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

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The New England
Journal of Medicine

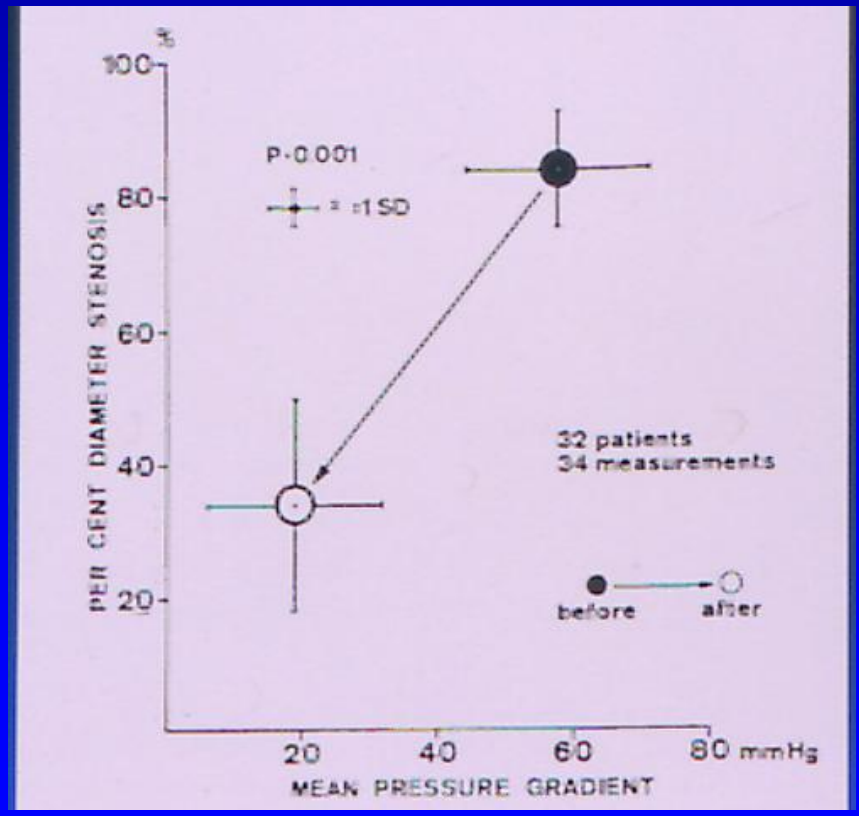
Volume 301 JULY 12, 1979 Number 2

NONOPERATIVE DILATATION OF CORONARY-ARTERY STENOSIS

Percutaneous Transluminal Coronary Angioplasty

ANDREAS R. GRÜNTZIG, M.D., ÅKE SENNING, M.D., AND WALTER E. SIEGENTHALER, M.D.

Gruentzig and other early investigators, intuitively noticed the importance of coronary pressure measurement

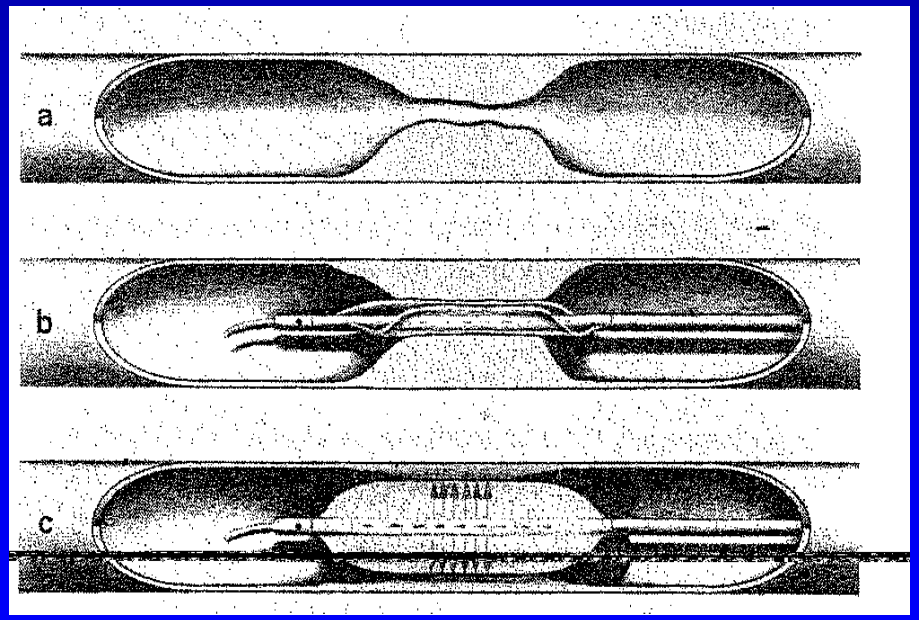


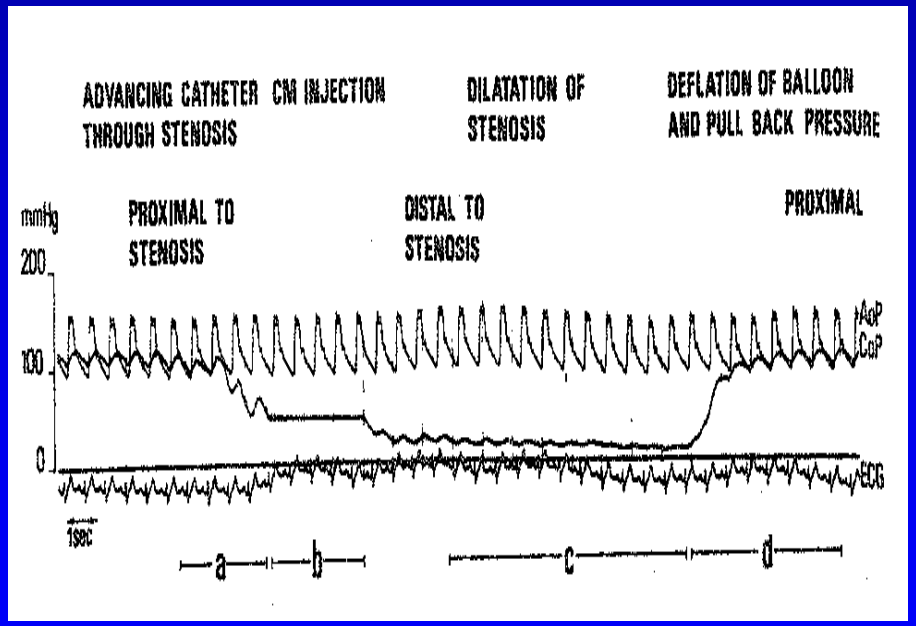
But....they were limited by

- 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***





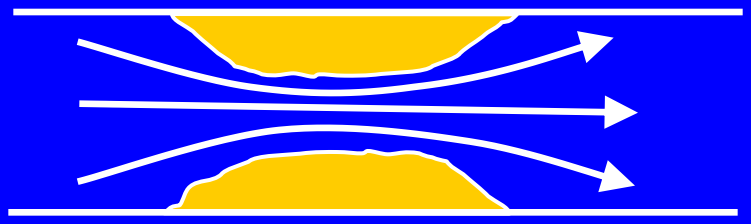
But....they were limited by

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

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

$\Delta P = f.Q + s.Q^2$

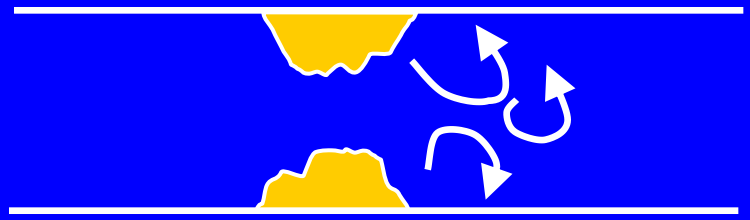
f = friction coefficient



Moderate gradient at rest

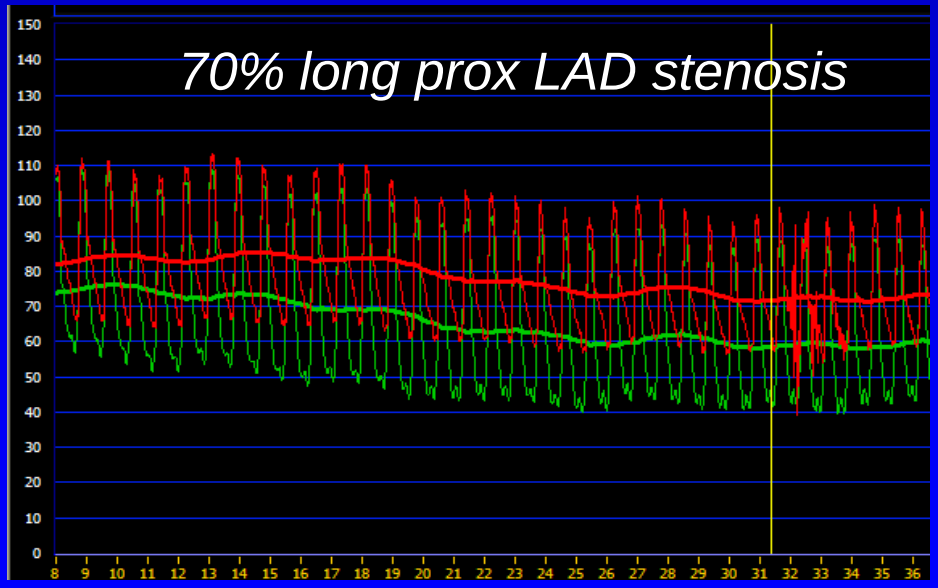
Moderate increment at hyperemia

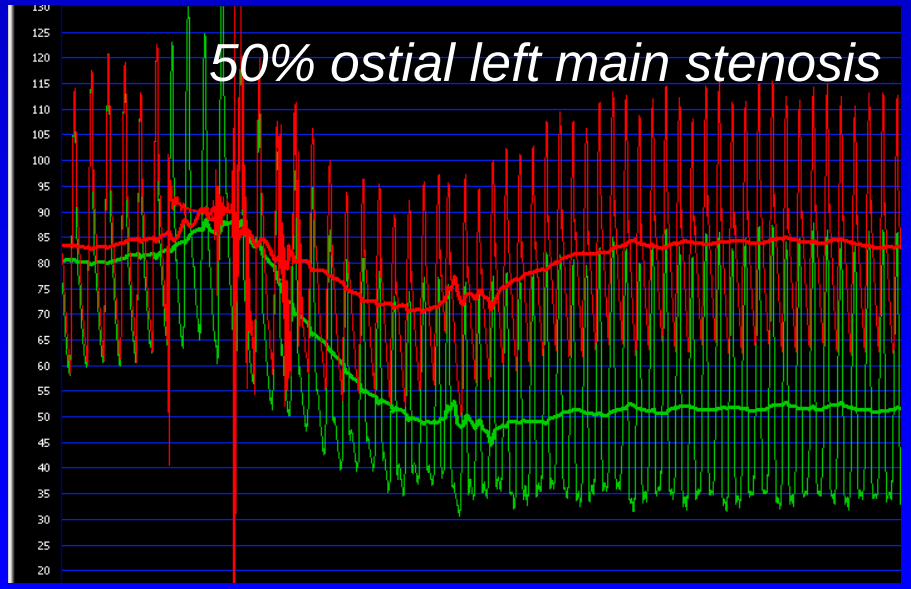
S = separation coefficient



Small gradient at rest

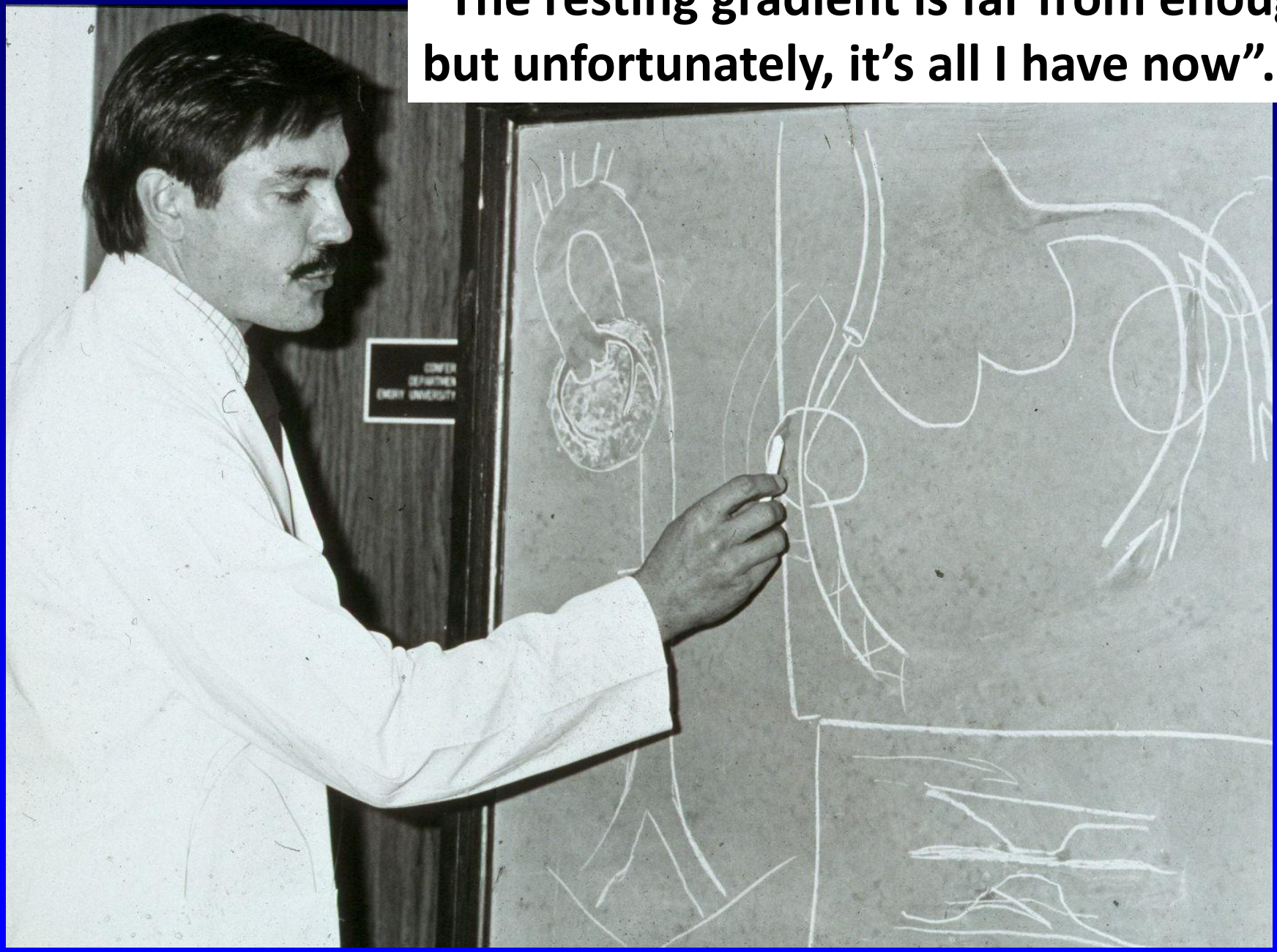
Large gradient at hyperemia





→ **resting gradient cannot predict hyperemic gradient**

“The resting gradient is far from enough but unfortunately, it’s all I have now”.



