CORONARY PHYSIOLOGY IN THE CATHLAB:

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

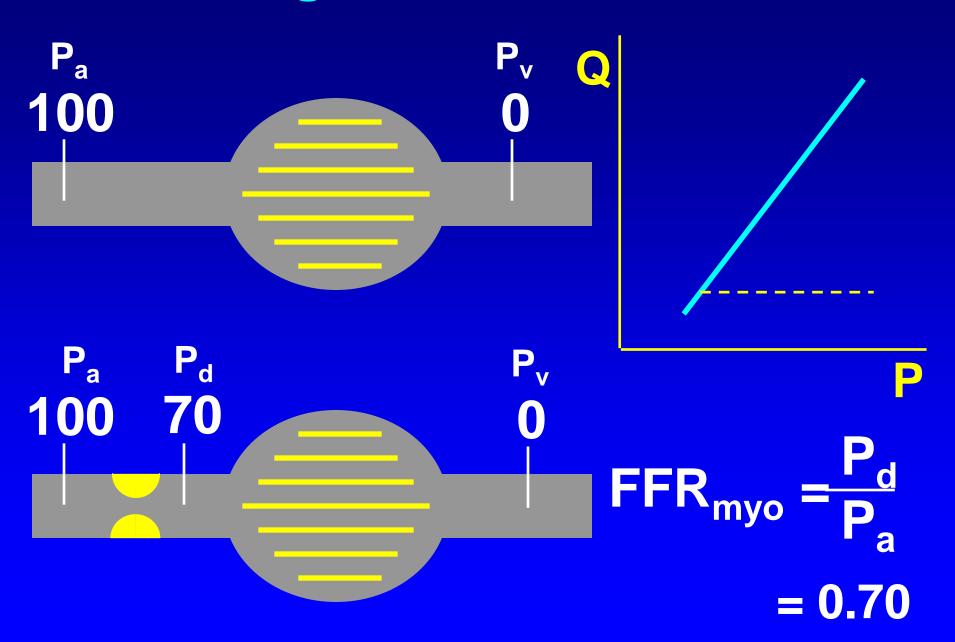


FRACTIONAL FLOW RESERVE:

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



$$FFR myo = \frac{P_d}{P_a}$$

P_a = mean aortic pressure at maximum hyperemia

P_d = mean distal coronary pressure at maximum hyperemia

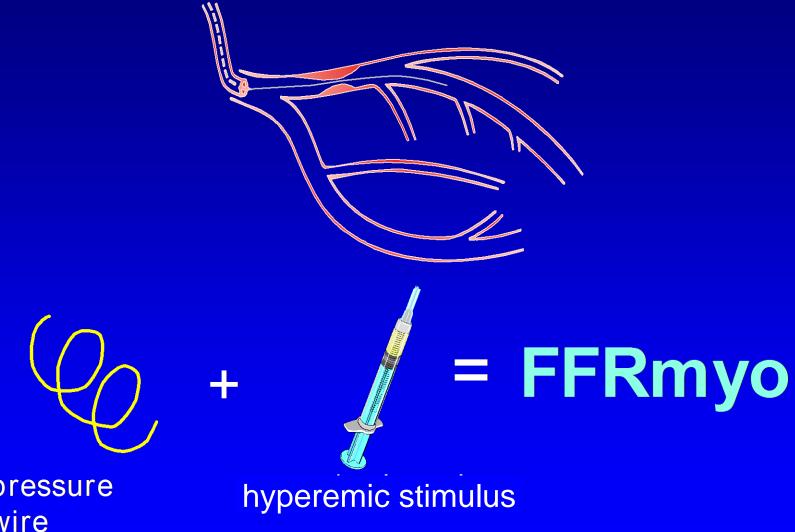
FFR = 0.6 means:

"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"

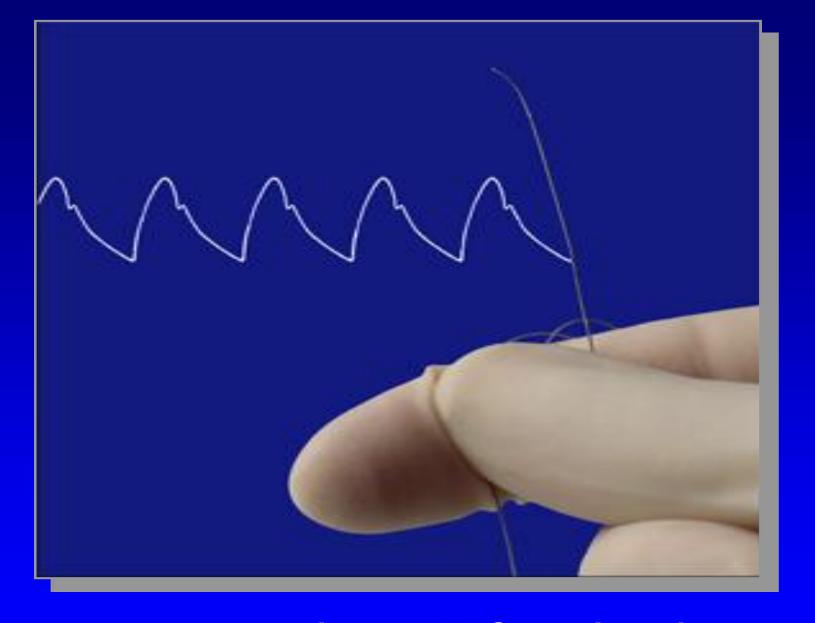
If, after PCI, FFR increases to 0.9, this means:

"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



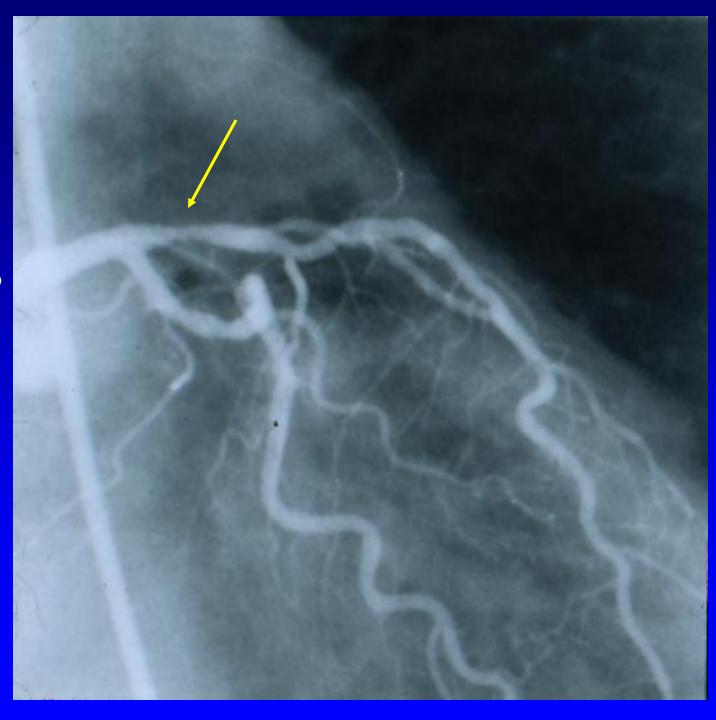
pressure wire



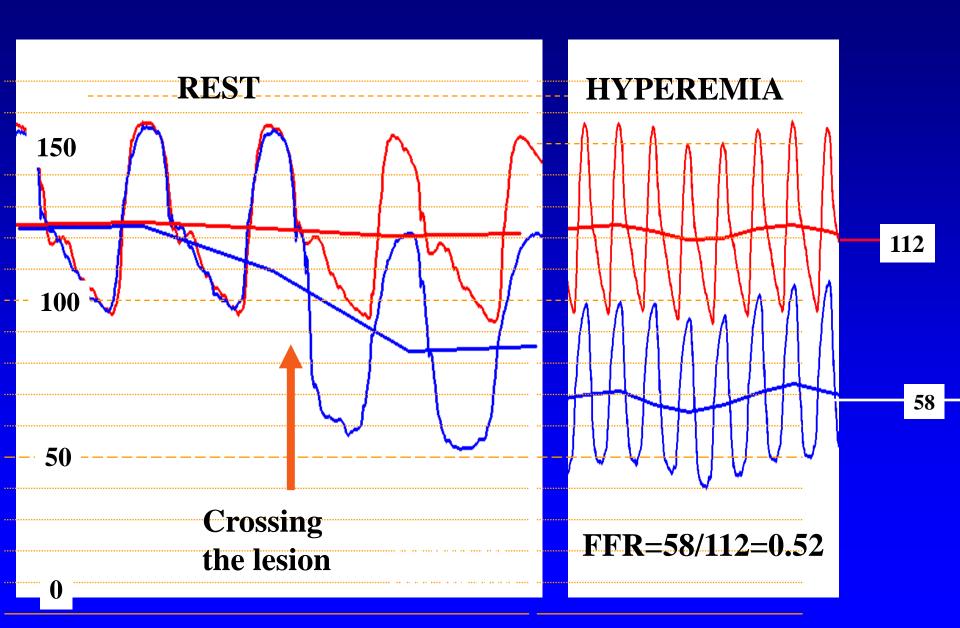
0.014 sensor-tipped PTCA guidewire (electronic or fiberoptic)

CLINICAL PRACTICE:

Mr van Z.
77 years,
stable ang 2-3
posit ET



Fractional Flow Reserve in Clinical Practice

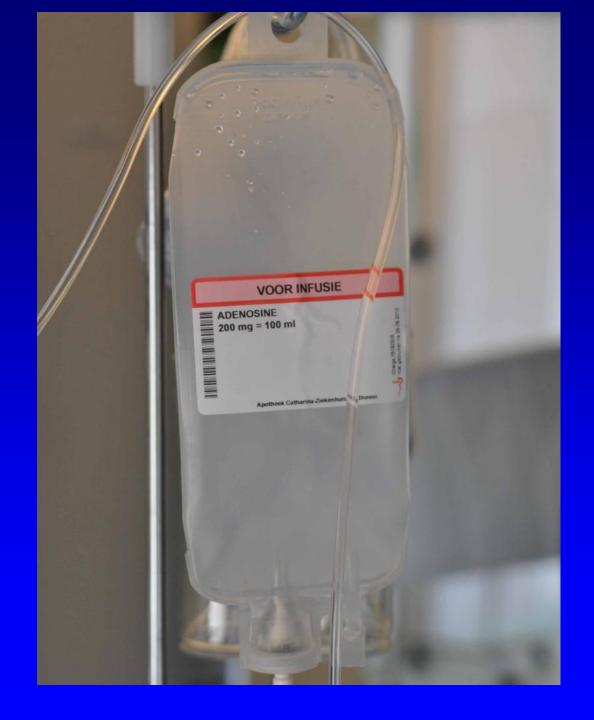


A Few Words About Hyperemia: (next speaker, Dr De Bruyne)

