, there would be no need to measure at all)

Of the total population you need to examine, only a small percentage is close to the cut-off value and might “cross the border” (387/6000 = 6 % in case of GFR & hydration)
At 1200 consecutive in-duplo measurements of FFR, there was NOT ANY cross-over across the gray zone.