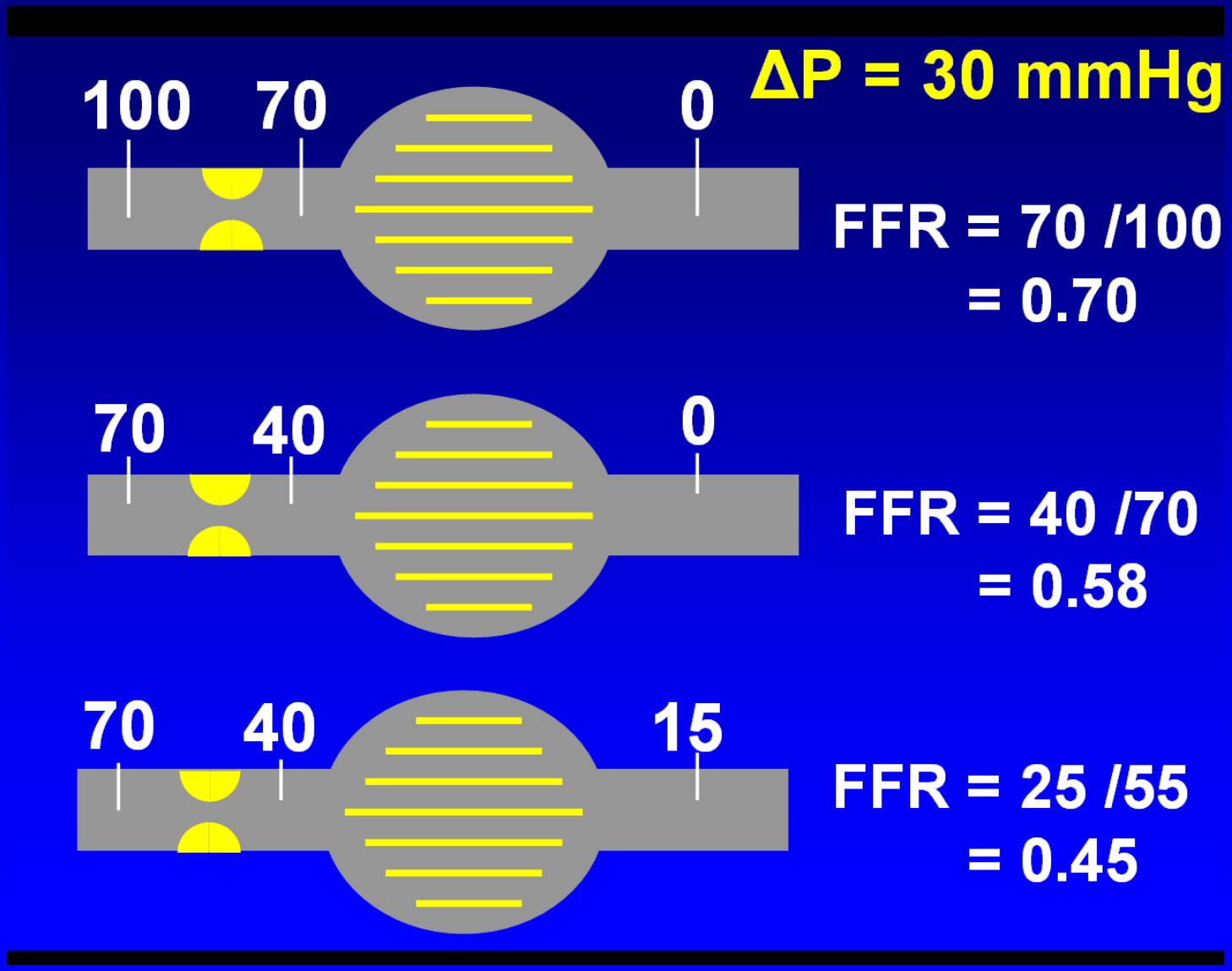
But....they were limited by

- 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:



Fortunately, these 3 limitations were overcome:

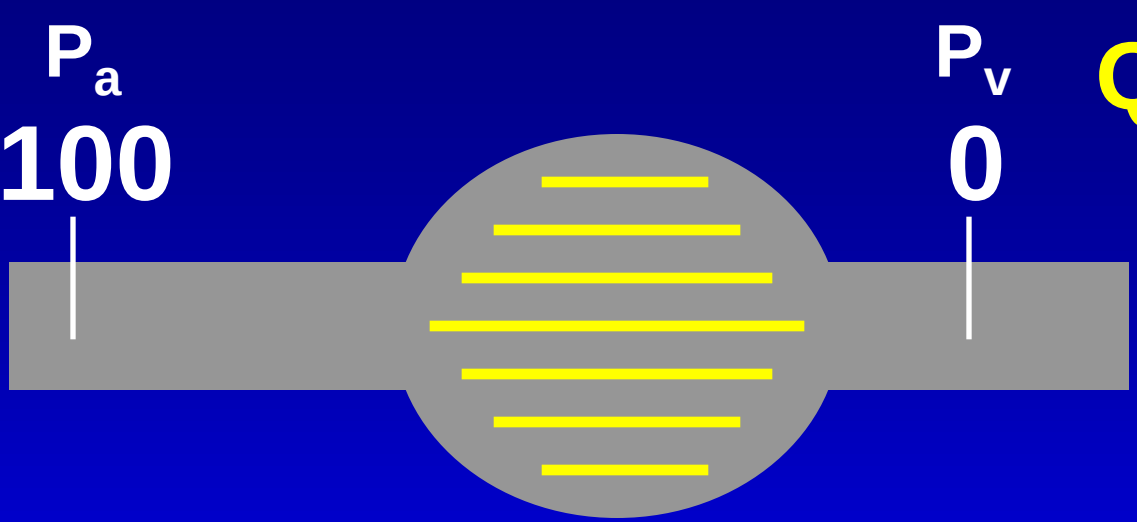
- In the late eighties, 0.014” pressure guide wires became available, enabling reliable distal coronary presssure *(Tenerz, 1988)*

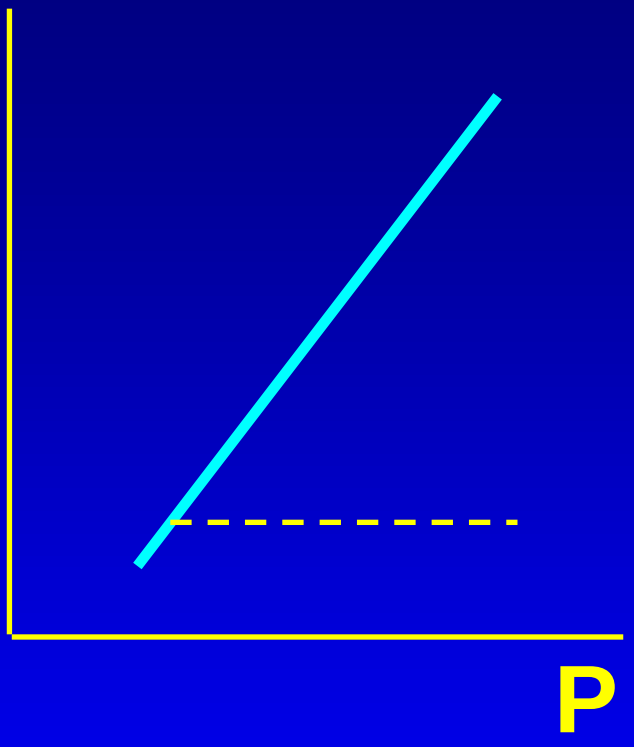
- Safe and reproducible hyperemic drugs were validated for use in the human coronary circulation *(Wilson, 1985)*

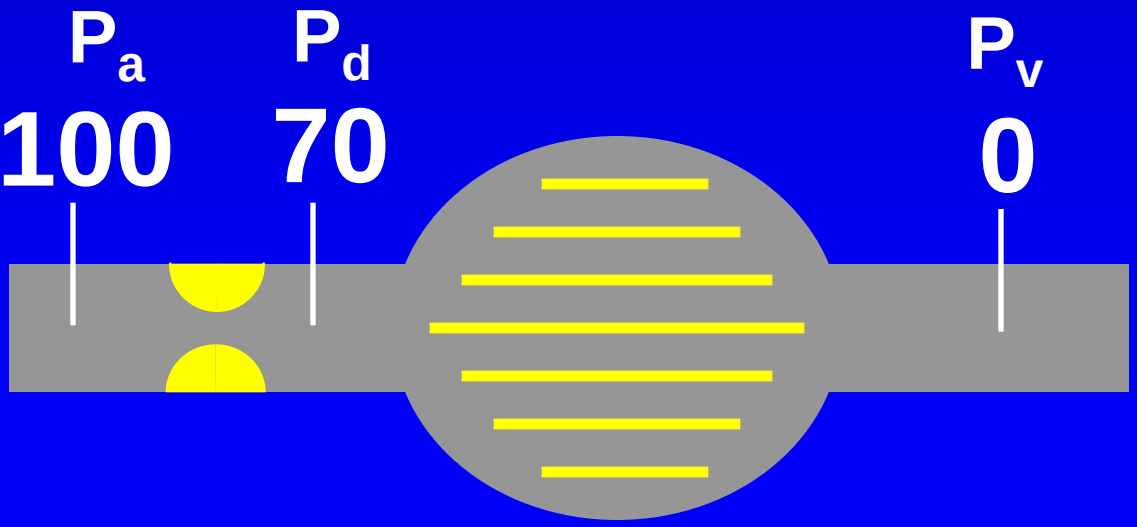
- And it was recognized that not gradients in itself are important, but the ratio of perfusion pressures at hyperemia *(Pijls & De Bruyne, 1991)*

→ **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

NORMAL MAXIMUM FLOW

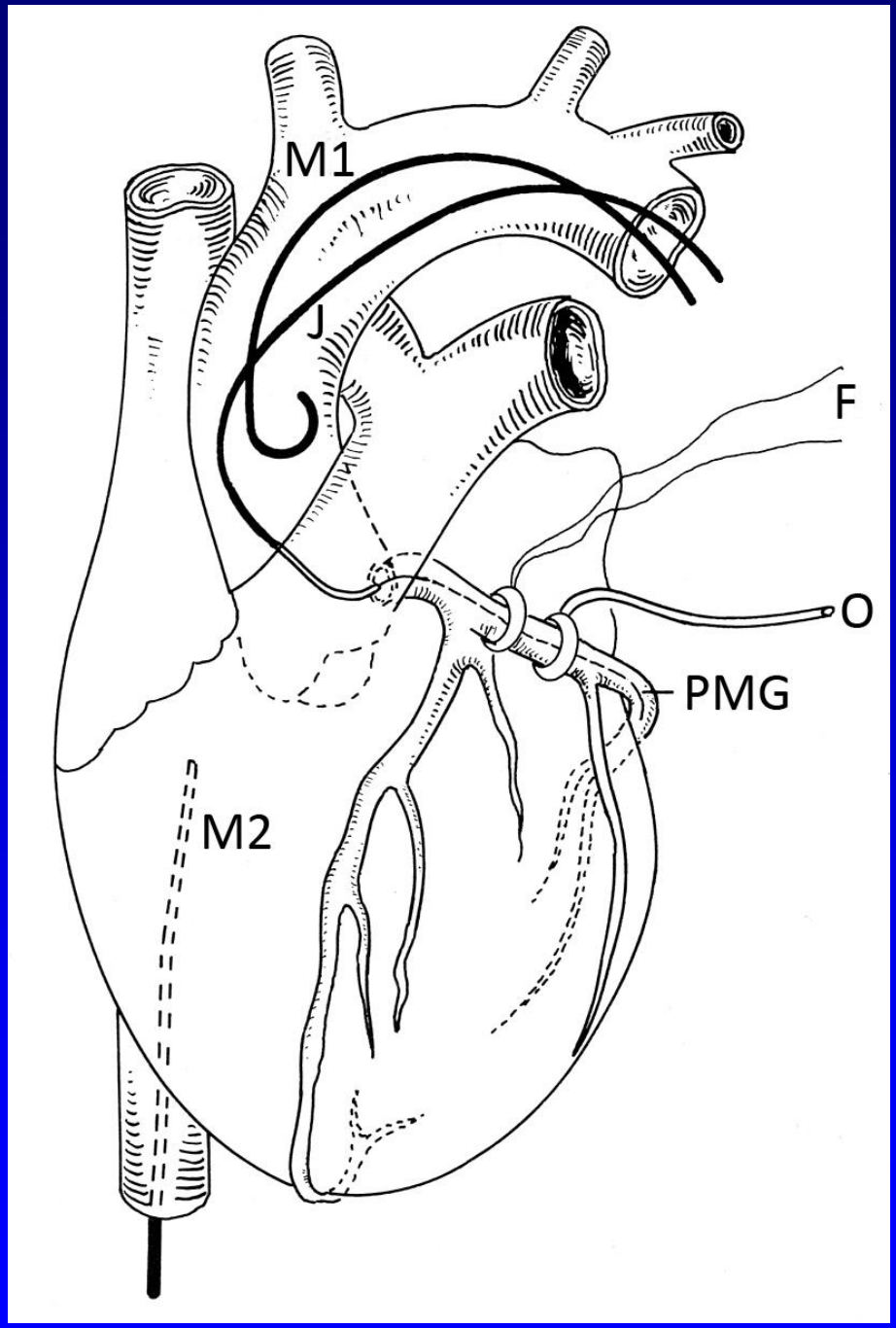
$$\approx \frac{\text{Distal coronary pressure at maximum hyperemia}}{\text{Aortic pressure}}$$

FRACTIONAL FLOW RESERVE:

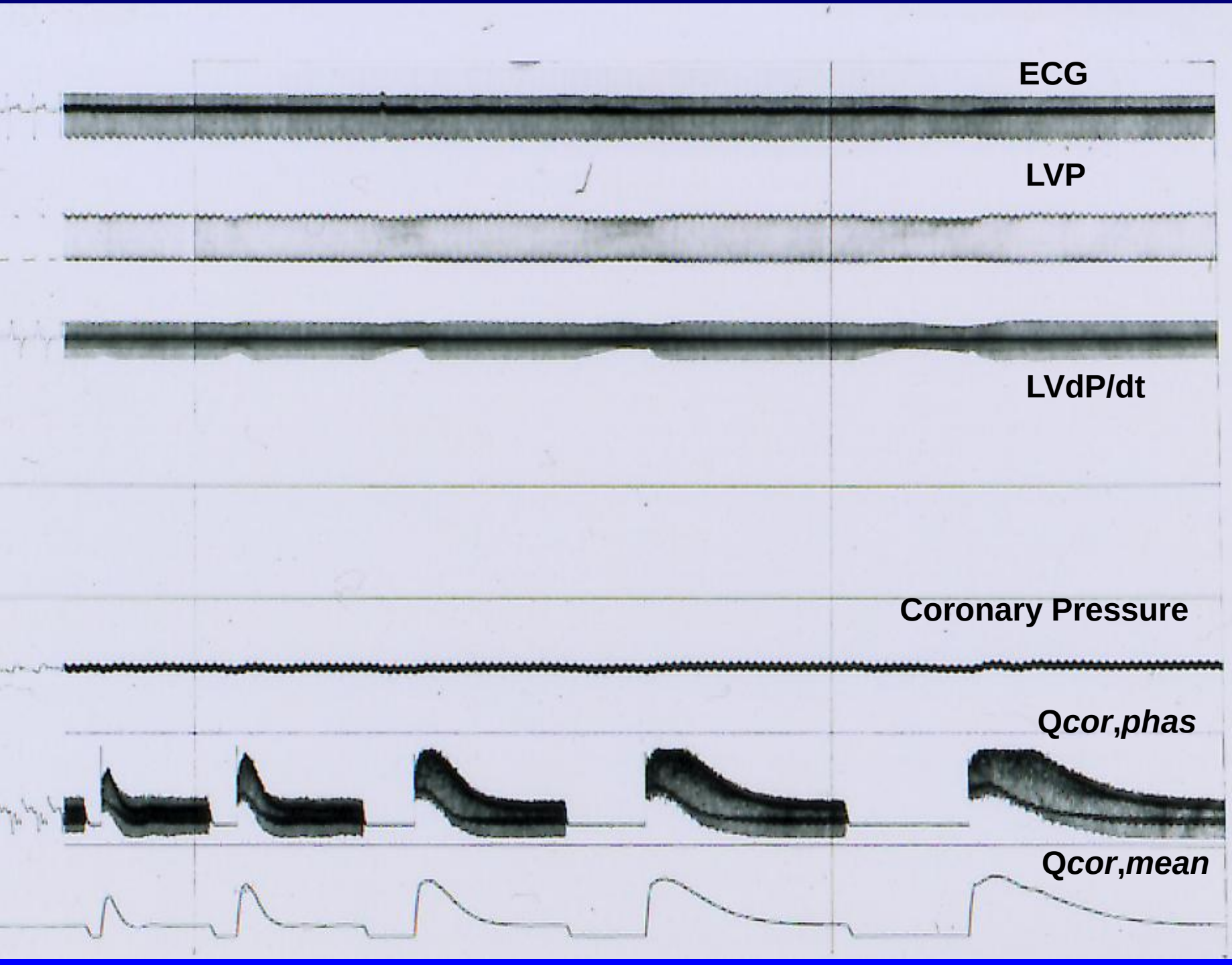
The index FFR (***Fractional Flow Reserve***)
is based upon the two following principles:

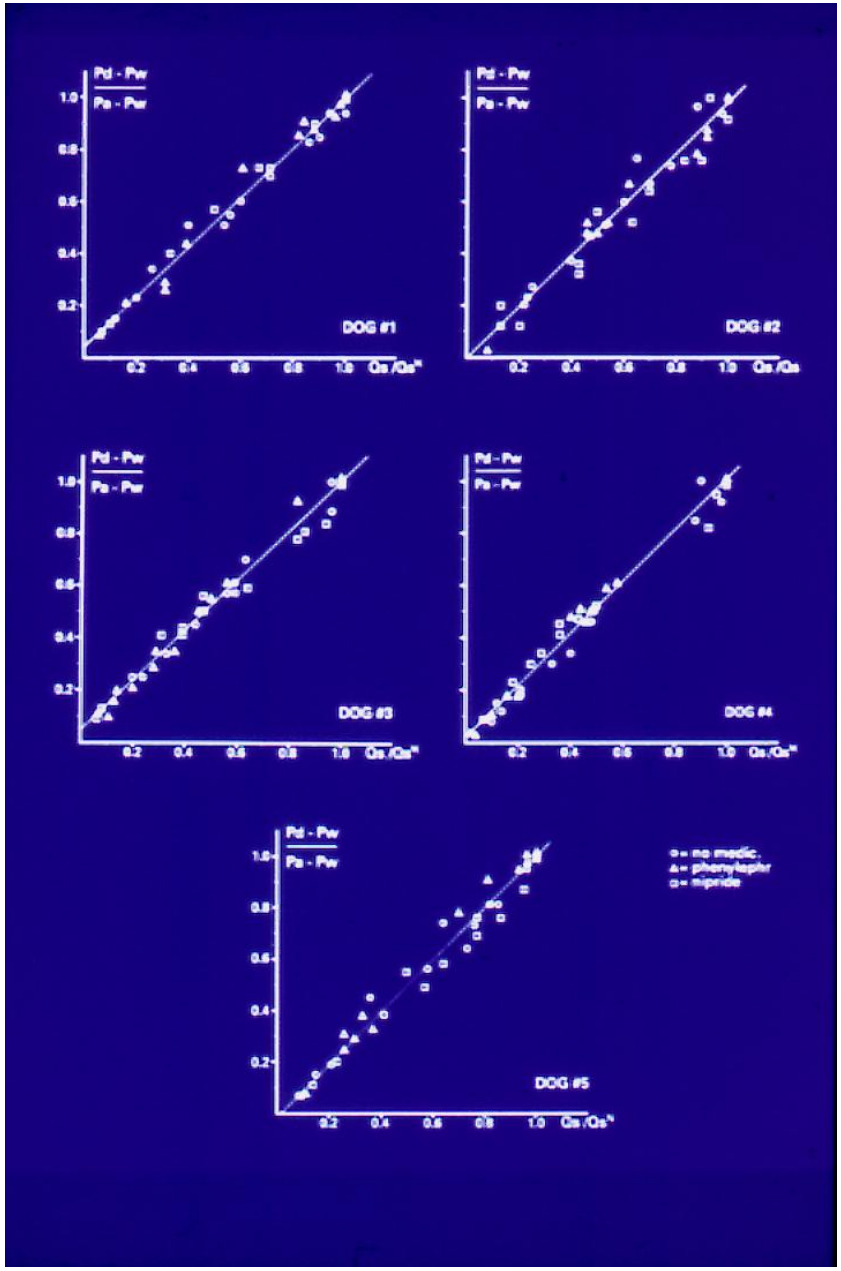
- *It is not resting flow, but **maximum achievable flow** which determines the functional capacity (exercise tolerance) of a patient*

- *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


ECG
LVP
LVdP/dt
Coronary Pressure
Qcor,phas
Qcor,mean

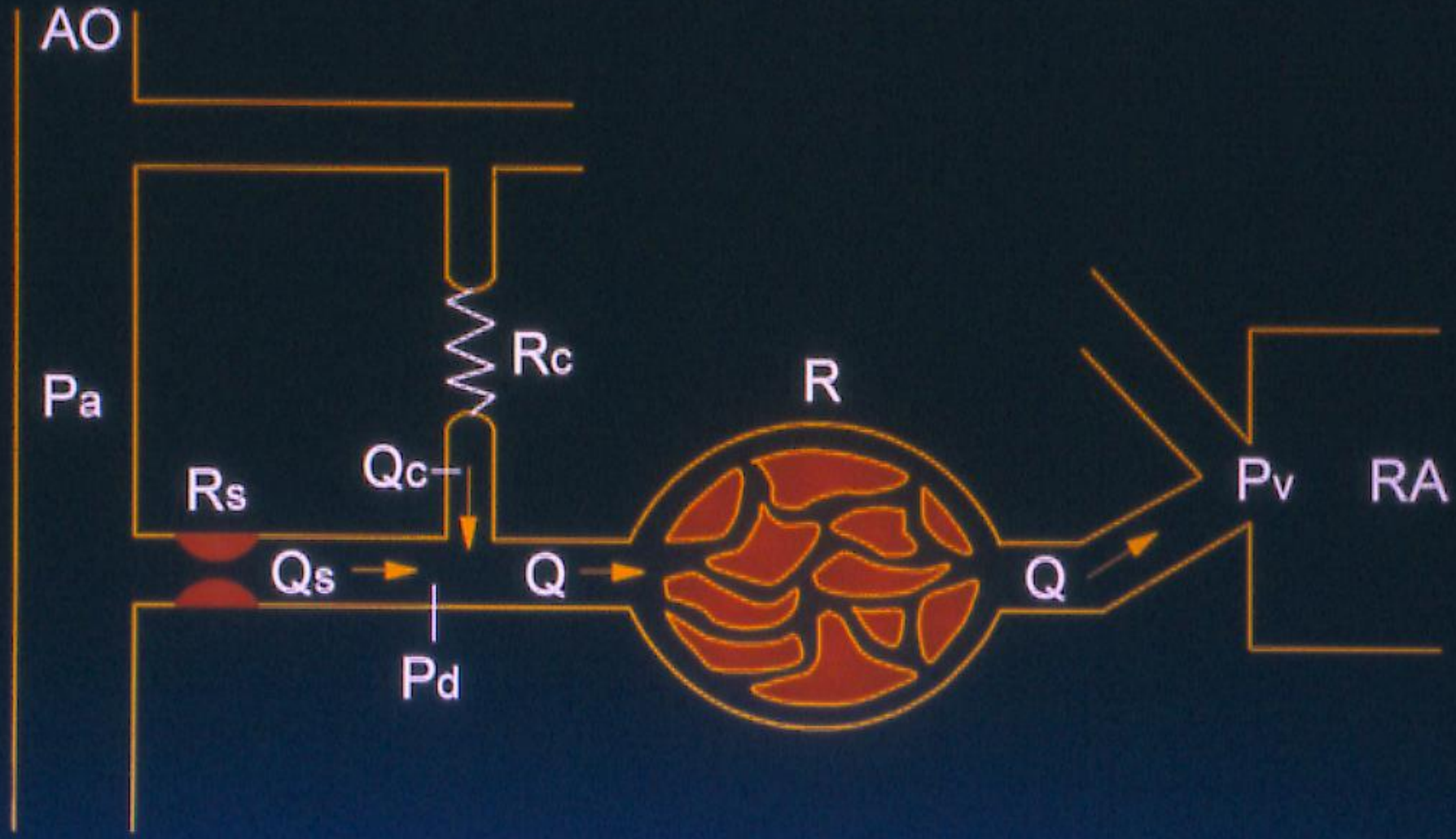


Experimental basis of FFR

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 $$\mathrm{FFR}_{cor} = \frac{P_d - P_w}{P_a - P_w} = 1 - \frac{\Delta P}{P_a - P_w}$$

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

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

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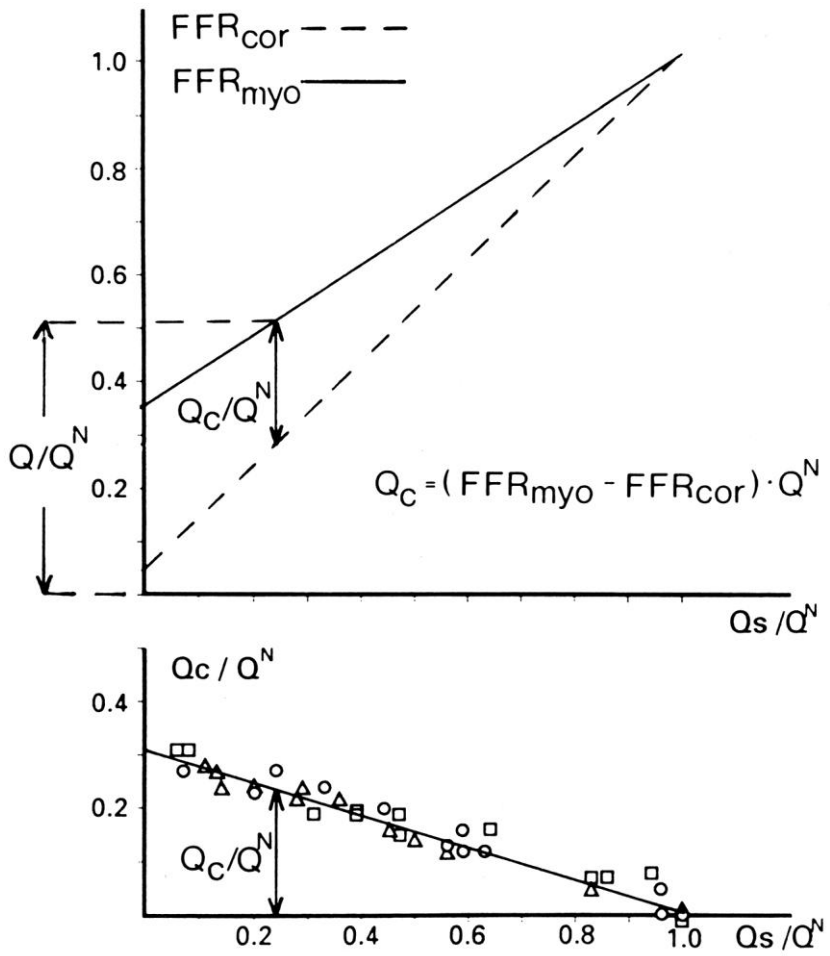

Experimental basis of FFR

<u>Horizontal axis:</u>

$FFR_{\mathbf{cor}}$ measured by true flow

<u>Vertical axis:</u>

$FFR_{\mathbf{myo}}$ and *$FFR_{\mathbf{coll}}$ measured by Hyperemic pressure ratio*

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 ful paper in Circulation:may 1993

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Circulation *Vol 87, No 4 April 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 ar-

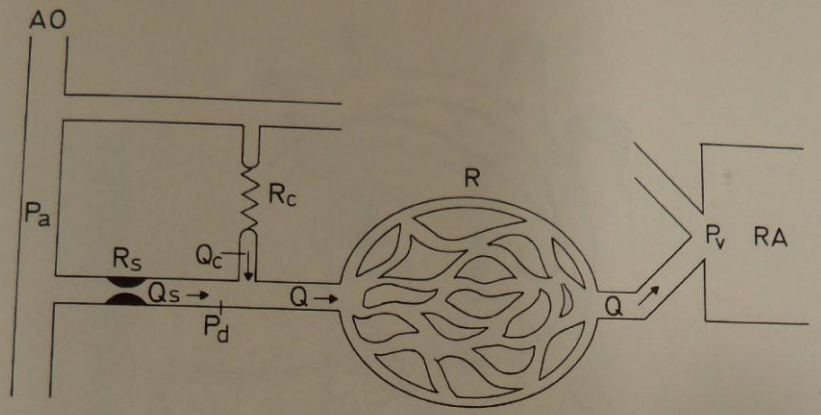

FIGURE 1. *Schematic model representing the coronary circulation. AO, aorta; P_a, arterial pressure; P_d, distal coronary pressure; P_v, venous pressure; Q, blood flow through the myocardial vascular bed; Q_c, collateral blood flow; Q_s, blood flow through the supplying epicardial coronary artery; R, resistance of the myocardial vascular bed; R_c, resistance of the collateral circulation; R_s, resistance of the stenosis in the supplying epicardial coronary artery; RA, right atrium.*

tery 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.[1,2] However, a unique strength of the model described here is the theoretical capacity

Circulation *Vol 87, No 4 April 1993*

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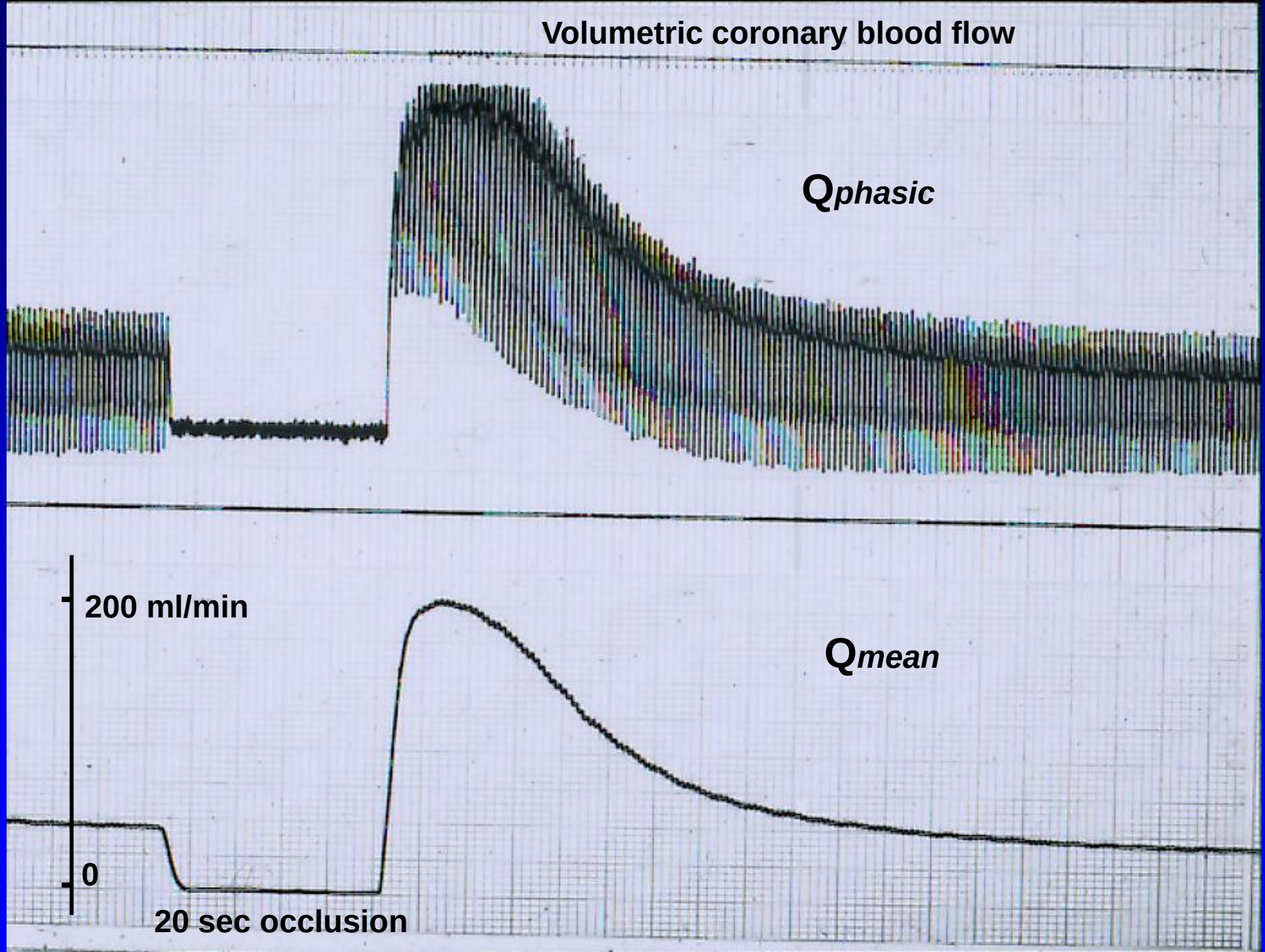
"Official introduction" of Fractional Flow Reserve

Do we have to bother about P_V ?