- 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

manifacturing protocol available at carias@cze.nl



Infusion rate simply adjusted according to body weight (....kg →ml/min)



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, Pd/Pa 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 Pd/Pa 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

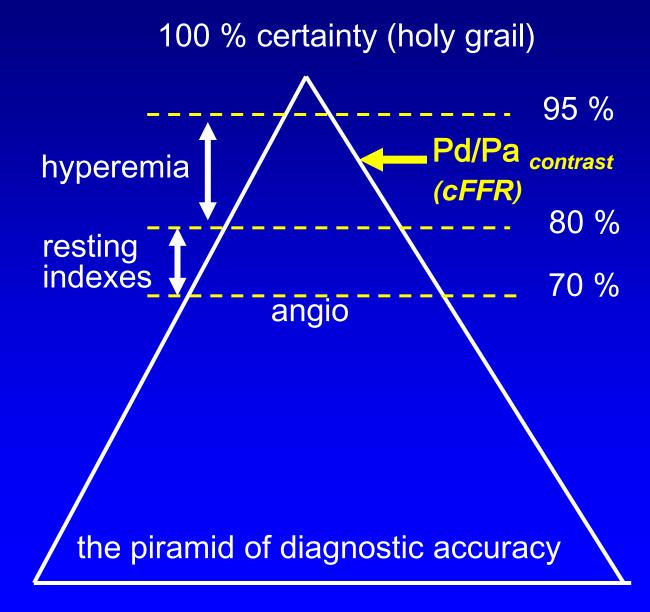
(Dr Ribichini, N. Johnson, Friday afternoon; LBT at PCR 2015)

Correct Classification of Ischemic Stenosis

FFR

resting Pd/Pa, iFR, bSVr

angiography

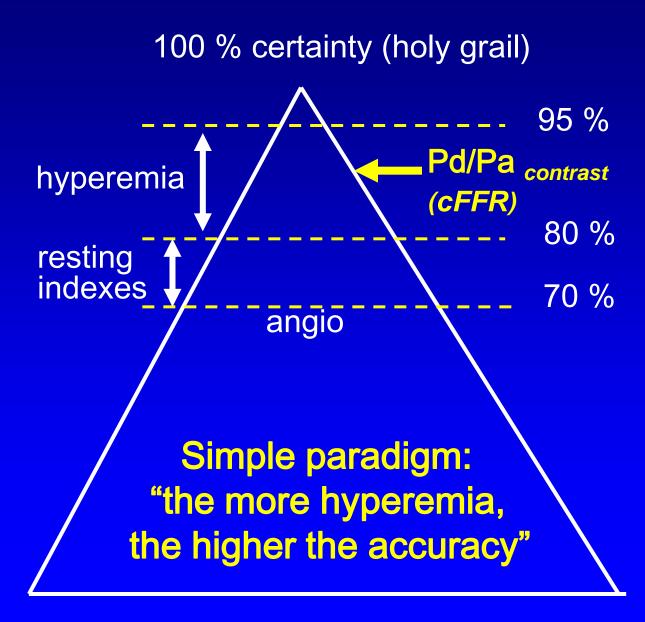


Correct Classification of Ischemic Stenosis

FFR

resting Pd/Pa, iFR, bSVr

angiography



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

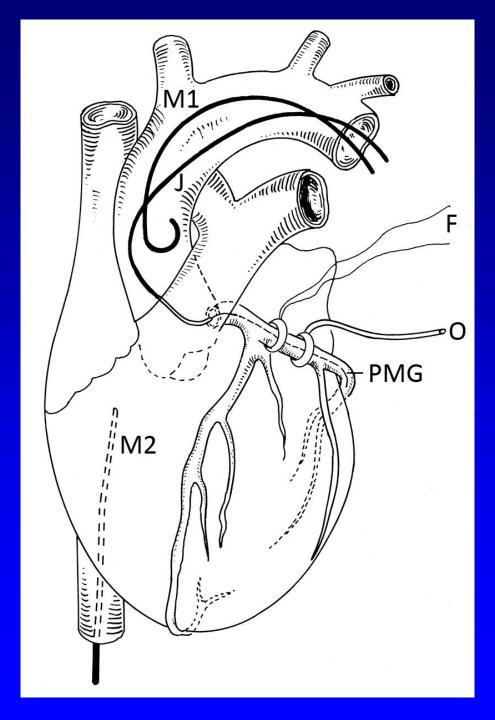
1993-2006: 5 original papers in Circulation on

animal studies in dogs and swine

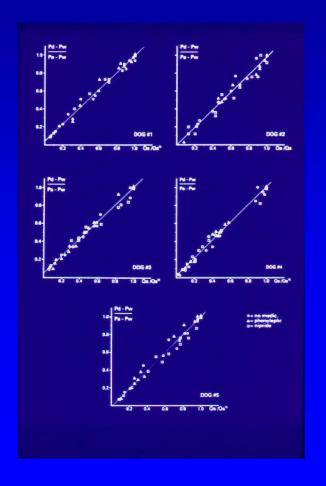
1994-2012: 64 original papers in NEJM, Circulation,

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 performpredict outcome

Fractional Flow Reserve in Normal Coronary Arteries

33 truely <u>normal</u> coronary arteries in patients\ without coronary artery disease:

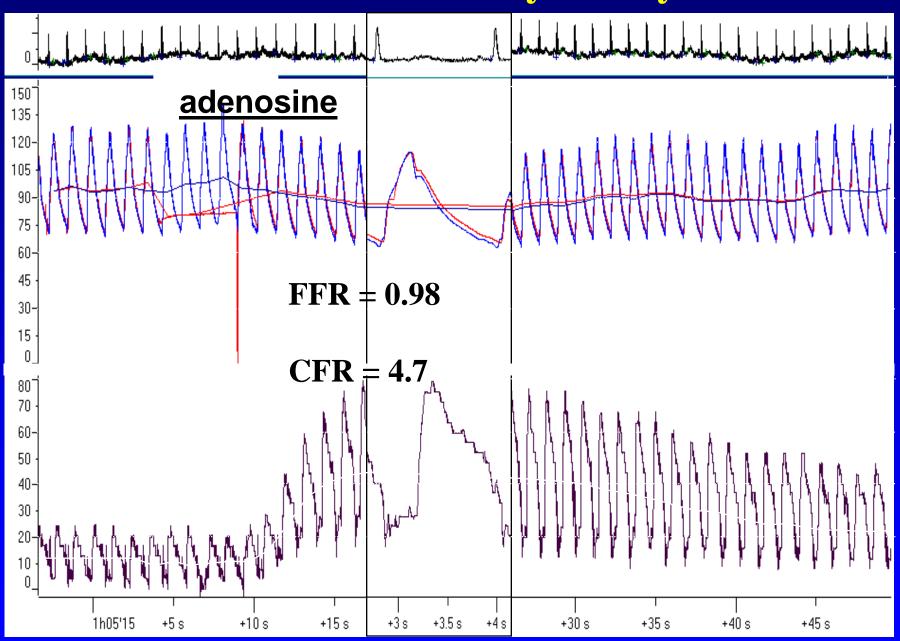
FFR = 0.98 + - 0.02 (range 0.93 - 1.00)

Pijls, Circulation 1995;92: 183-193

86 <u>apparently normal</u> contralateral arteries In patients with coronary disease:

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

Normal Coronary Artery



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 !!!

| <u>Author</u> | Meeting or Citation | <u>Date</u> | <u>N</u> | iFR cutoff* |
|---------------|---------------------|---------------|----------|-------------|
| Davies | TCT | 2011 November | 157 | none** |
| Sen | JACC 59:1392 | 2011 December | 137 | 0.83 |
| Park | EuroPCR | 2012 May | 238 | 0.89 |
| Petraco | EuroIntervention | 2012 August | 339 | 0.89 |
| Jeremias | TCT | 2012 October | 1548 | 0.90 |
| Indolfi | TCT | 2012 October | 71 | 0.93 |
| Johnson | JACC 61:1428 | 2013 February | 1129 | 0.89 |
| Sen | JACC 61:1409 | 2013 April | 51 | 0.86 |

→ 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?