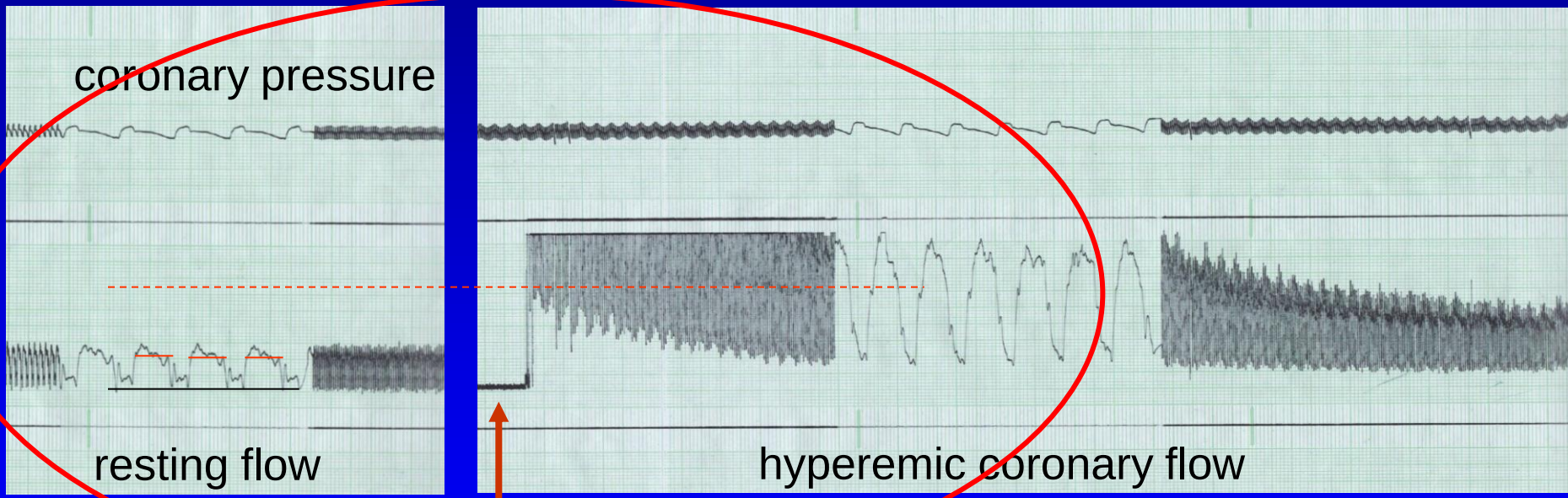
→ ***Only*** in case of studies to collateral Function, or severely elevated Pv

$$FFR_{coll} = \frac{Pw - Pv}{Pa - Pv}$$

$$\frac{75 - 5}{100 - 5} = 0.74 \qquad \frac{75}{100} = 0.75 \qquad \frac{20\text{-}5}{100\text{-}5}$$

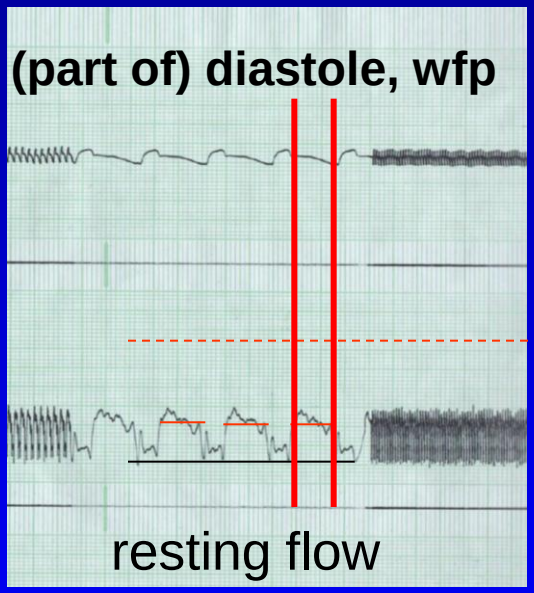

Volumetric coronary blood flow
Qphasic
200 ml/min
Qmean
0
20 sec occlusion

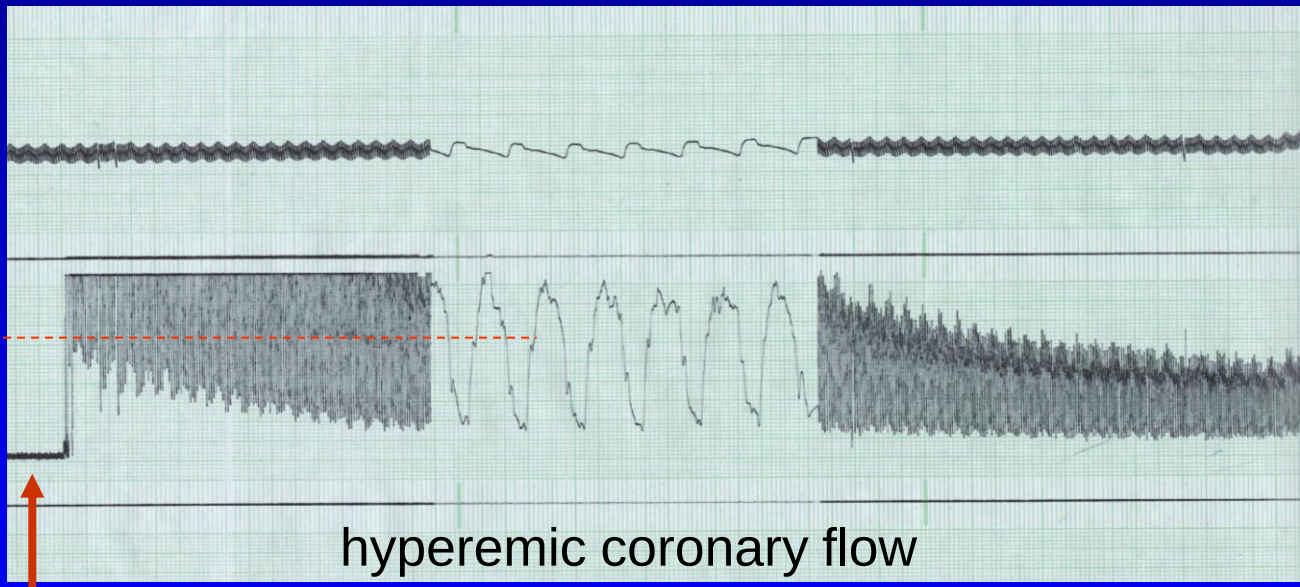
Highest flow achieved at rest in any part of the heart cycle
Is far below average hyperemic coronary flow in all dogs



coronary occlusion

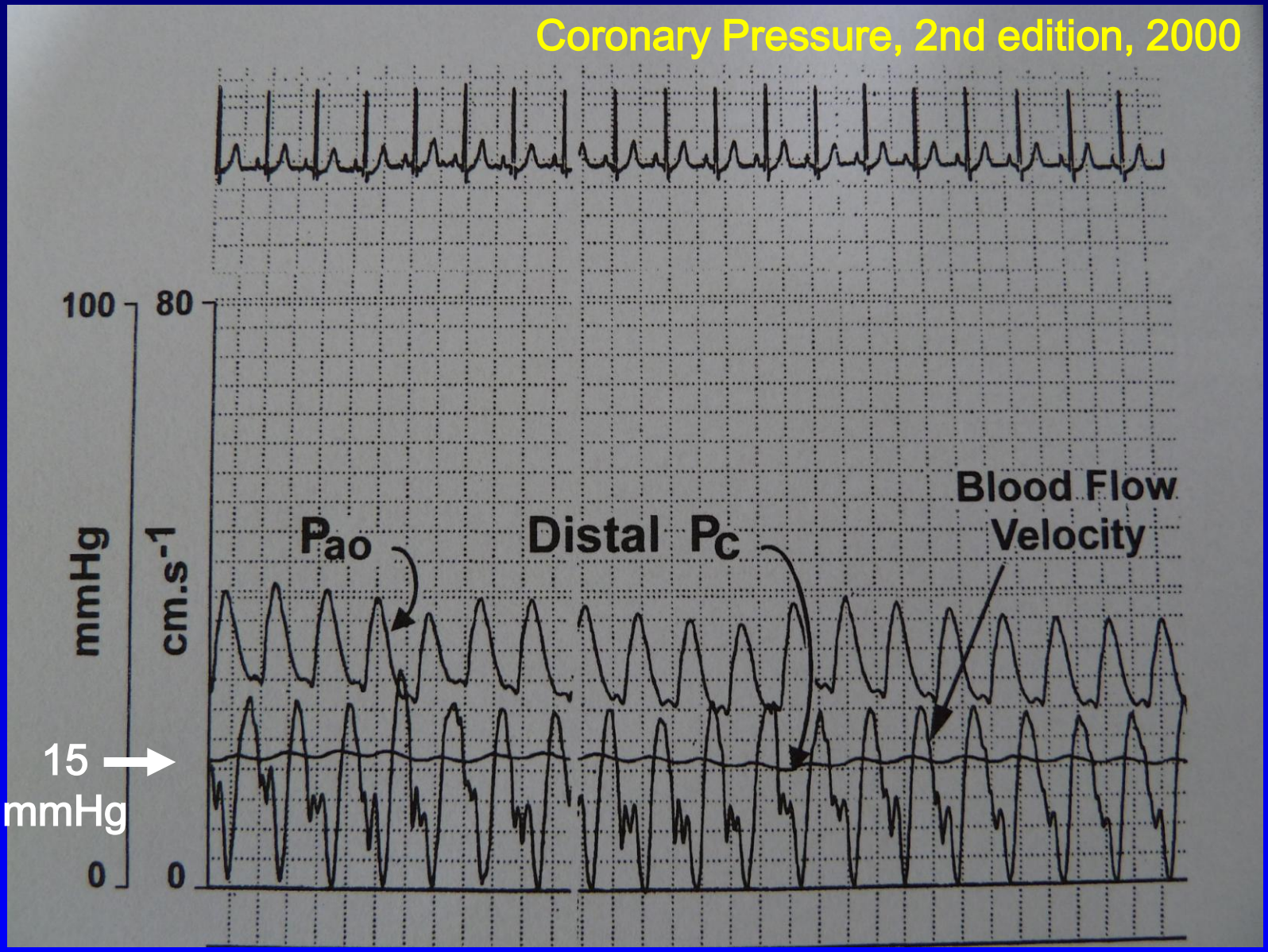
minimal myocardial resistance during any period in diastole at rest, is ~ 250 % higher than average myocardial resistance at maximum hyperemia in all dogs





coronary occlusion

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

FFR = 0.98 +/- 0.02 (range 0.93 – 1.00)

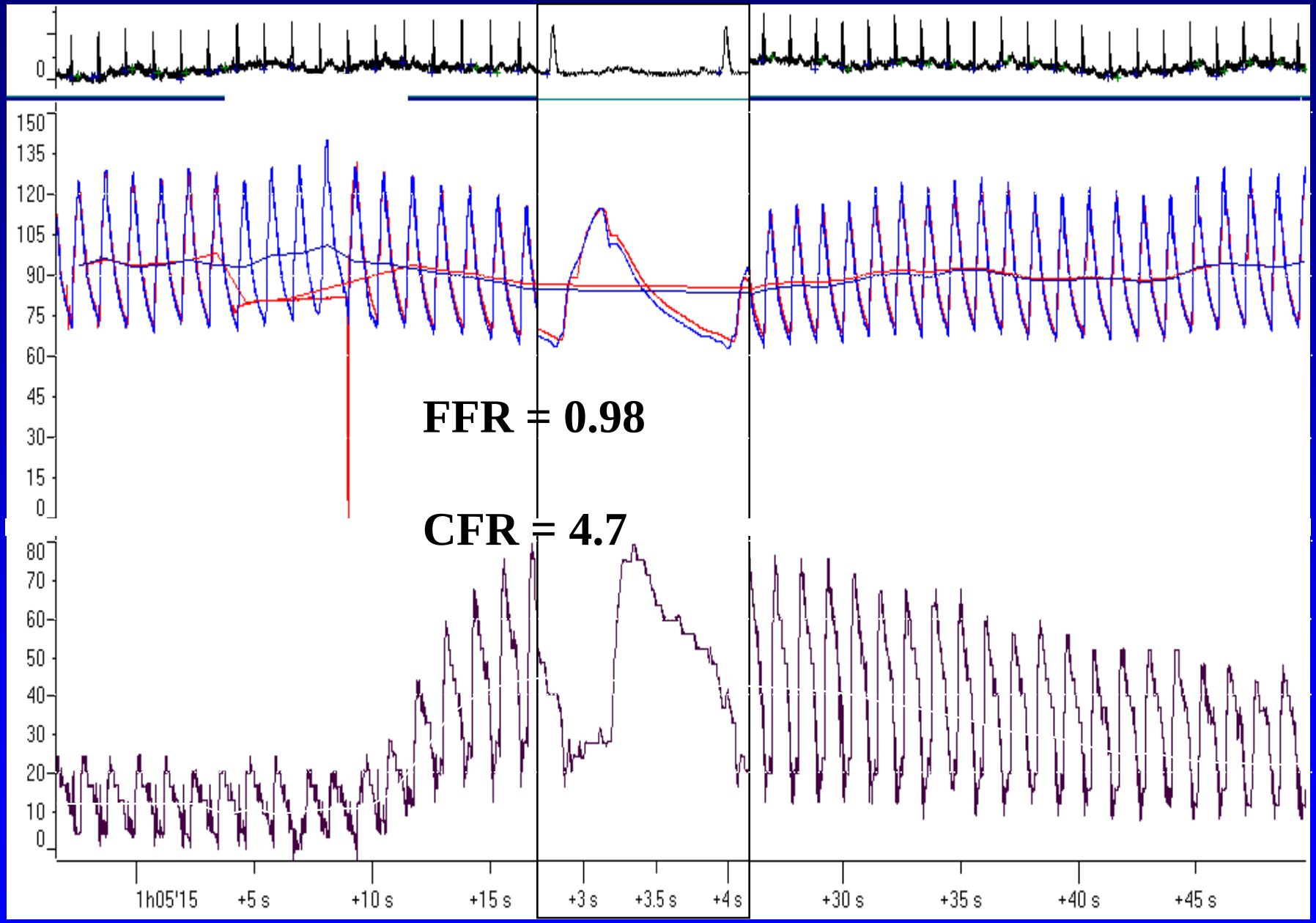
Pijls, Circulation 1995;92: 183-193

86 apparently normal contralateral arteries In patients with coronary disease:

FFR = 0.87 +/- 0.09 (range 0.64 – 0.97)

De Bruyne, Circulation 2001; 104:2401-2406

Normal Coronary Artery



Threshold value of FFR to detect significant stenosis in humans

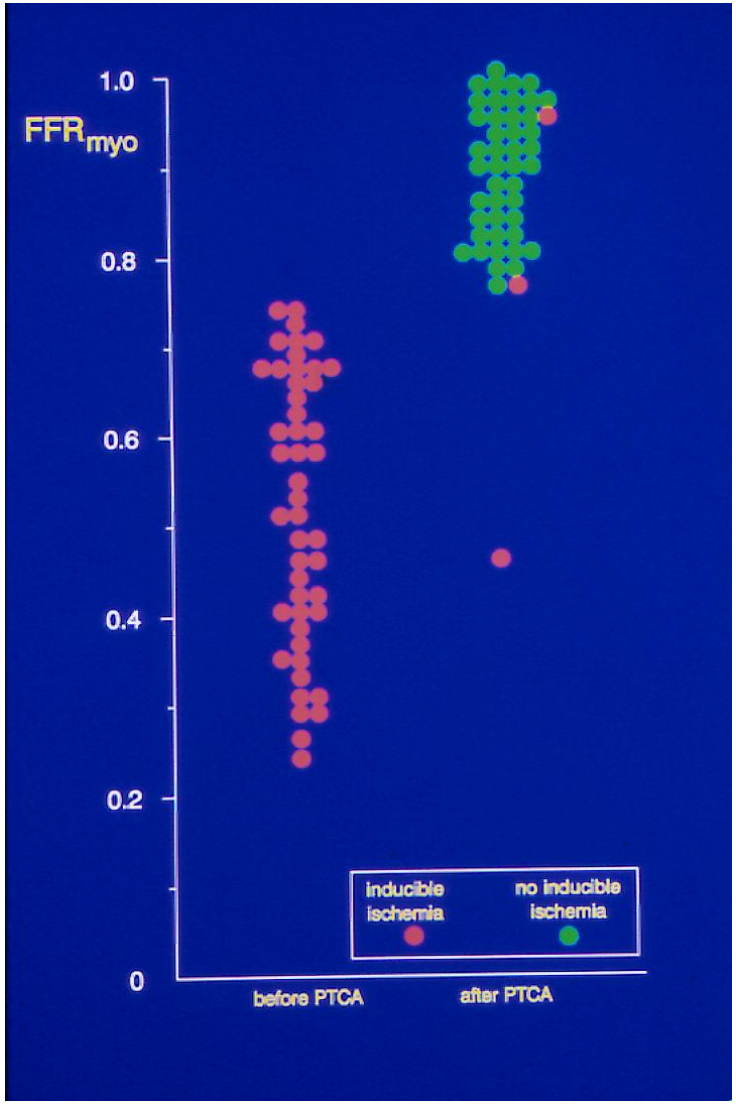
FFR is the ***only*** functional index which has ever been validated versus a **true gold standard**.
(Prospective multi-testing Bayesian methodology)