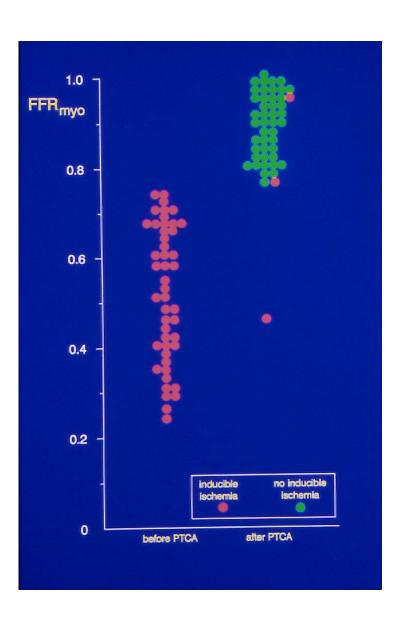
The right way to go is a 2-step approach:

- Exploration of range where a true threshold is expected: in a population in whom you can definitely conclude if there is disease or not
- Truly <u>prospective</u> validation of that particular threshold in an arbitrary population, using a combined gold standard

(prospective multitesting Bayesian approach; NEJM 1996; 334:1703-08)



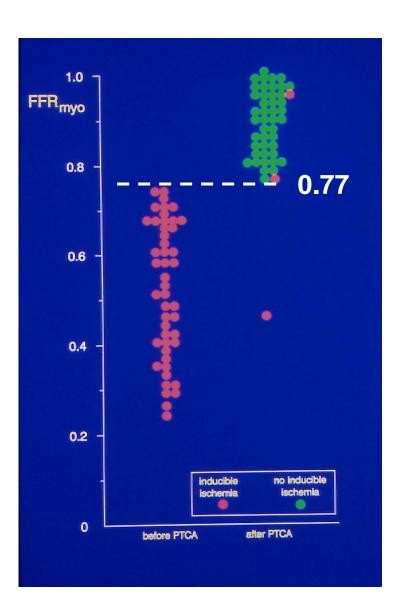
Validation of FFR in humans (step 1)



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

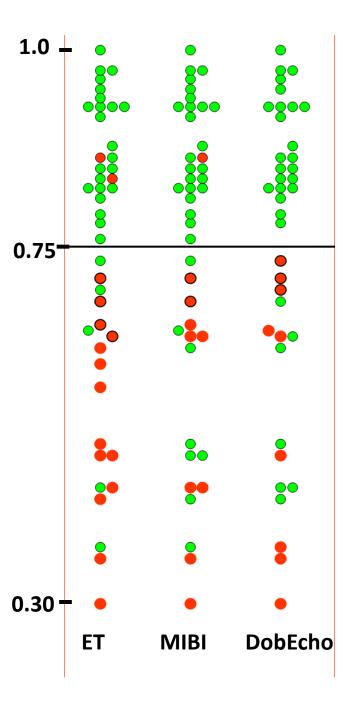
Validation of FFR in humans (step 1)



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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 =

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

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**. (*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

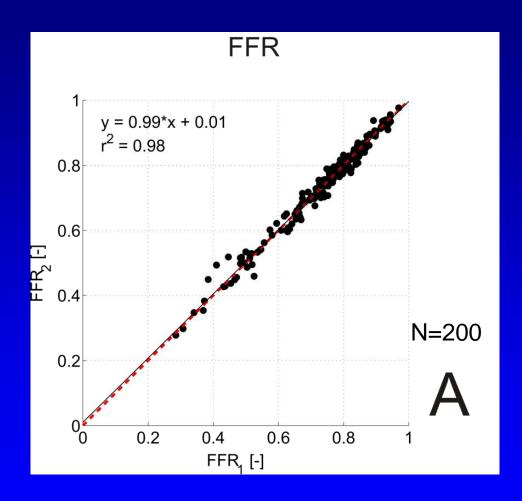
Diagnostic accuracy ≥ 93%

Let's have a closer look to FFR

Prerequisites for a reliable index for decision making

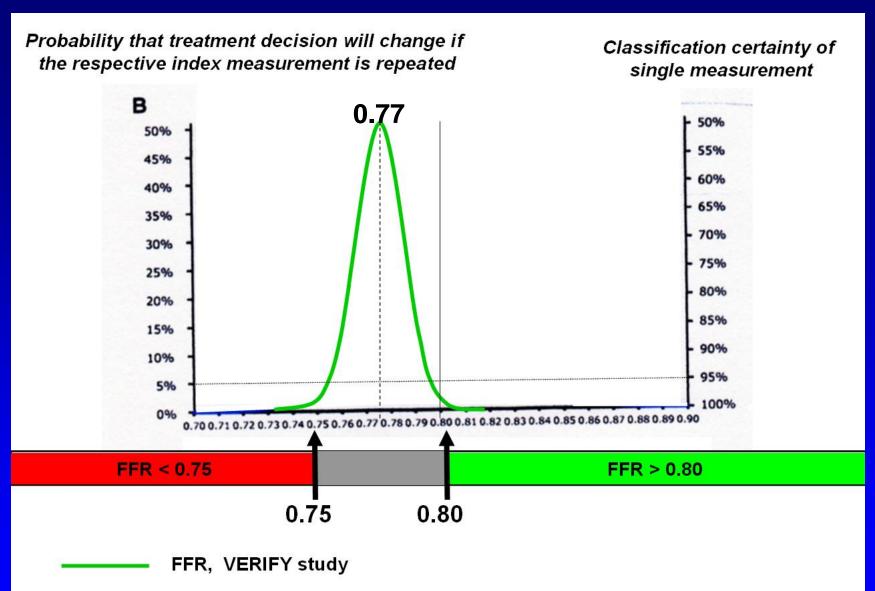
- sound scientific basis and experimental validation
- accurate
- reproducible
- easy to performpredict outcometomorrow

Reproducibility of FFR

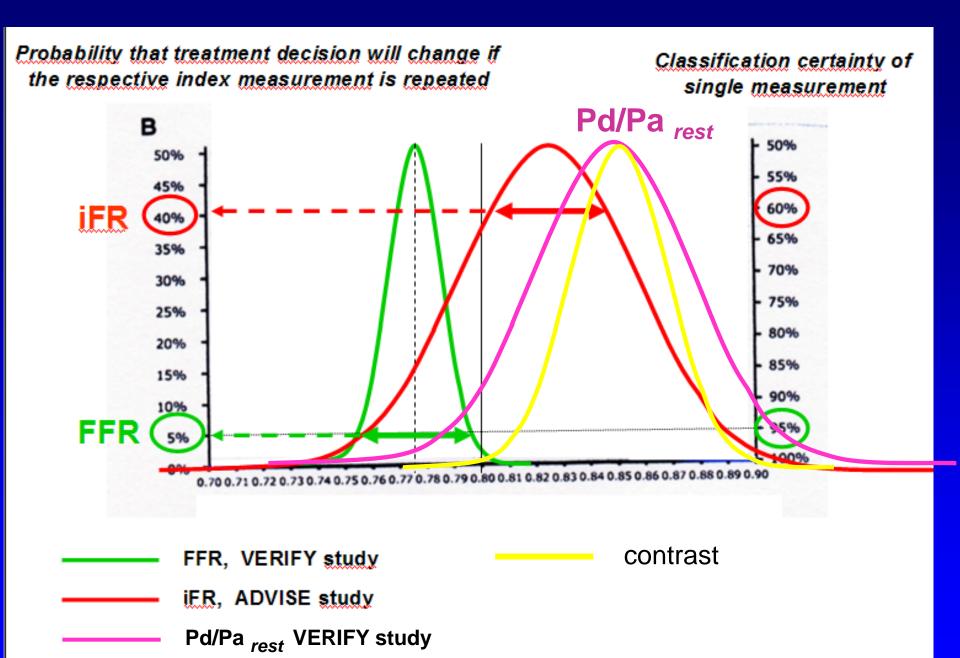


VERIFY study, Berry et al, JACC 2013 (published februari 2013) (all-comers during one month in 5 large centers)

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

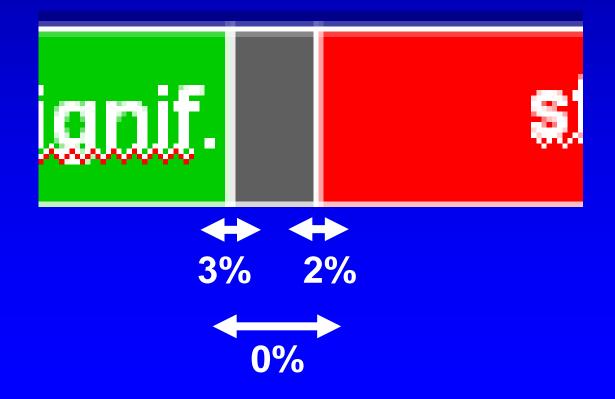


2.4 % of patients go from green to gray or v.v. and 2.4 % from red to gray Almost nobody ever crosses from red to green or v.v.



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





Let's have a closer look to FFR

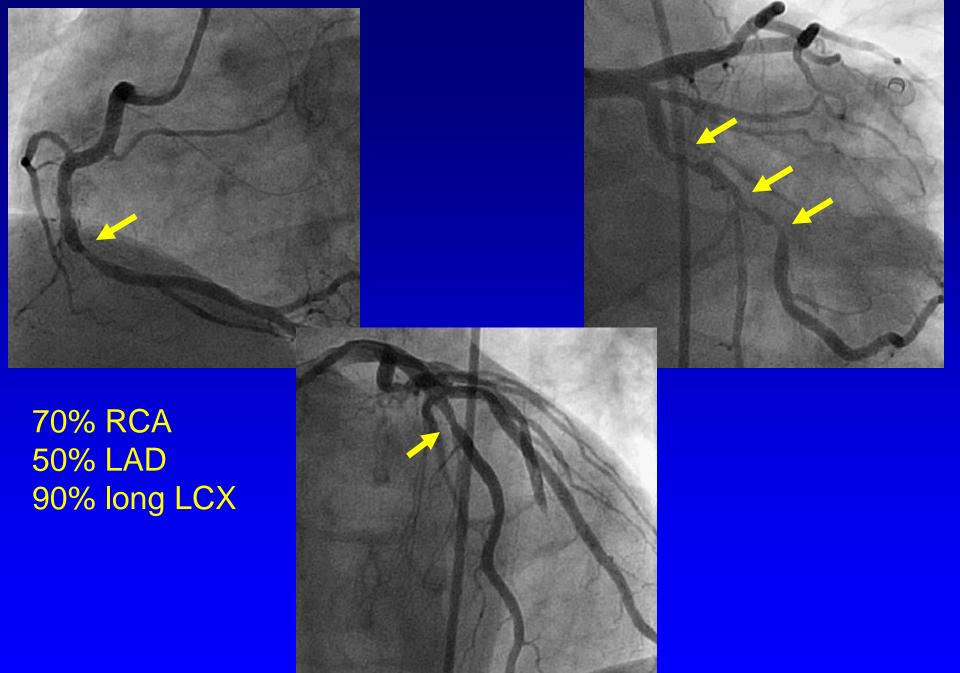
Prerequisites for a reliable index for decision making

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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



Nitroglycerine

Note!

As in any intracoronary manipulation, before entering the coronary circulation, administer 200-300 µg NTG i.c.



 $200 - 300 \mu g$ NTG i.c.

Ready to measure:

Pressure Wire

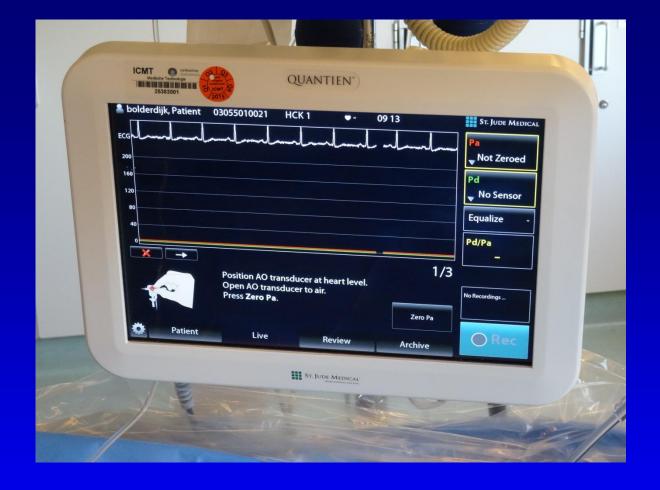
Interface

St Jude Medical, Philips/Volcano, Opsens, Acist

Saturday morning session

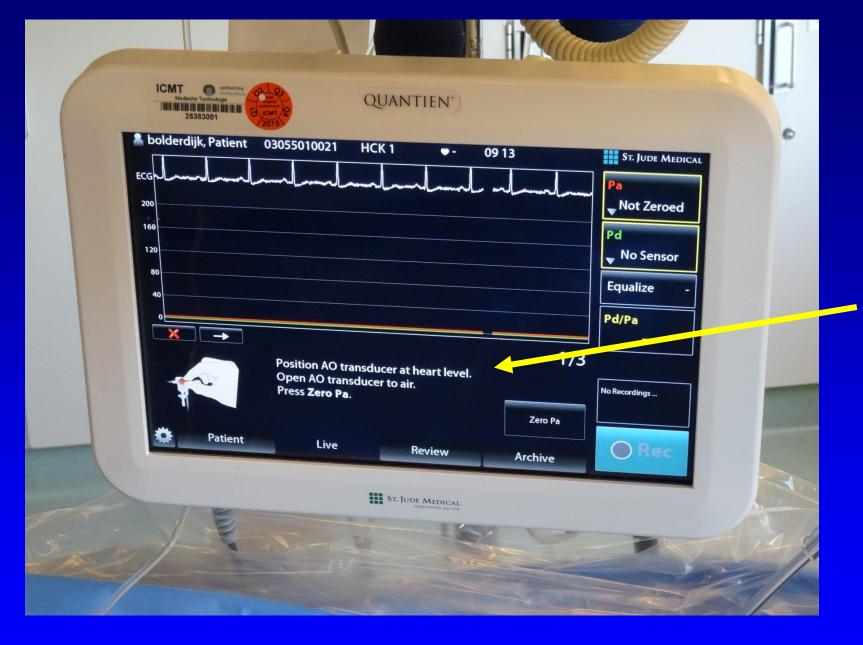
users friendly, "quiet" interface





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

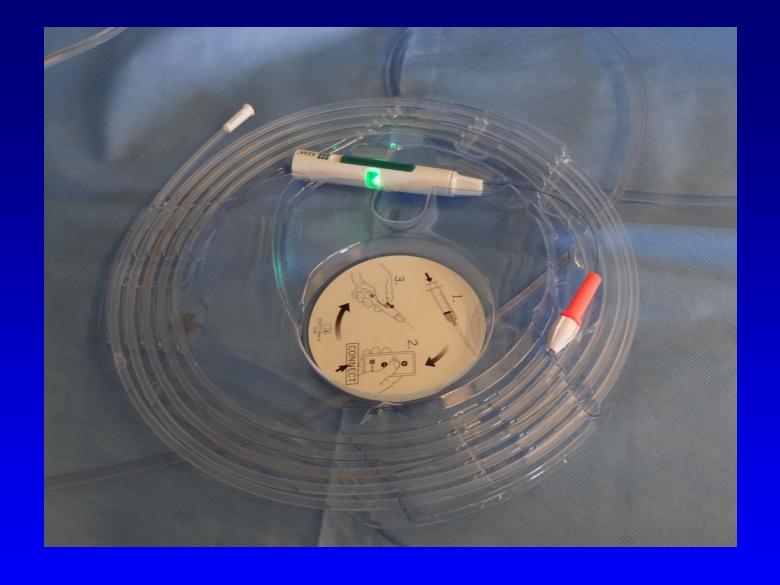




Unpacking of the Pressure Wire



Flushing the Pressure Wire



Green light indicates that pressure wire is ready



Pressure Wire introduced into Y-connector



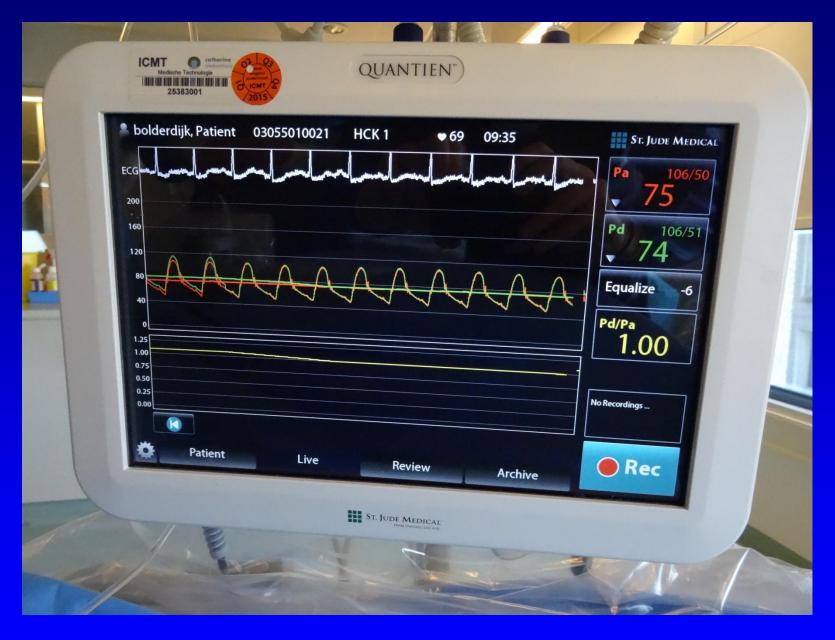
Shaping of the tip of the PW



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

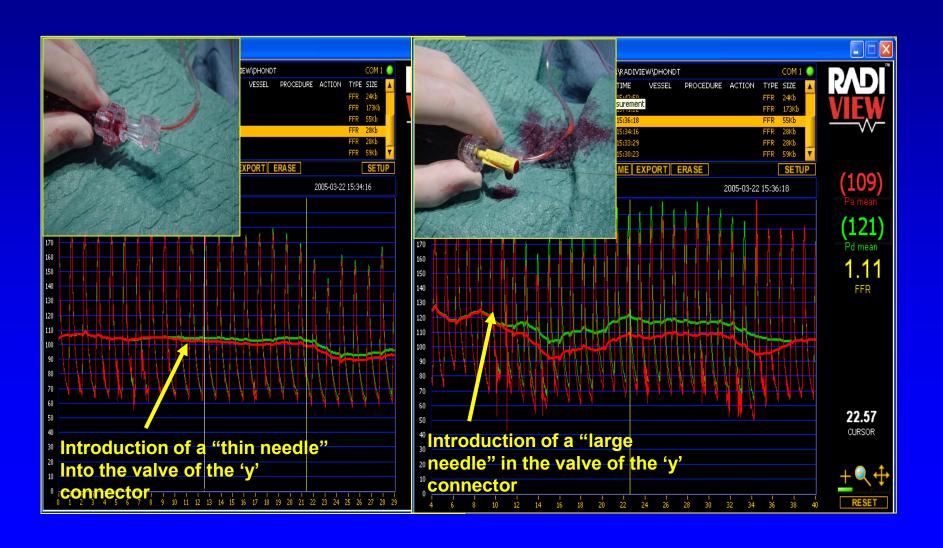
NOTE:

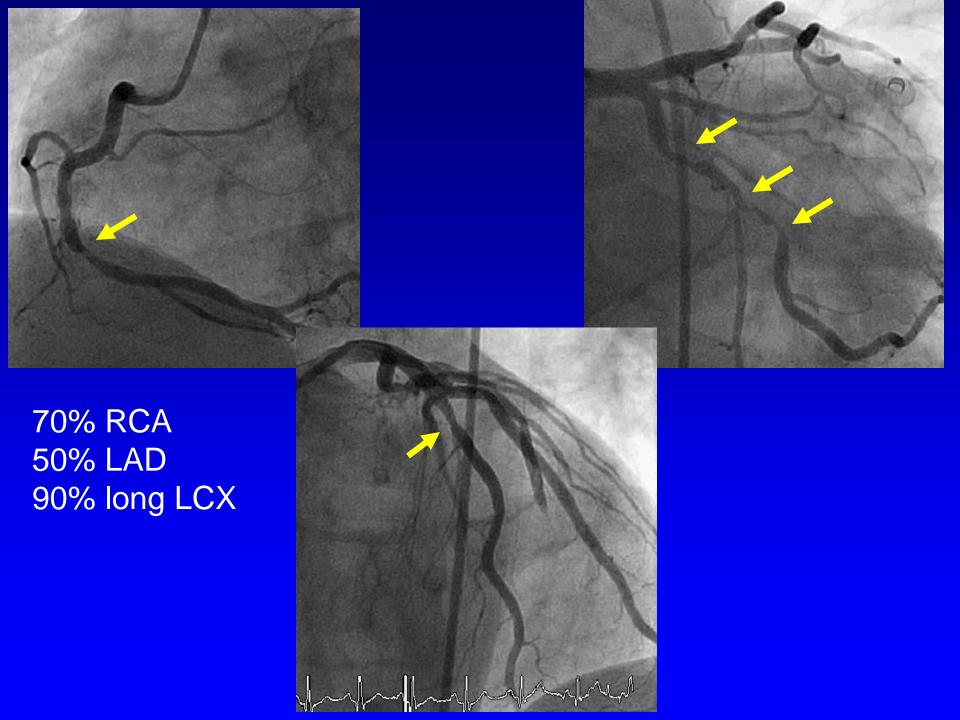
introducer needle in or out !?!