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

Diagnostic accuracy ≥93%

Pijls et al, N Engl J Med 1996; 334:1703-1708
Oldroyd et al, Circulation 2010

Validation of FFR in humans (step 1)

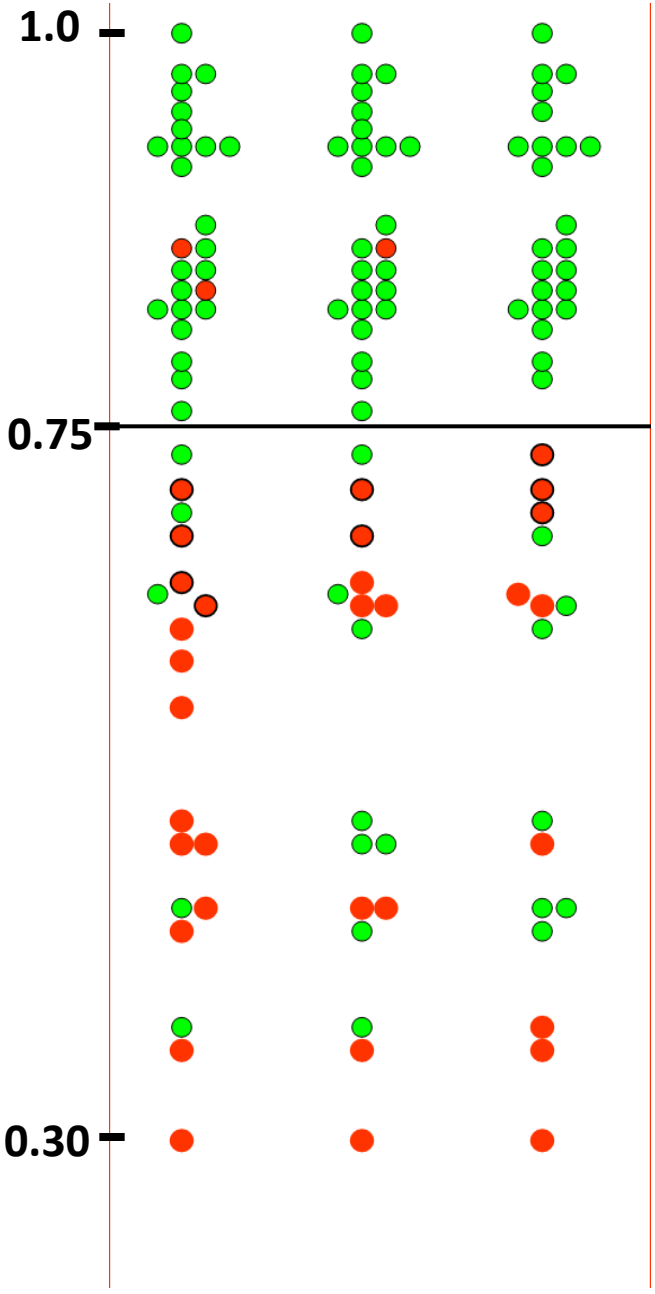


Proper validation of any index needs ***2 steps:***

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



Testing of FFR versus True Gold Standard

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

Threshold value of FFR to detect significant stenosis in humans

FFR is the ***only*** functional index which has ever been validated versus a **true gold standard**.
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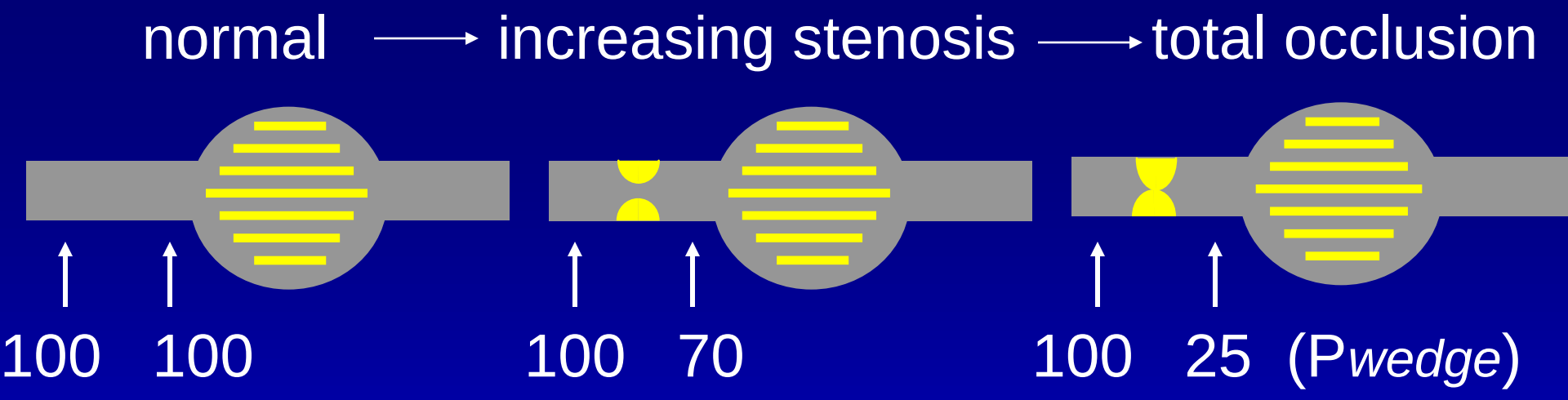


Maximum myocardial perfusion:

100% ⟶ ***70%*** ⟶ ***25%***

FFR: **1.0** ⟶ **0.7** ⟶ **0.25**

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

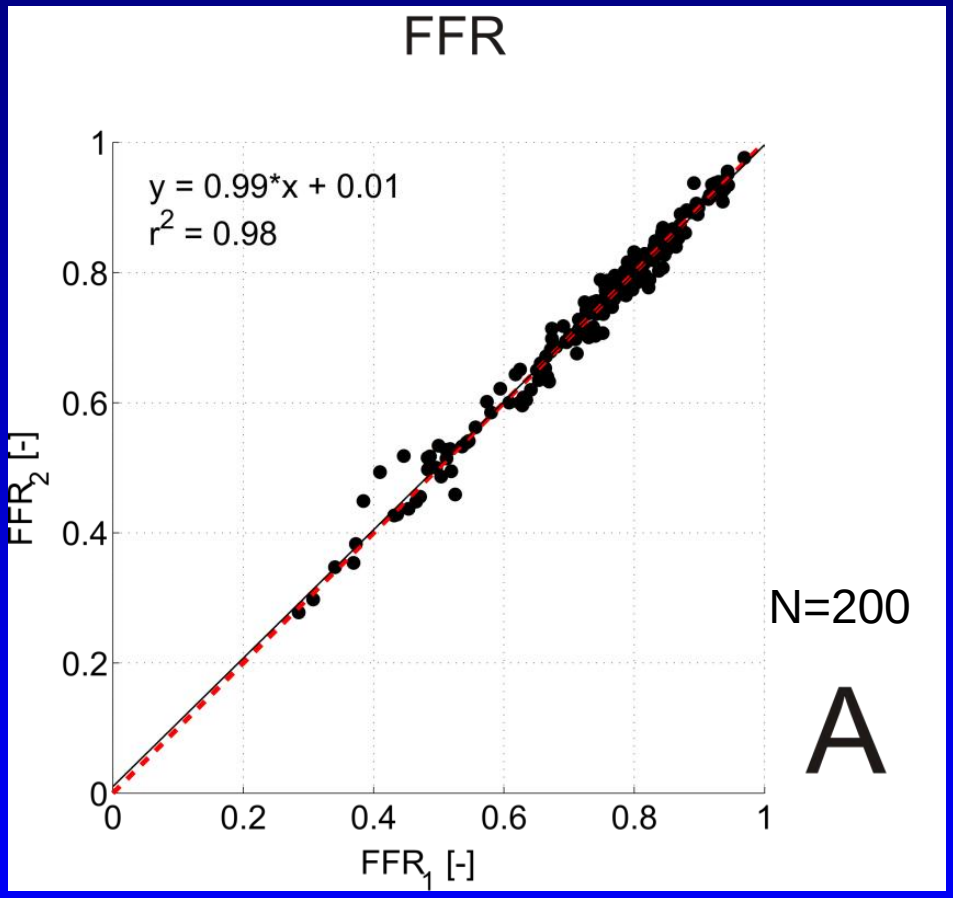
Let's have a closer look to FFR

Prerequisites for a reliable index for decision making

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

} tomorrow

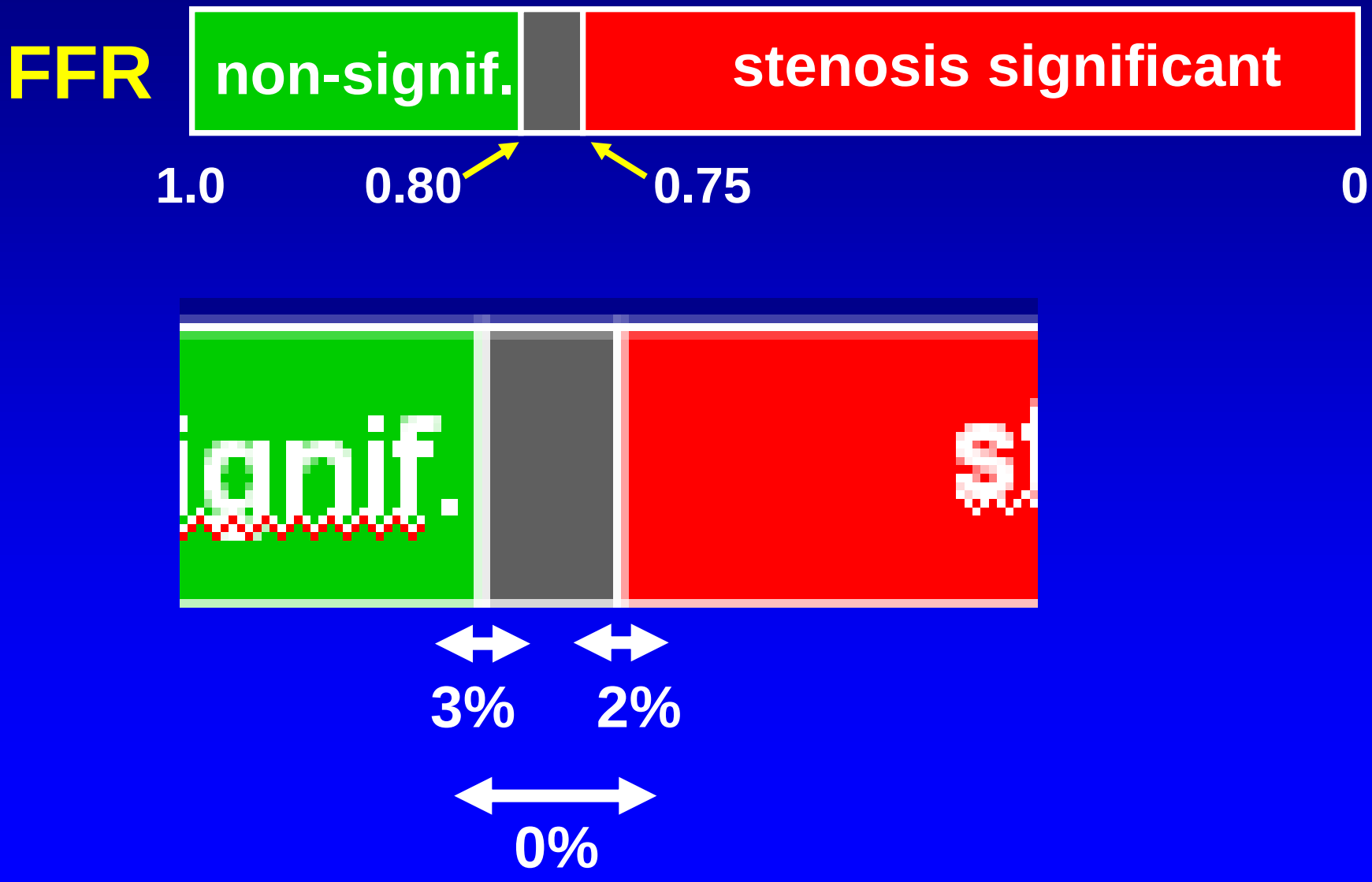
Reproducibility of FFR



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

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

At <u>1200</u> consecutive in-duplo measurements of FFR, there was <u>NOT ANY cross-over</u> 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

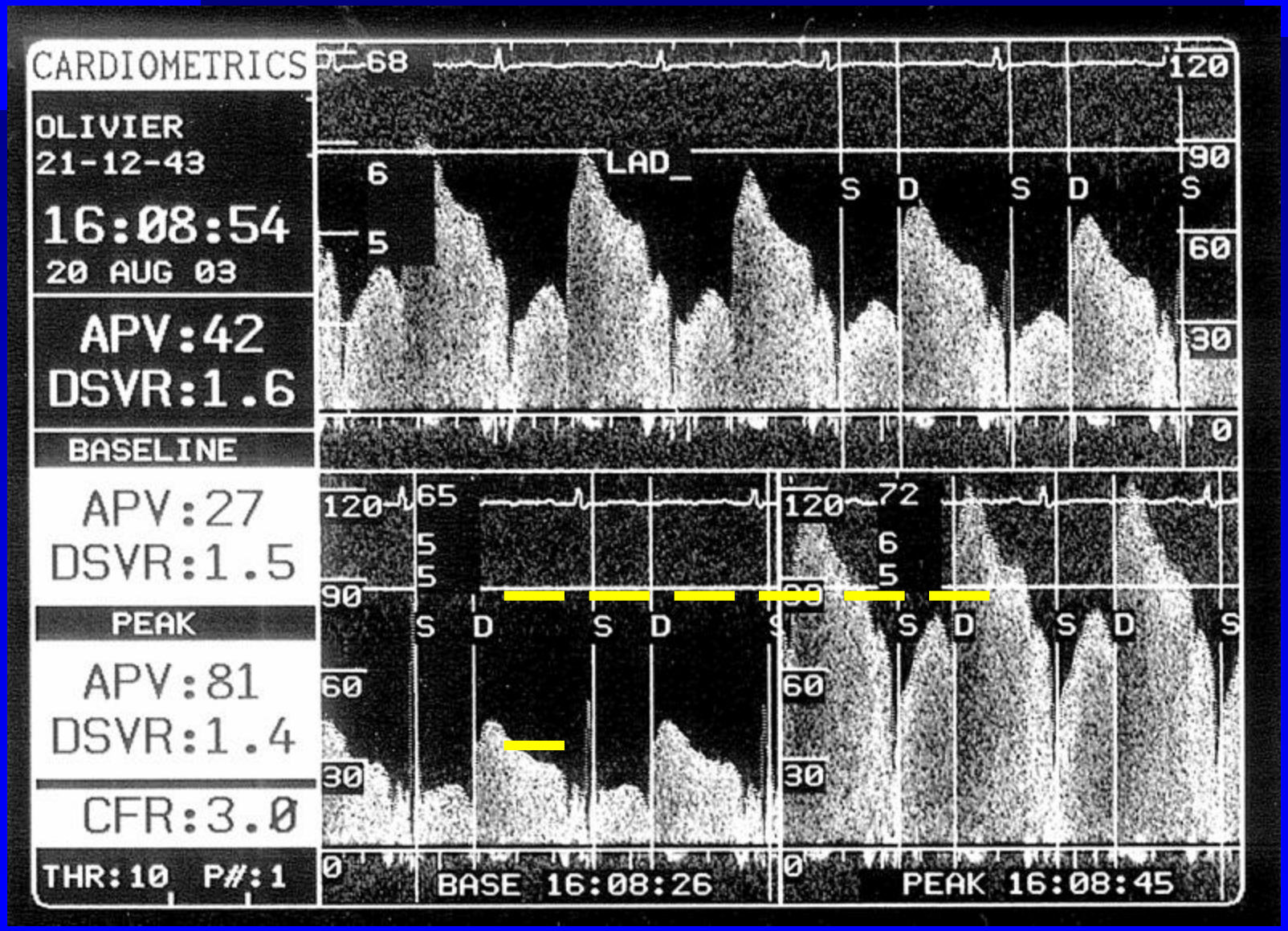
- The concept comprises not only maximum myocardial perfusion (most important from clinical point of view), but also coronary and collateral flow and describes the complete coronary circulation in terms of pressures