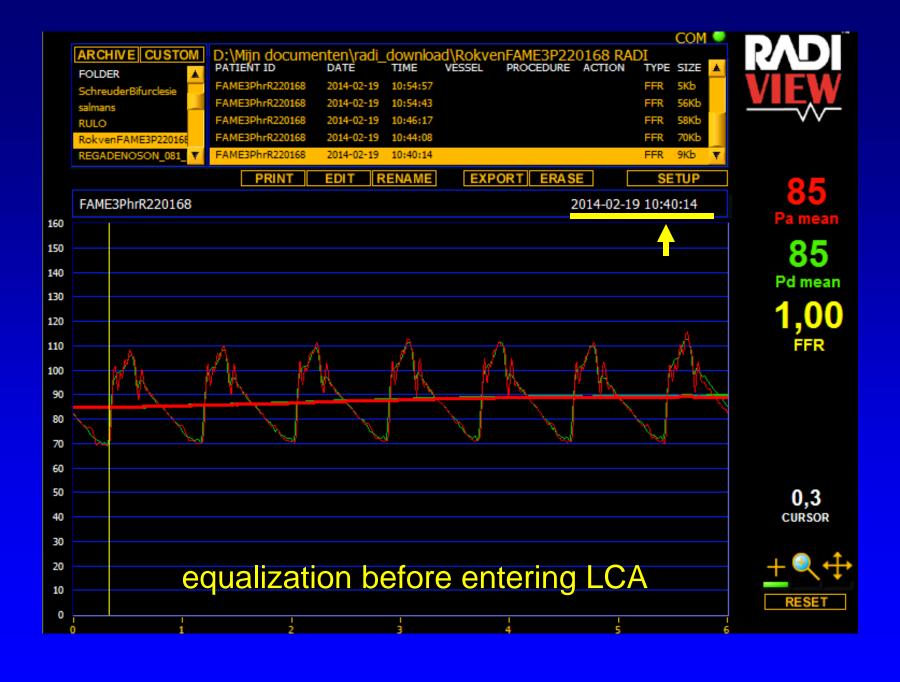
→ doesn't matter as long as you realize what you are doing

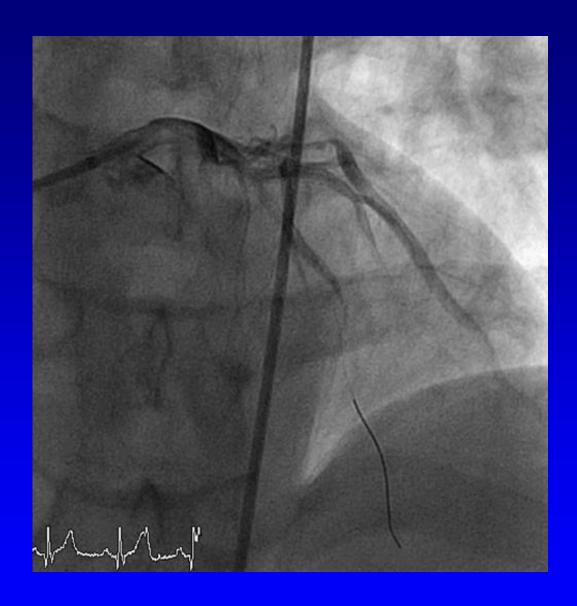
- 1. Know your needle
- 2. Realize that some apparent "drift" at the end is not drift per se but can be caused by the presence of the introducer when doing the initial measurement and absence of the (removed) introducer at the end

Introducer effect (mistake in live case in PCR 2010)