SUMMARY (2):

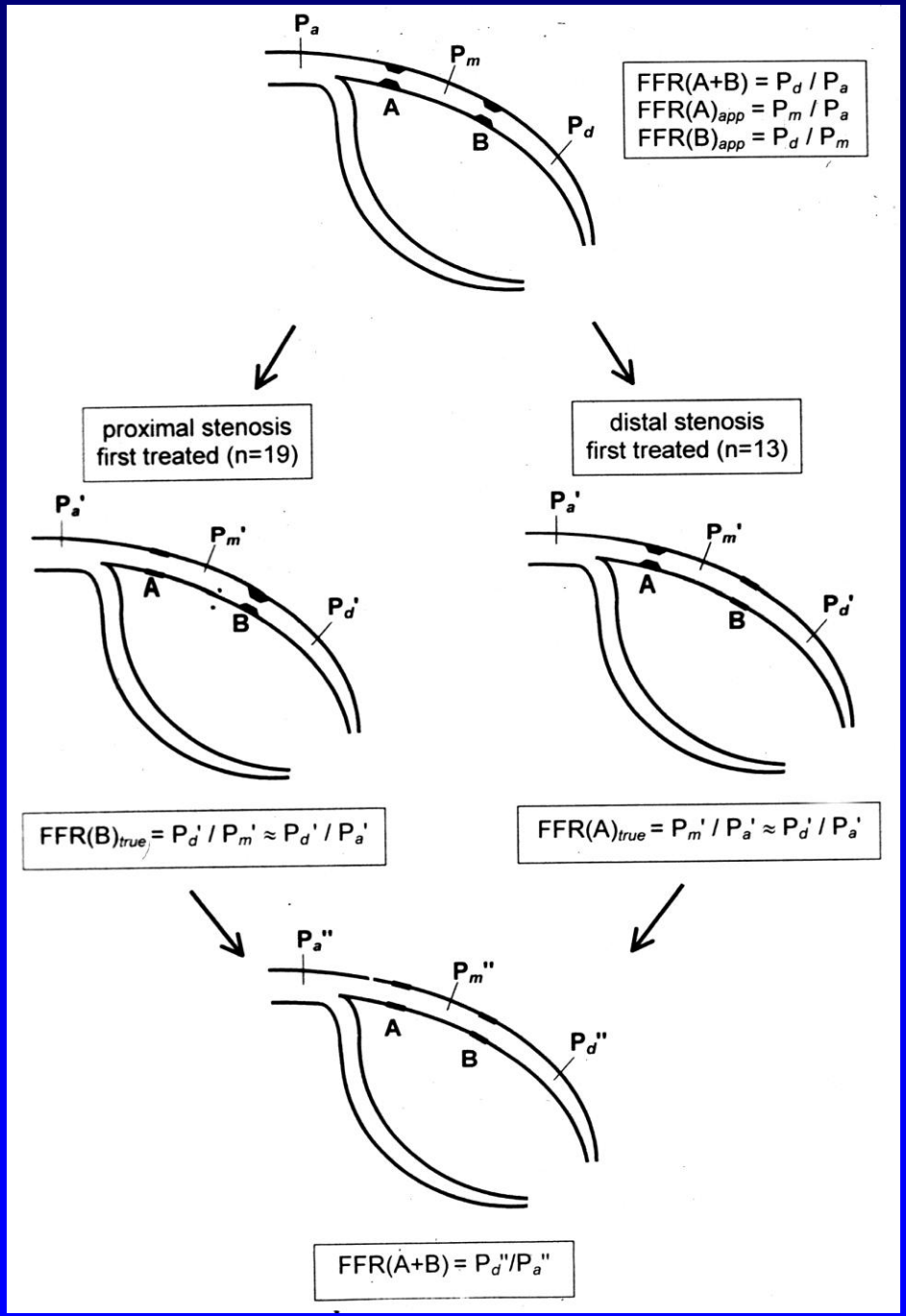
- There is a sharp cut-off value between ischemic and non-ischemic values with a narrow “gray zone”. And FFR is the only physiologic index for which this has been prospectively validated versus a true gold standard

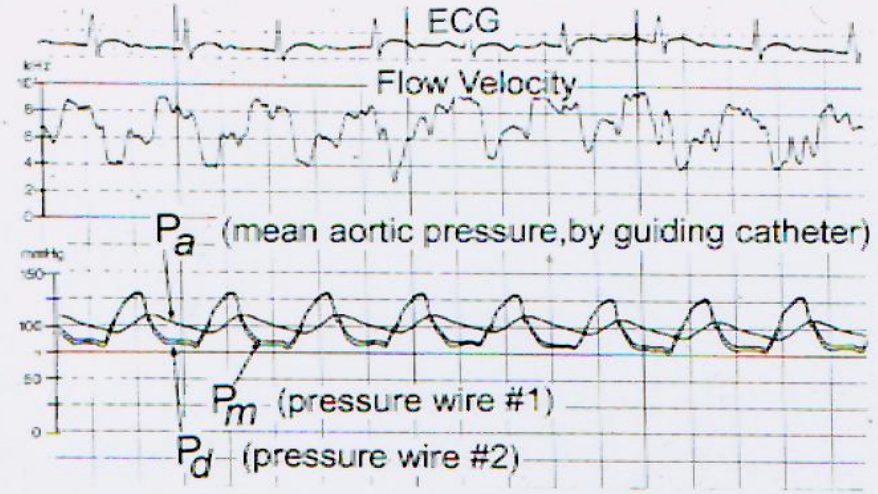
- The reproducibility of FFR is unsurpassed by any other index.

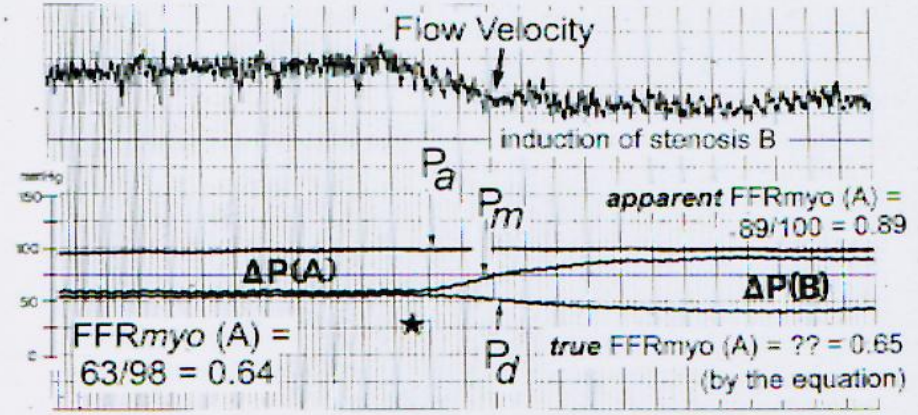
Doppler flow velocity recording in a human coronary artery

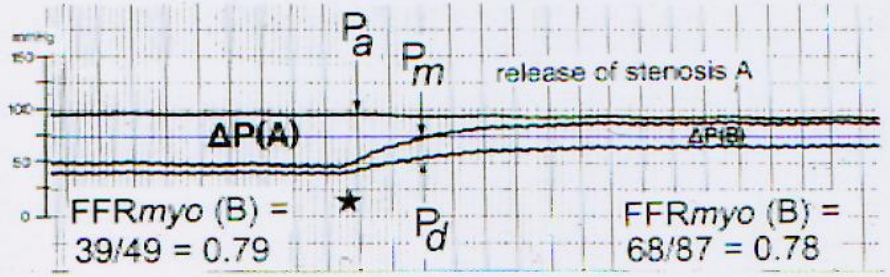


resting hyperemia (adenosine)

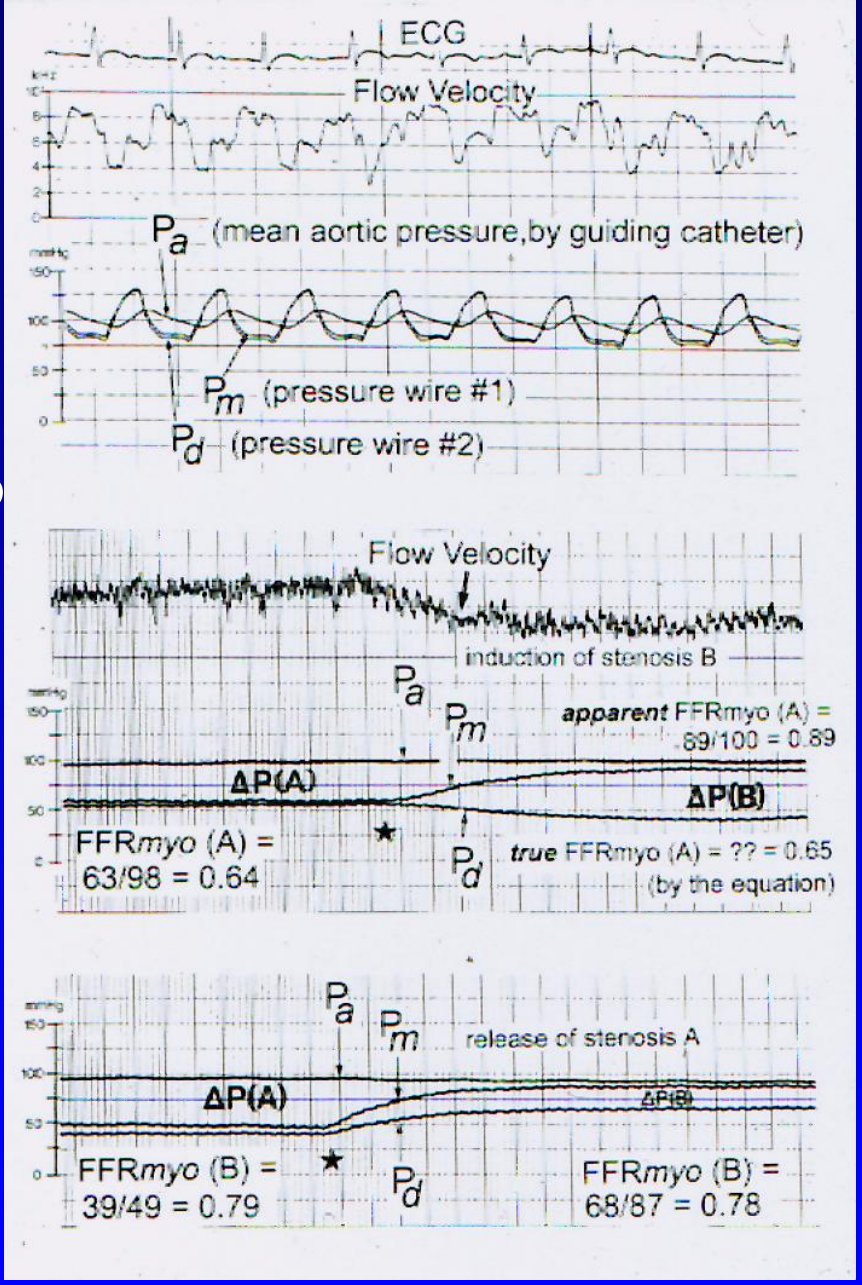

P_a
P_m
A
B
P_d
FFR(A+B) = P_d / P_a
FFR(A)$_{app}$ = P_m / P_a
FFR(B)$_{app}$ = P_d / P_m
proximal stenosis first treated (n=19)
distal stenosis first treated (n=13)
P_a'
P_m'
P_d'
FFR(B)$_{true}$ = P_d' / P_m' ≈ P_d' / P_a'
FFR(A)$_{true}$ = P_m' / P_a' ≈ P_d' / P_a'
P_a''
P_m''
P_d''
FFR(A+B) = P_d''/P_a''


ECG
Flow Velocity
P_a (mean aortic pressure,by guiding catheter)
P_m (pressure wire #1)
P_d (pressure wire #2)


Flow Velocity
induction of stenosis B
P_a
P_m
apparent FFRmyo (A) = 89/100 = 0.89
ΔP(A)
ΔP(B)
FFRmyo (A) = 63/98 = 0.64
P_d
true FFRmyo (A) = ?? = 0.65 (by the equation)


P_a
P_m
release of stenosis A
ΔP(A)
ΔP(B)
FFRmyo (B) = 39/49 = 0.79
P_d
FFRmyo (B) = 68/87 = 0.78

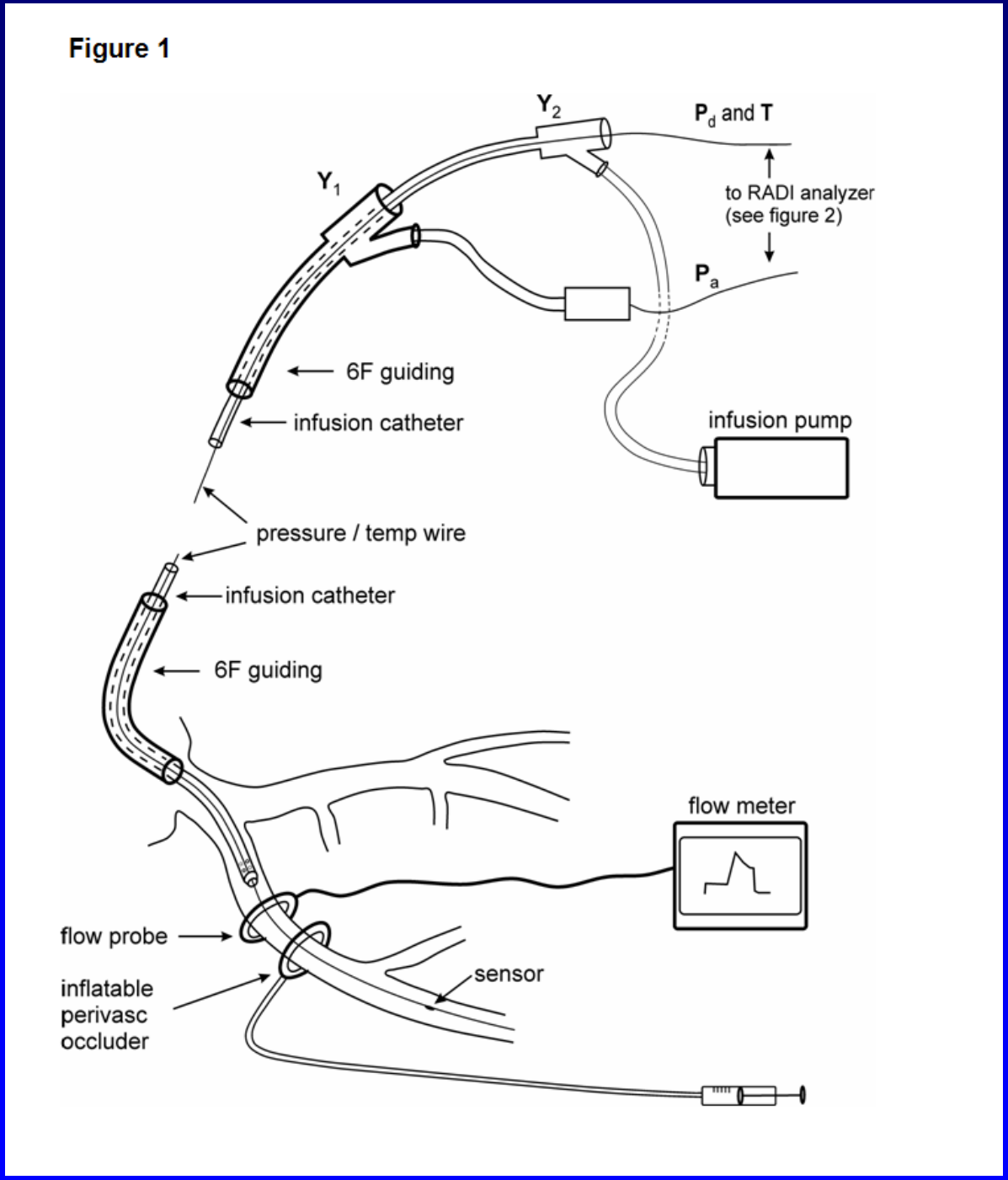
- 22 SSS



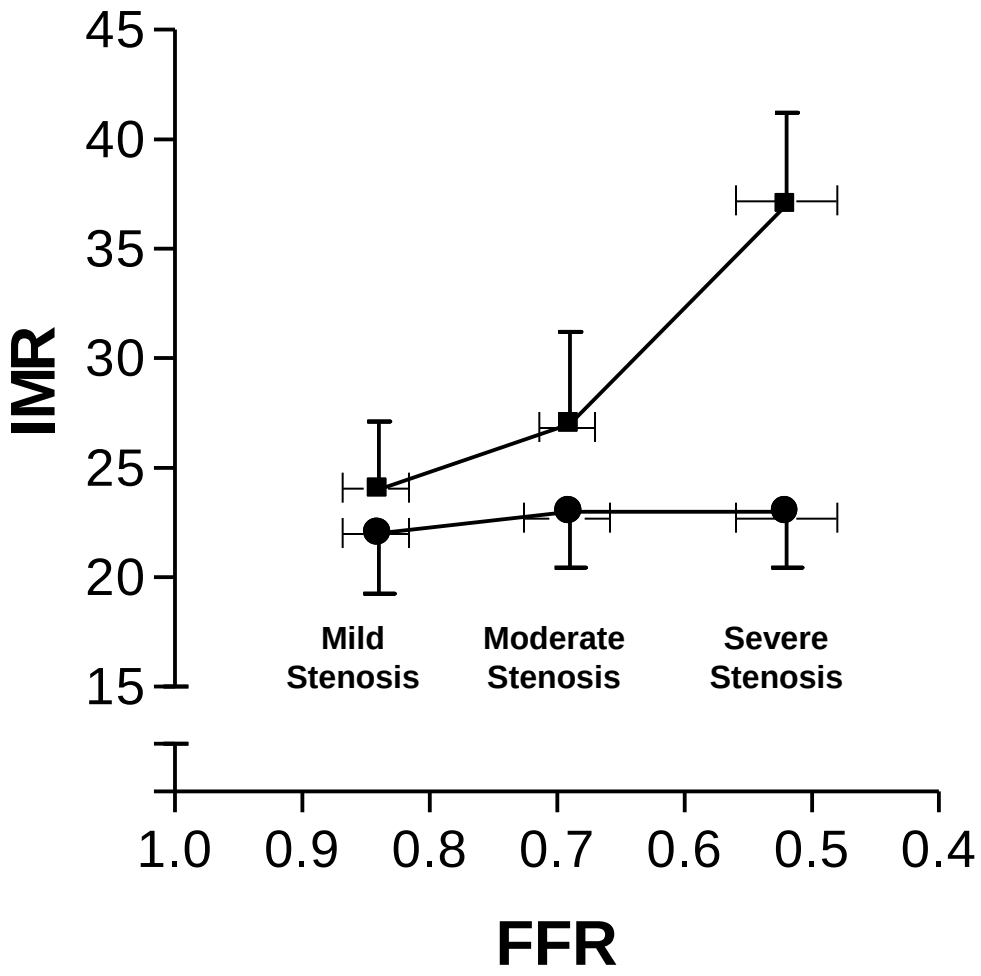
22 SSS/registr. dier study

Animal study:

instrumentation



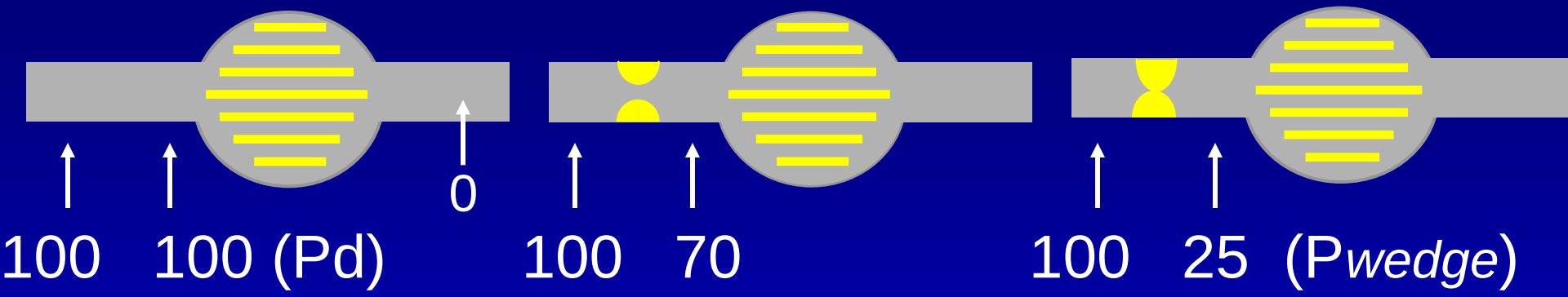
Average myocardial resistance with increasing stenosis severity



not taking into account collateral flow

taking into account collateral flow

normal ⟶ increasing stenosis ⟶ total occlusion



$Q_{myo} = Q_{cor}$

$Q_{myo} = Q_{cor} + Q_{collat}$

$Q_{myo} = Q_{collat}$
$Q_{cor} = 0$

True microcirculatory resistance: $R_{myo} = P_d / Q_{myo}$

$P_d / Q_{cor} = R_{myo}$

$P_d / Q_{cor} > R_{myo}$

$P_d / Q_{cor} = \infty$

30 patients

Aarnoudse et al, Circulation 2004

Severe stenosis

After stenting

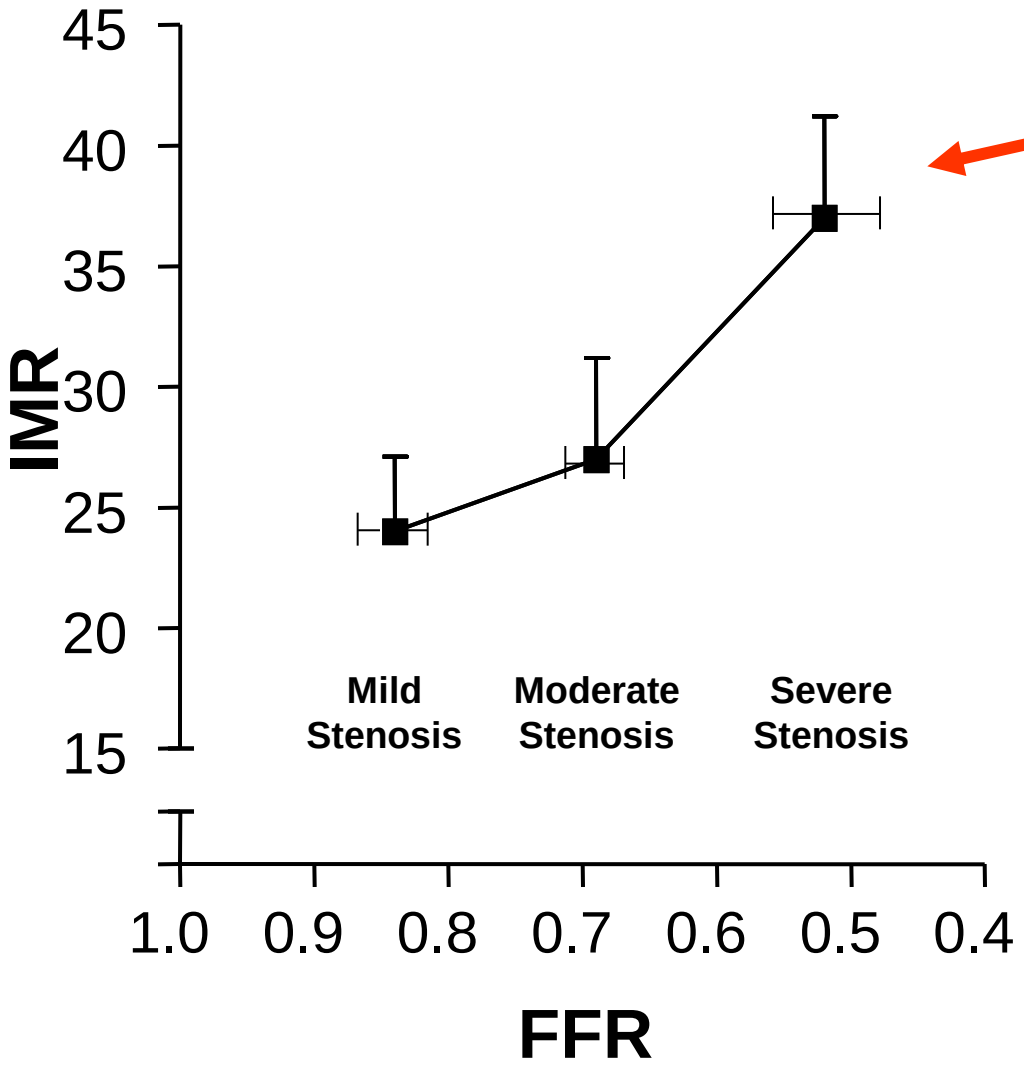
After stenting: ballon size 1mm smaller than stent

Empty balloon: ≈10% area stenosis
FFR ≈ 0.85

4 atmospheres: ≈50% area stenosis
FFR ≈ 0.70

12 atmospheres: ≈75% area stenosis
FFR ≈ 0.55

Apparent myocardial resistance with increasing stenosis severity



apparent microvascular resistance calculated as **P*distal* / Q*coronary***

(artificial increase due to using Qcor instead of Qmyo!!)

Fearon et al, Circulation 2004
Aarnoudse et al, Circulation 2004

$$R_{micro} = P_{distal} \,/\, Q_{myo}$$

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**

(seminal paper on the introduction of FFR, Circulation 1993)

True microcirculatory resistance can be represented by:

IMR = P*a* . T*mn* . ((P*d* - P*w*) / (P*a* - P*w*))

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

Similarly, if Doppler is used:

H-MRv *"true"* = (P*a* / V*max*) . ((P*d* - P*w*) / (P*a* - P*w*))

validation in in-vitro model (CCI2004;62:56-63)

validation in animals (Circulation 2004;109:2269-2272)

validation in humans (Circulation 2004;110:2137-2142)

30 patients

Aarnoudse et al, Circulation 2004

Severe stenosis

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Empty balloon: ≈10% area stenosis
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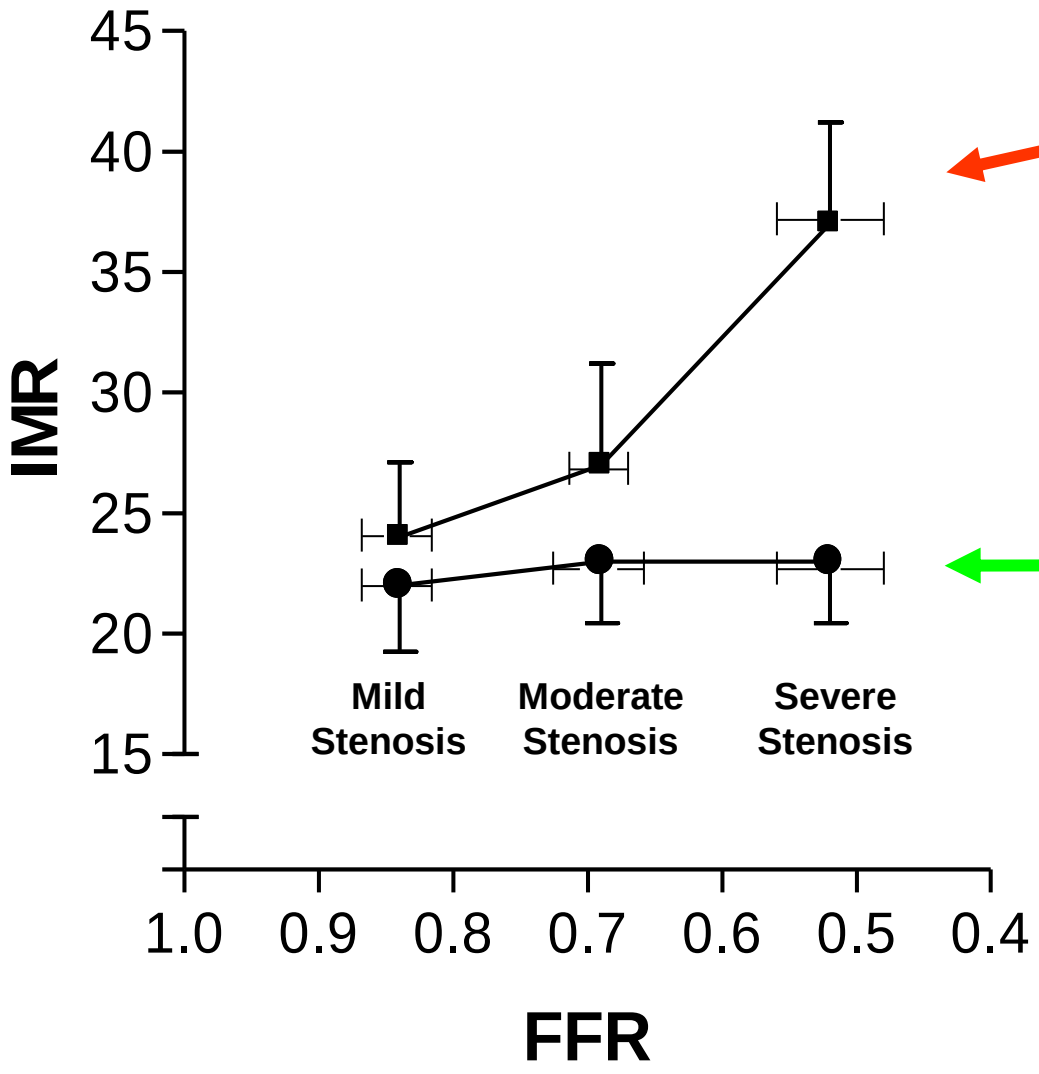
12 atmospheres: ≈75% area stenosis
FFR ≈ 0.55

Minimal myocardial resistance with increasing stenosis severity



apparent microvascular resistance calculated as **P*distal* / Q*coronary***

true microvascular resistance calculated as **P*distal* / Q*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

validation in in-vitro model (CCI2004;62:56-63)

validation in animals (Circulation 2004;109:2269-2272)

validation in humans (Circulation 2004;110:2137-2142)

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 *circumscript 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

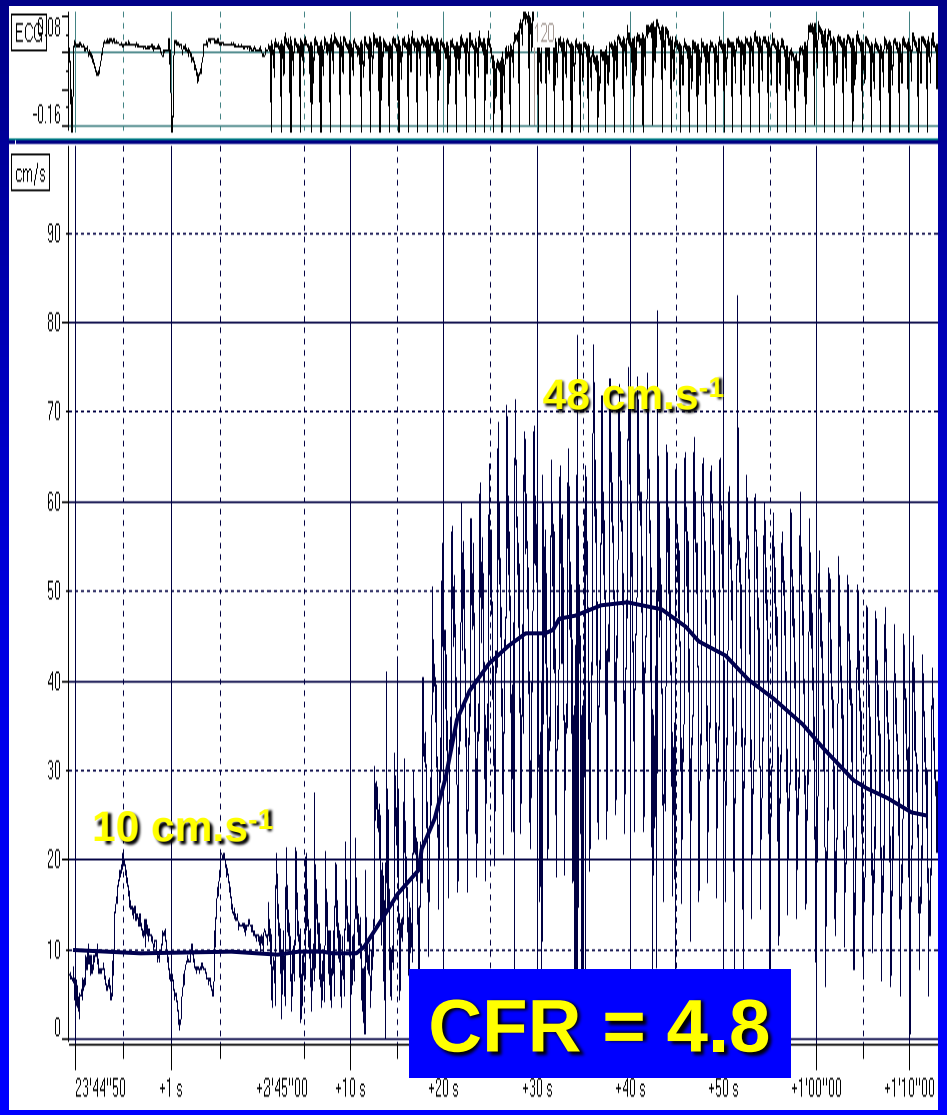
- sound scientific basis and experimental validation
- accurate
- reproducible
- easy to perform