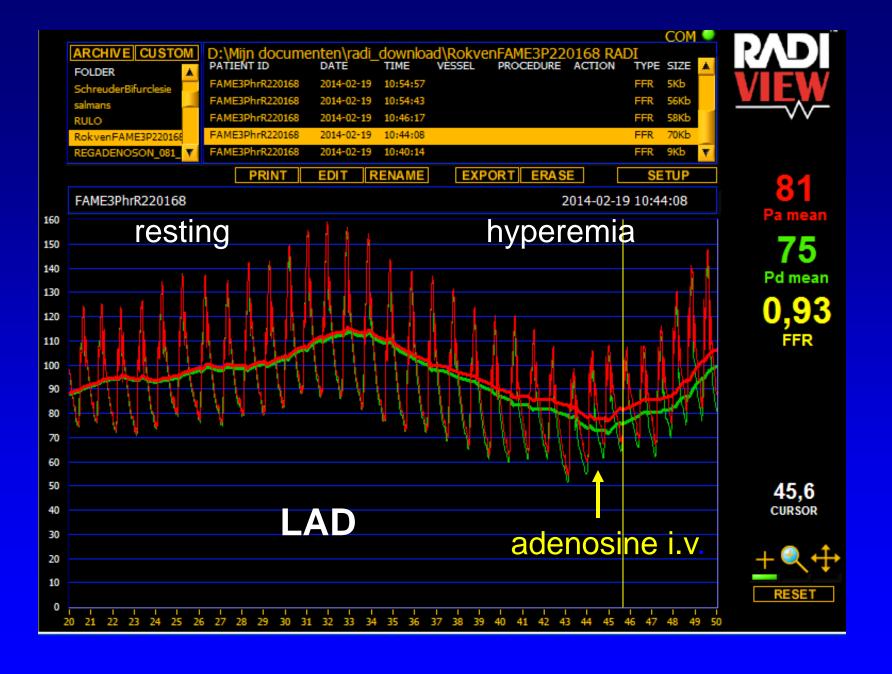


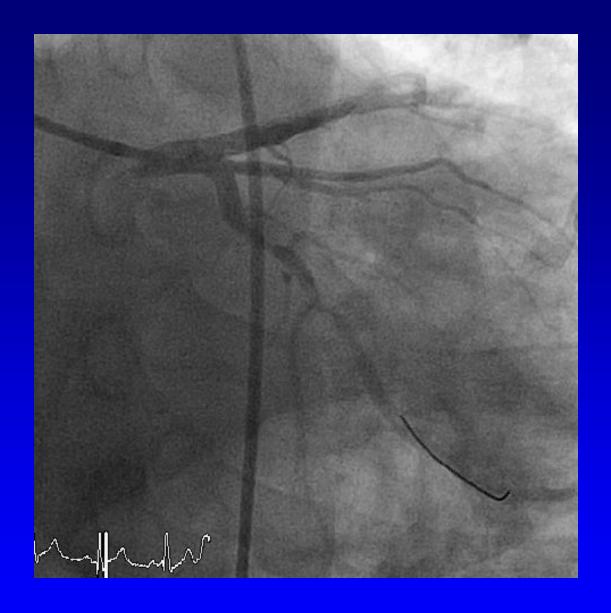




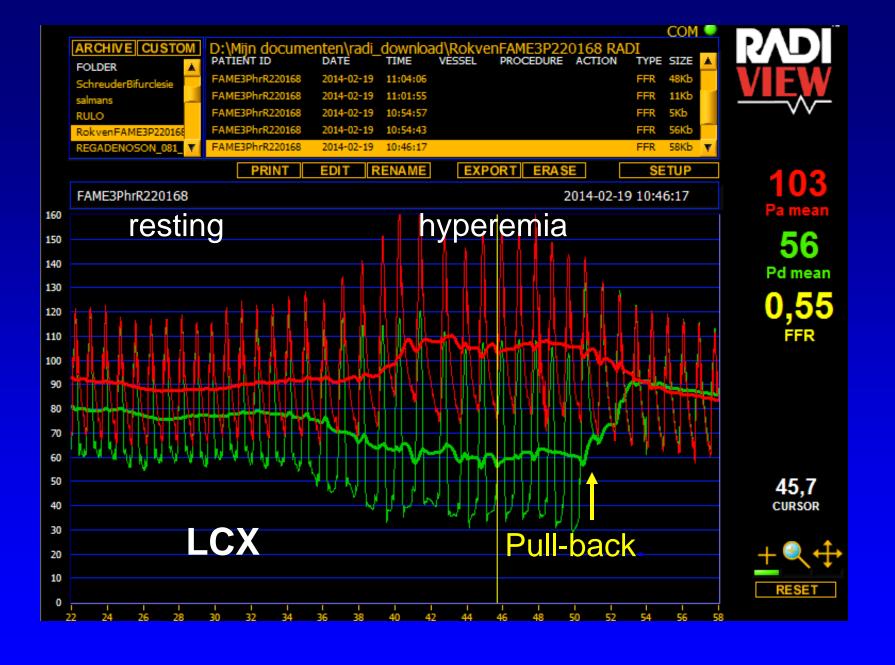


PressureWire in LAD

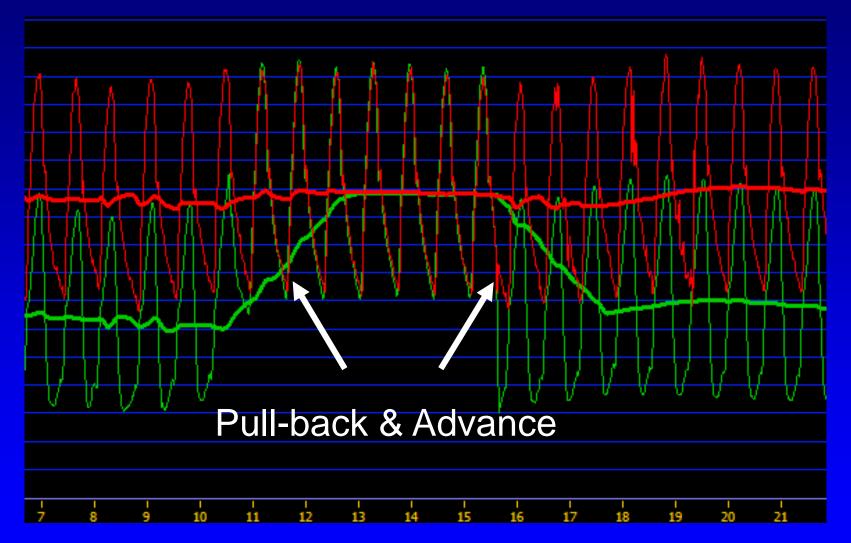




PressureWire in LCX



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

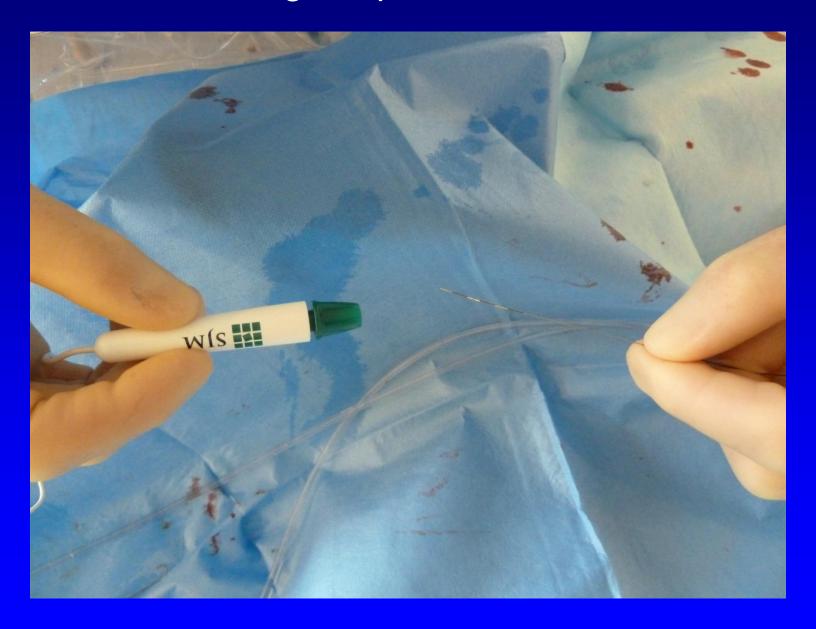


Pull-back recording for detailed spatial information about distribution of lesions along the complete artery

If you need to treat, disconnect pressure wire

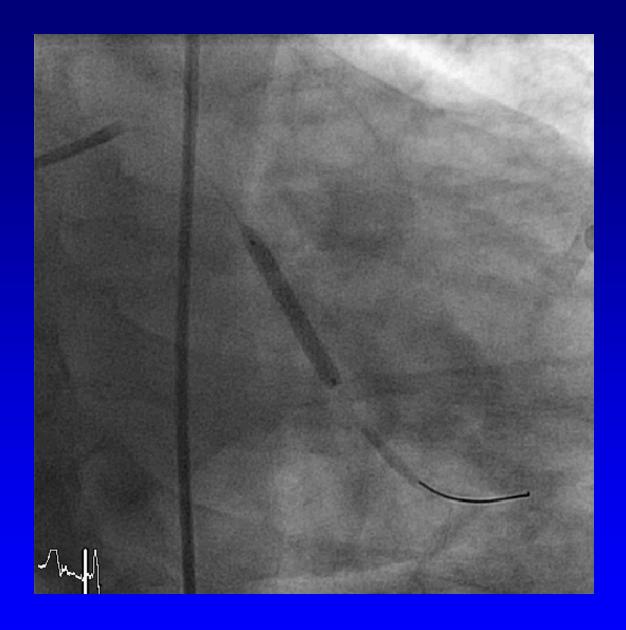


disconnecting the pressure wire.....

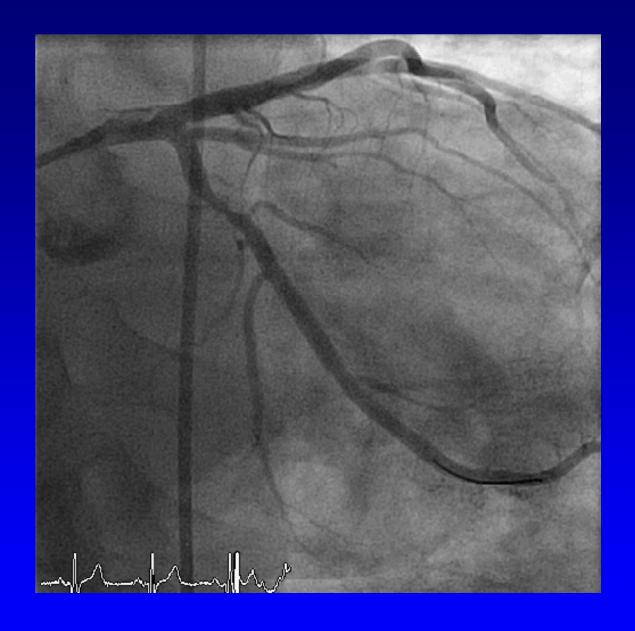




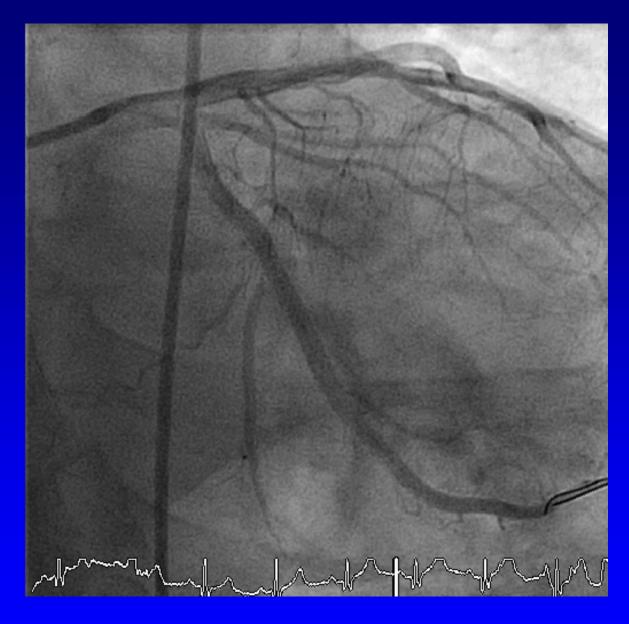
Wire disconnected→ indicator orange



first stent in LCX (3.0x22)



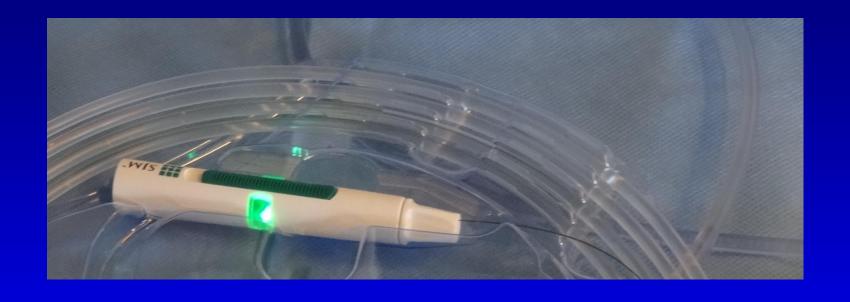
LCX after first stent



LCX after second stent

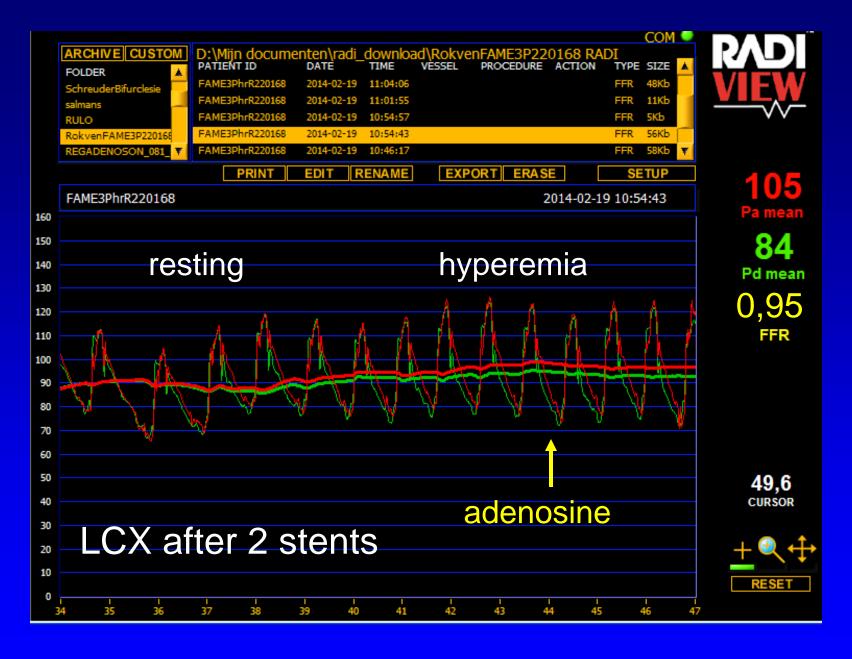
For post-stent FFR → simply connect the pressure wire



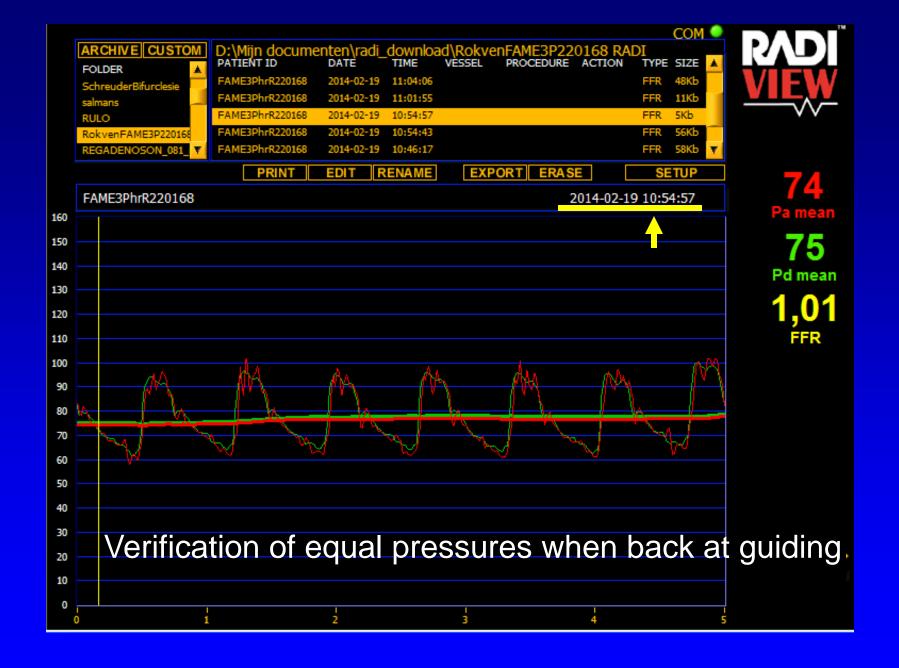


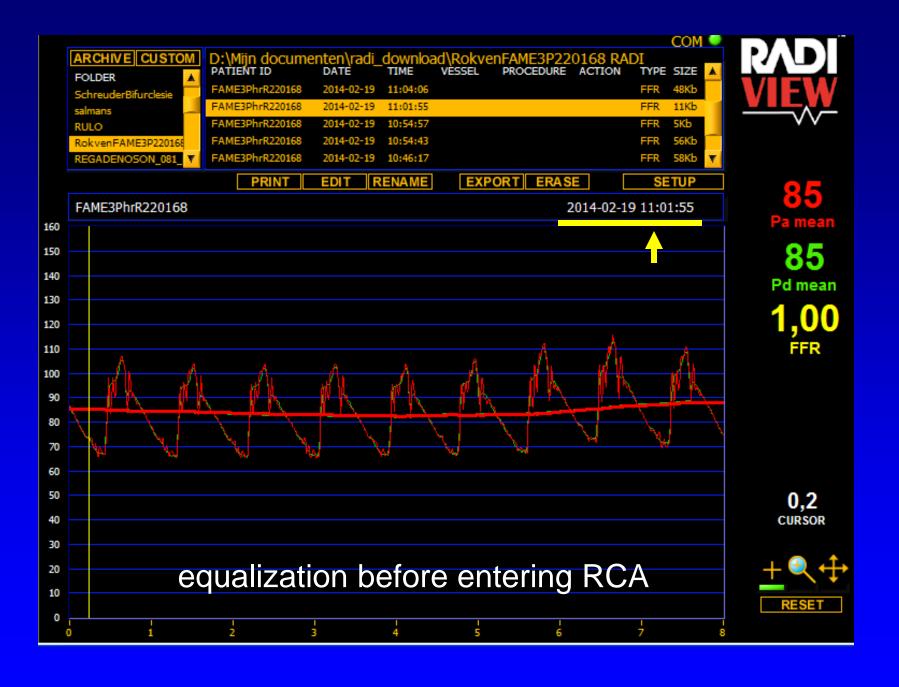
Re-connected -> indicator light green

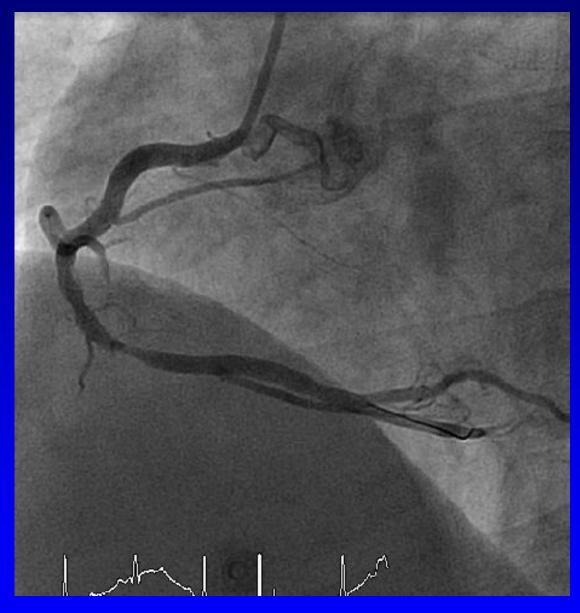
Note: after reconnecting it can take 15-20 Seconds for signal to stabilize



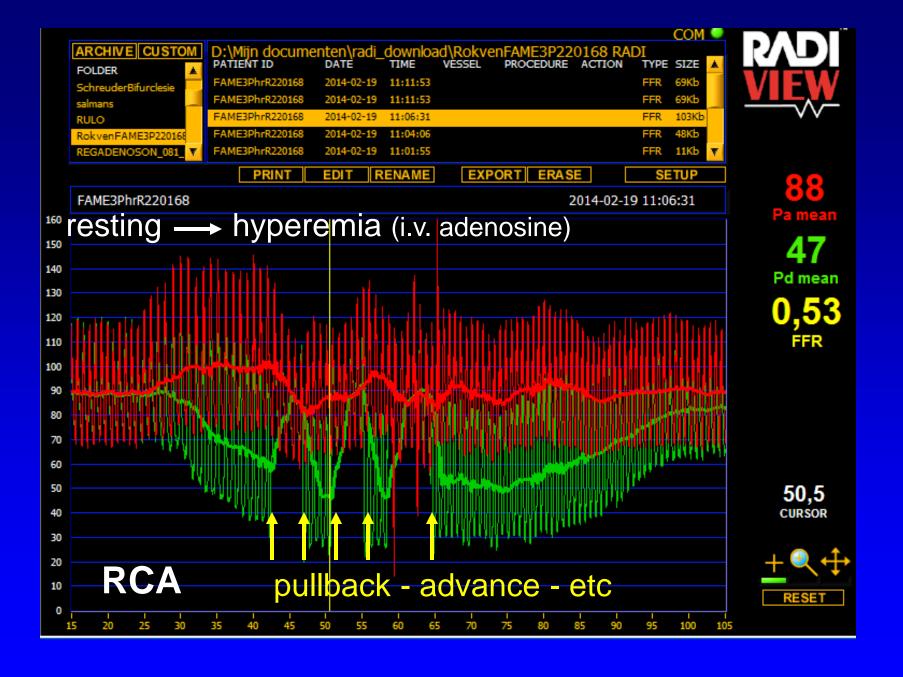
Post-stent FFR measurement to evaluate result