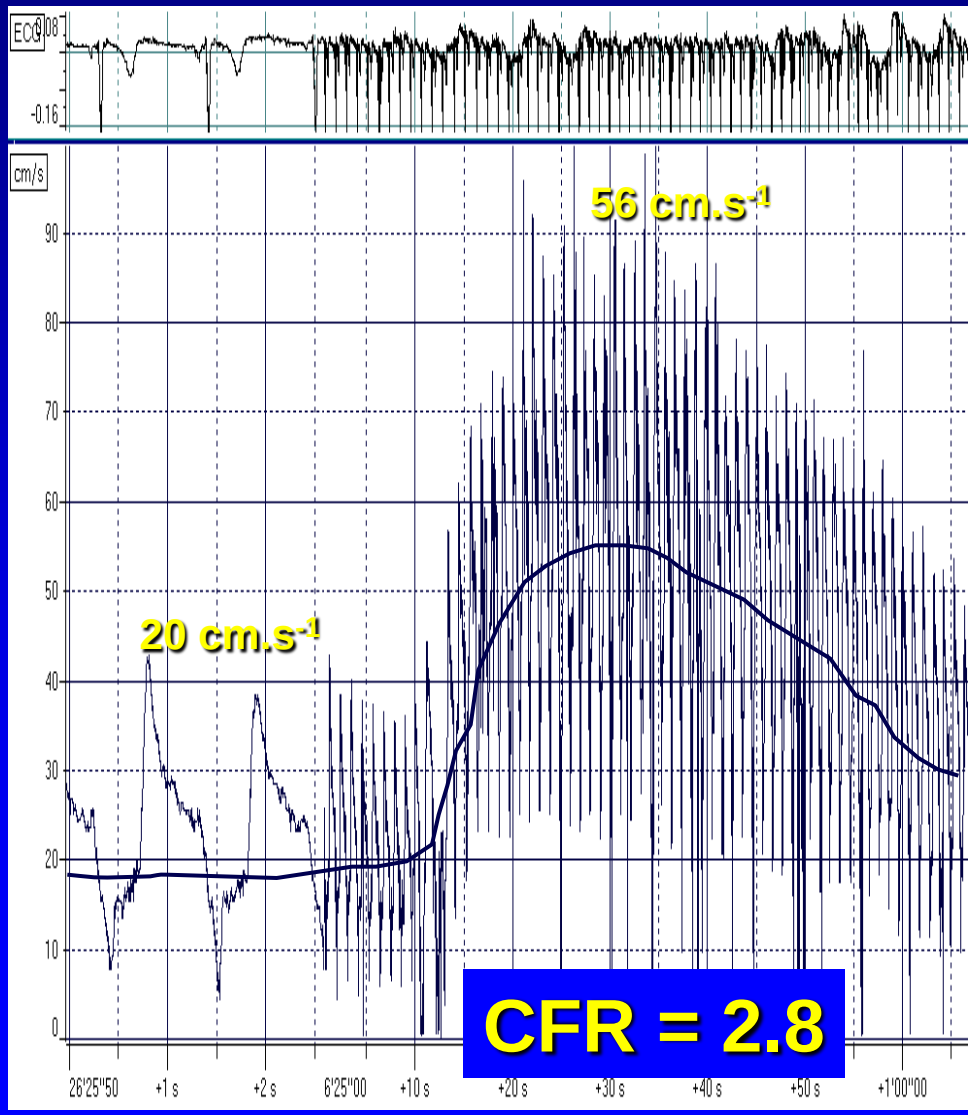
- ***predict outcome:***

    1. is it safe to DEFER FFR-negative lesions
    2. better outcome by PCI of FFR-positive lesions

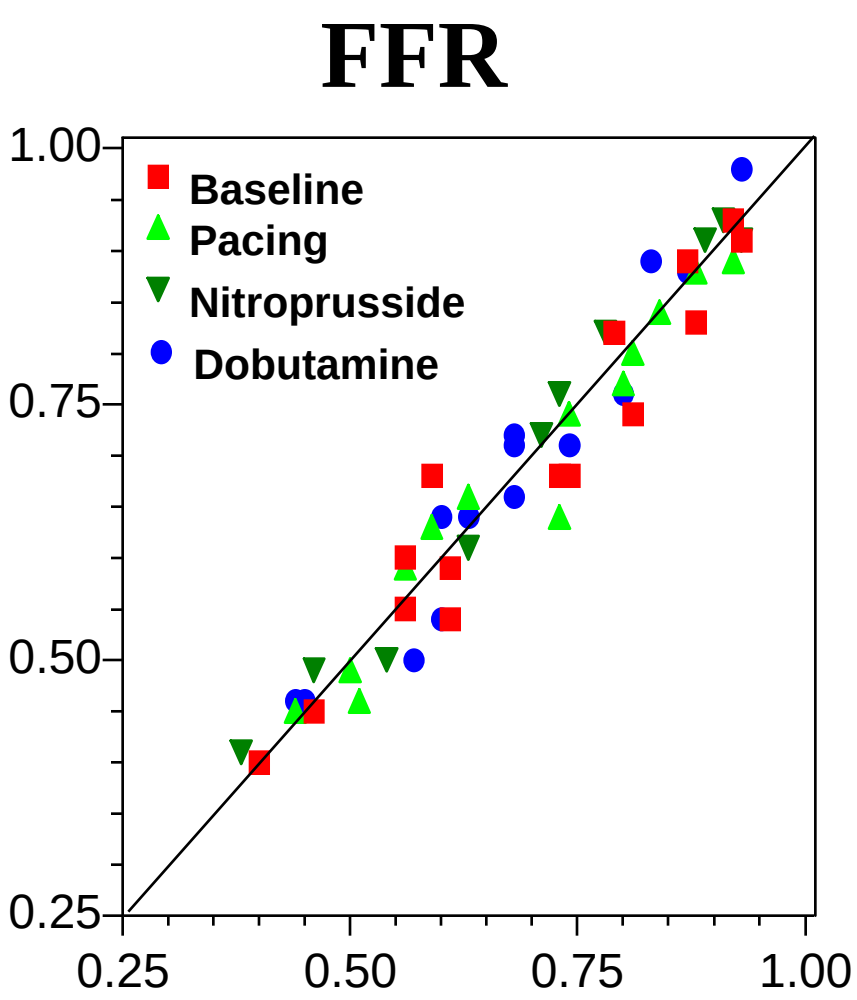
Resting flow in the cath lab is an illusion

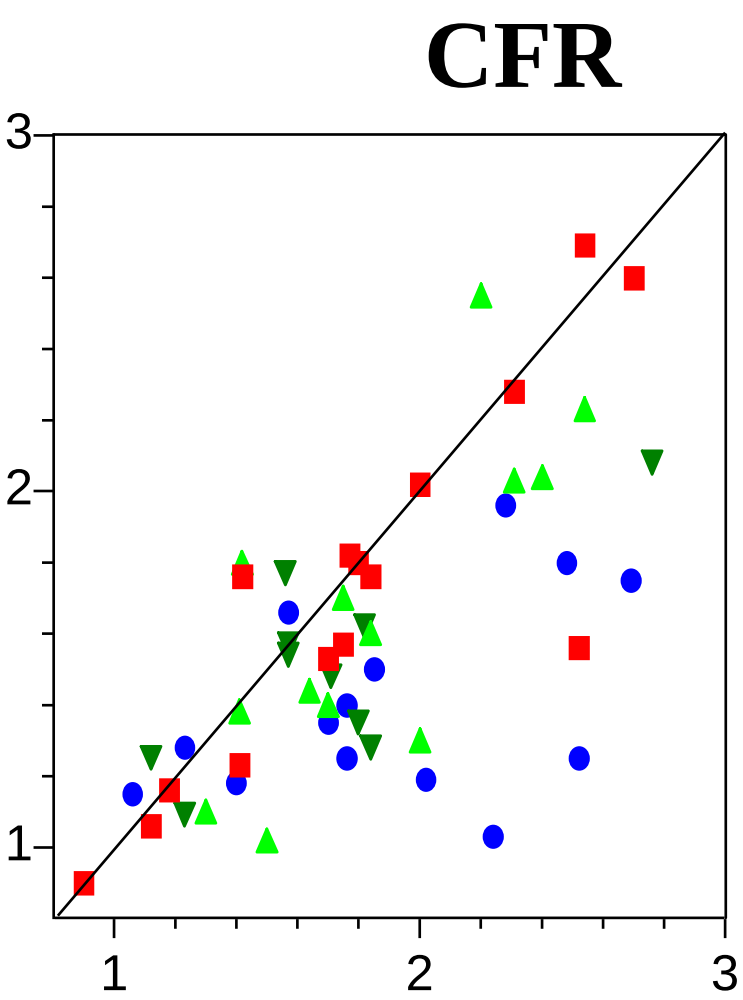
Influence of the “Resting Flow” on CFR





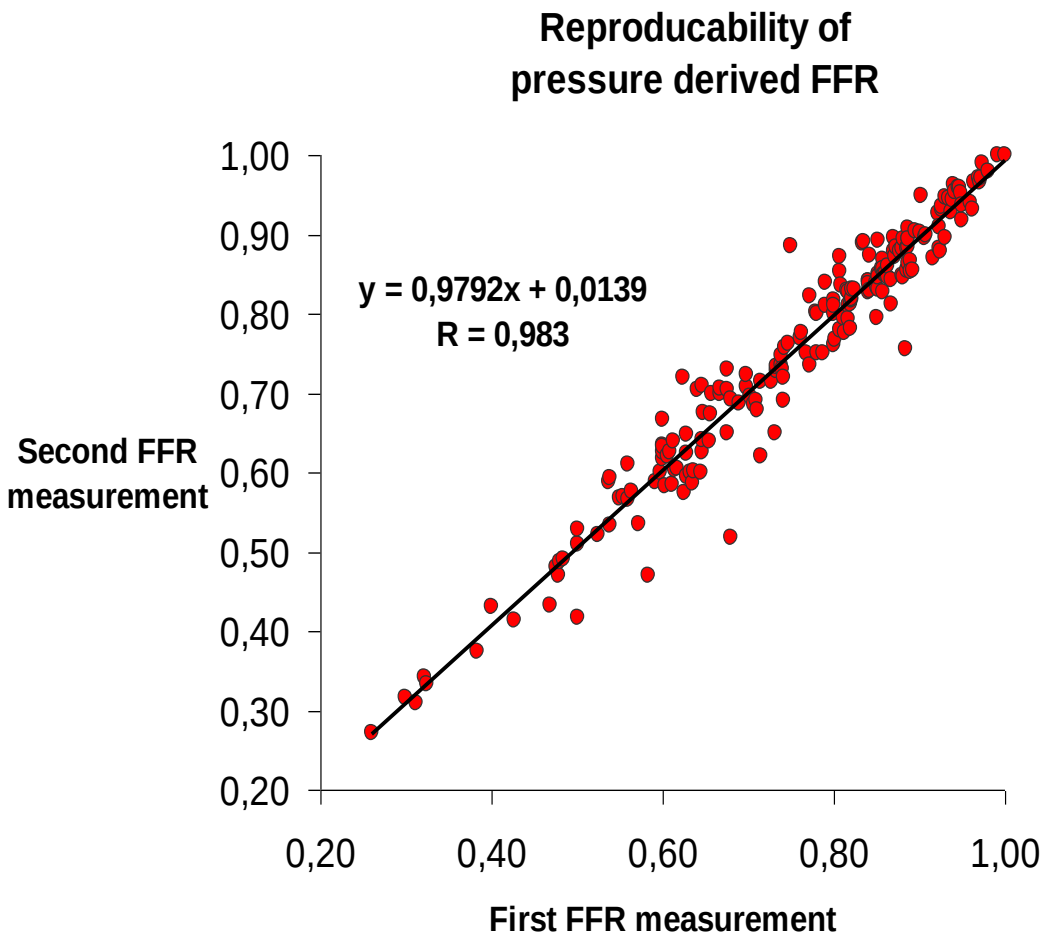
Hemodynamic Variability of FFR_{myo} and CFR





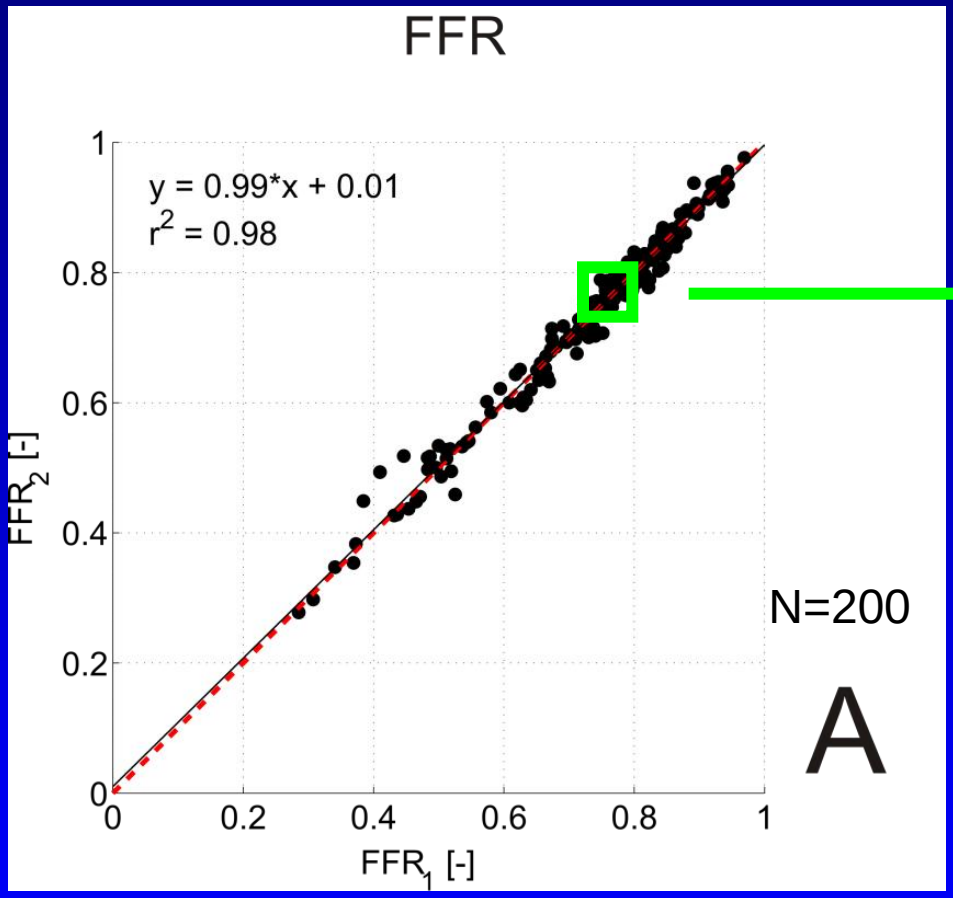
B. De Bruyne et al Circulation 1996

The *DEFER* Study: Reproducibility of FFR



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

Reproducibility of FFR



gray zone
0.76-0.80

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" ???*

Hocus-pocus with statistics (3)

About reproducibility and "wrong decisions"

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 <u>1200</u> consecutive in-duplo measurements of FFR, there was <u>NOT ANY cross-over</u> across the gray zone