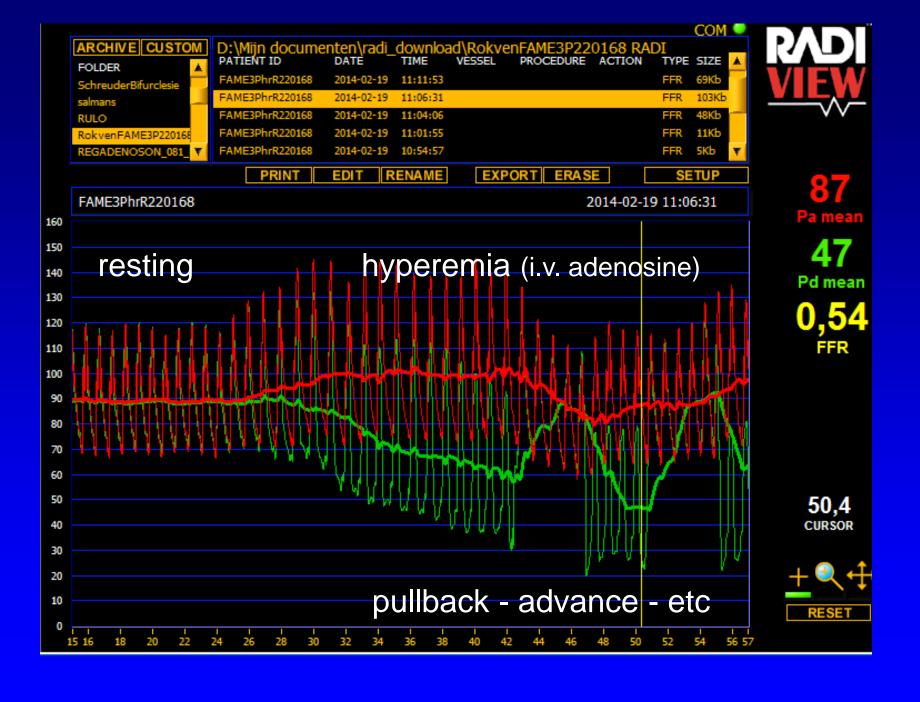


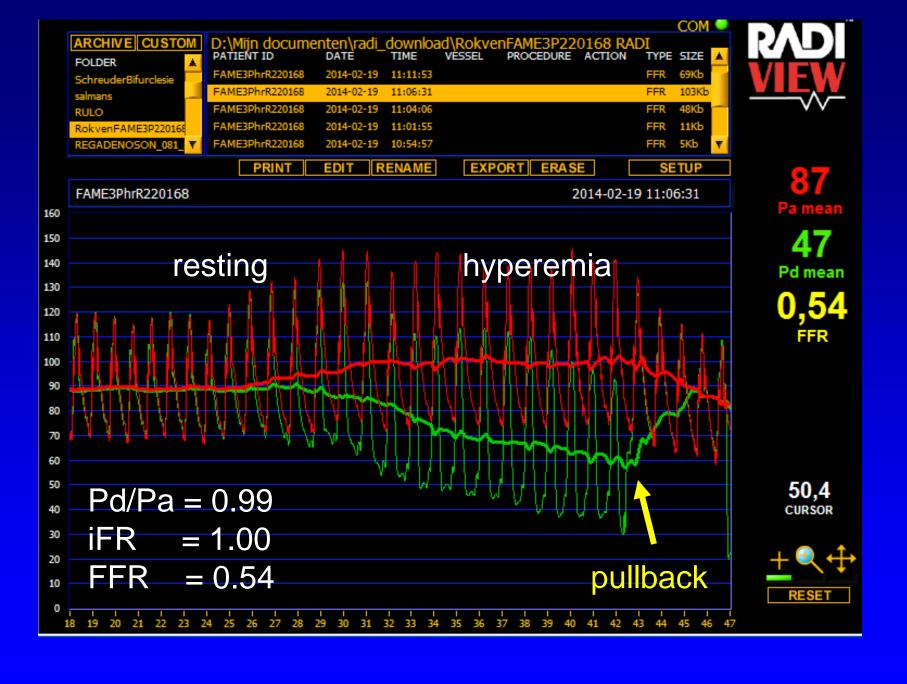


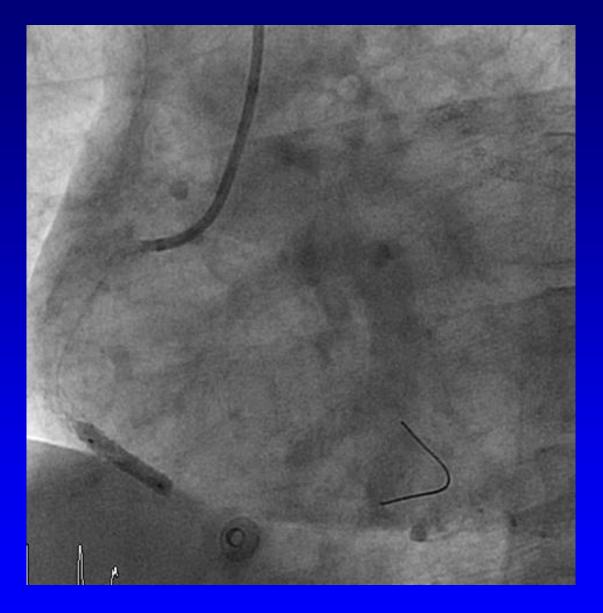


PressureWire in RCA

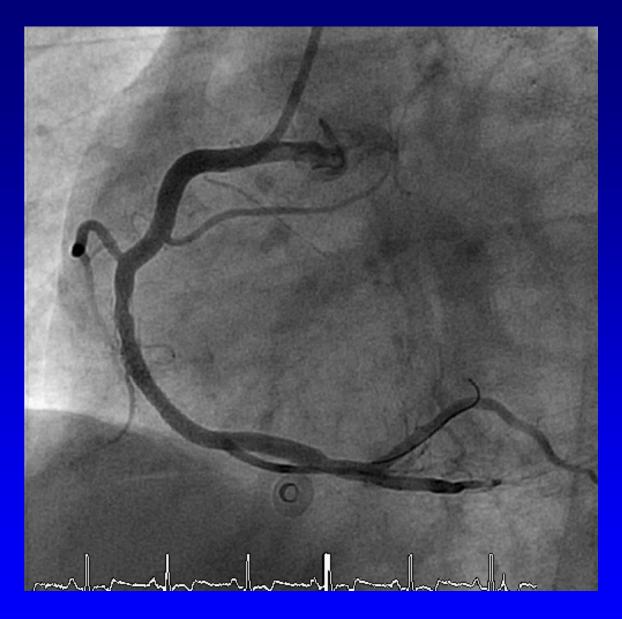




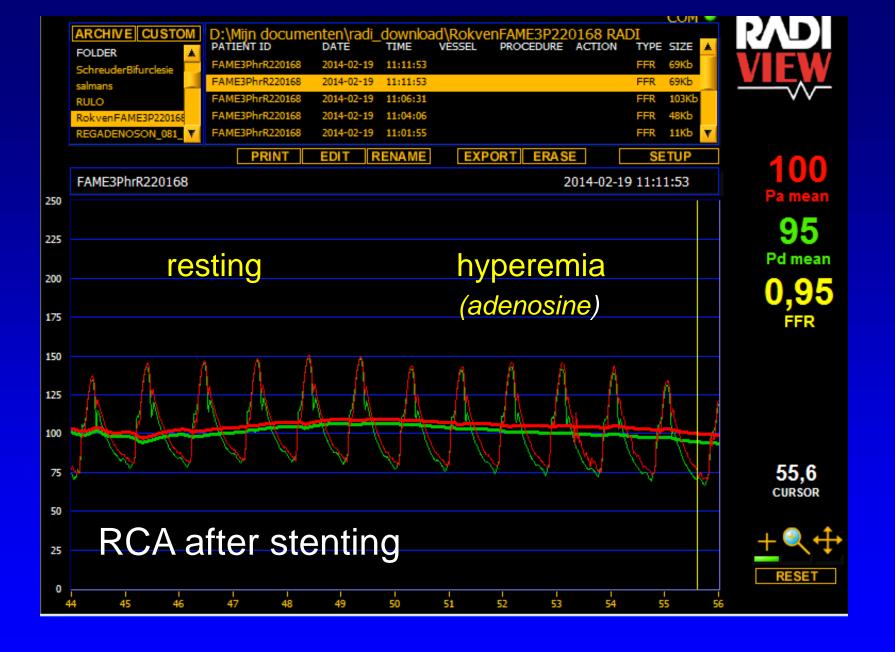


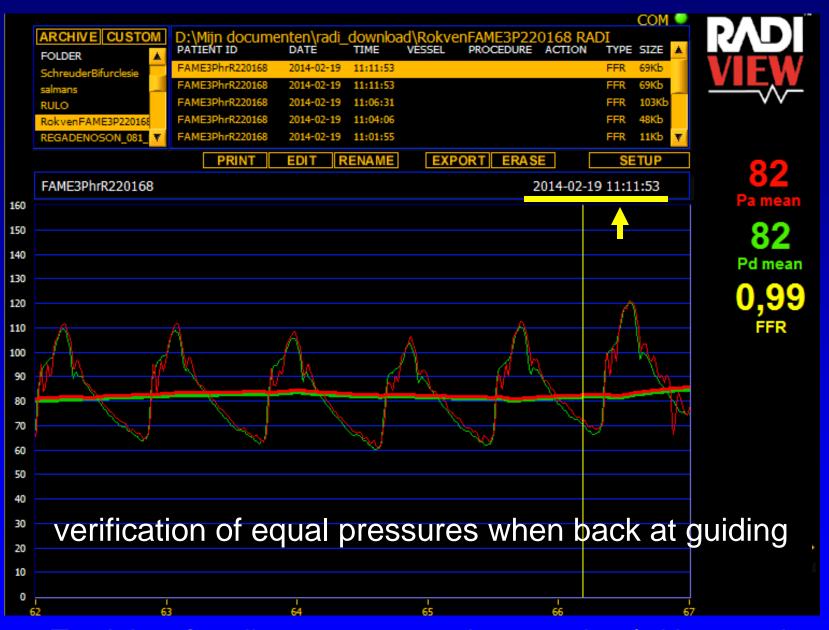


Stent in RCA (3,5x 18)

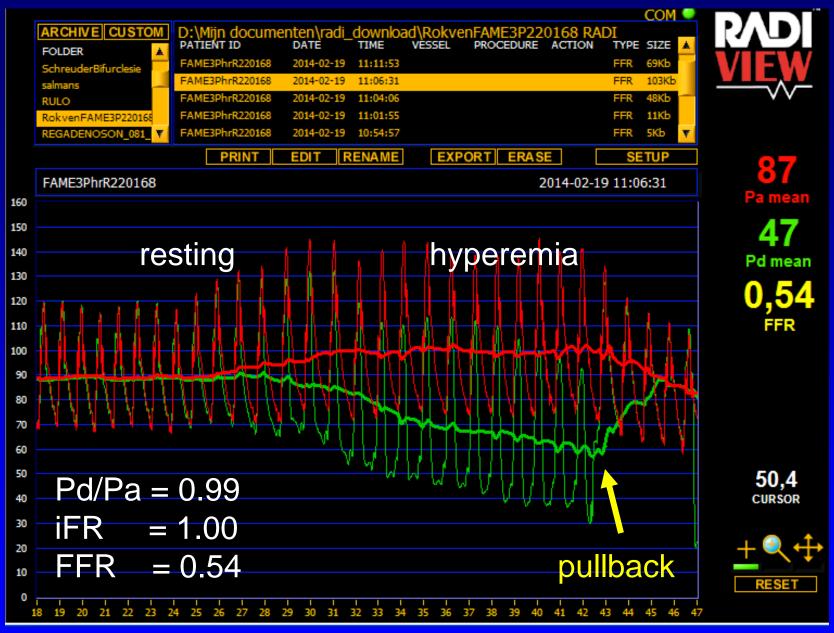


RCA after stenting





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

tomorrow morning

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

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!

GUIDELINES ESC SEPTEMBER 2010

FFR UPGRADED TO LEVEL I A INDICATION

10 - Procedural aspects of PCI

| Table 28: Specific PCI devices and pharmacotherapy | | |
|--|-------|-------|
| | Class | Level |
| FFR-guided PCI is recommended for detection of ischemia-related lesion(s) when objective evidence of vessel-related ischamia is not available | I | A |
| DES* are recommended for reduction of restenosis/reocclusion, if no contraindication to extended DAPT | I | A |
| Distal embolic protection is recommended during PCI of SVG disease to avoid distal embolisation of debris and prevent MI | I | В |
| 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 | I | C |

Finally, a few practical tips.....

OPTIMUM FFR TECHNIQUE: catheters

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

OPTIMUM FFR TECHNIQUE: manipulation of PW

How to prepare and manipulate the pressure wire

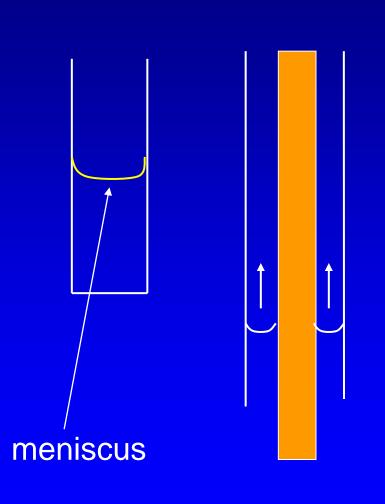
- short curve of 45-60 degree
- use the pressure wire with a torquer (cf Sion wire),
 i.e. true steering

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

<u>Starting – up FFR measurements in your Lab:</u>

- 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



adenosine

Infusion pump

Quantien interface

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