CORONARY PHYSIOLOGY IN THE CATHLAB:

THEORY AND PRACTICAL SET-UP OF FFR

Educational Training Program ESC
European Heart House
april 24th - 26th 2014

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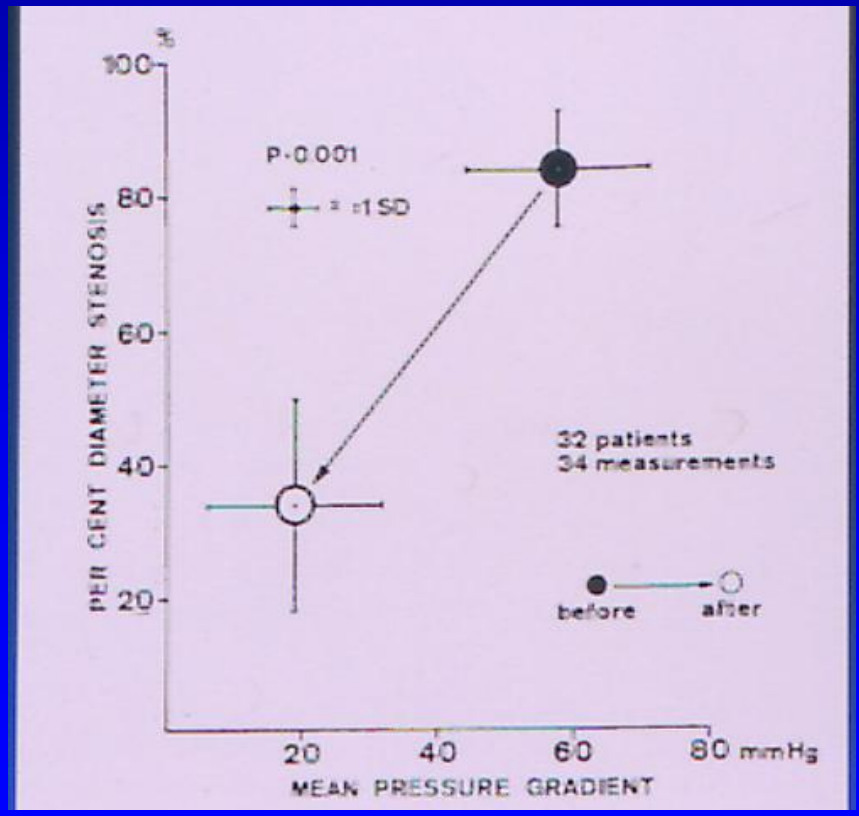
NONOPERATIVE DILATATION OF CORONARY-ARTERY STENOSIS

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

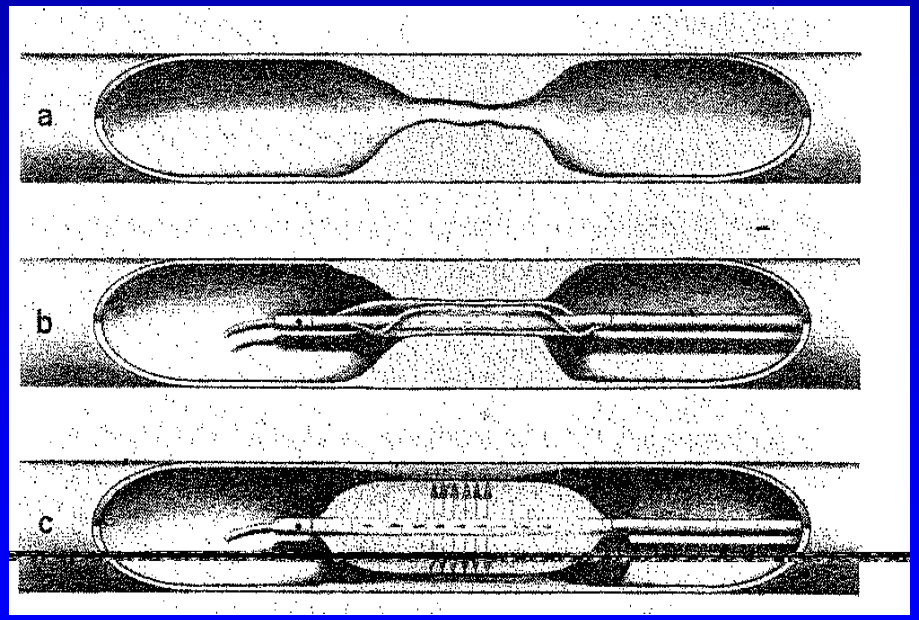


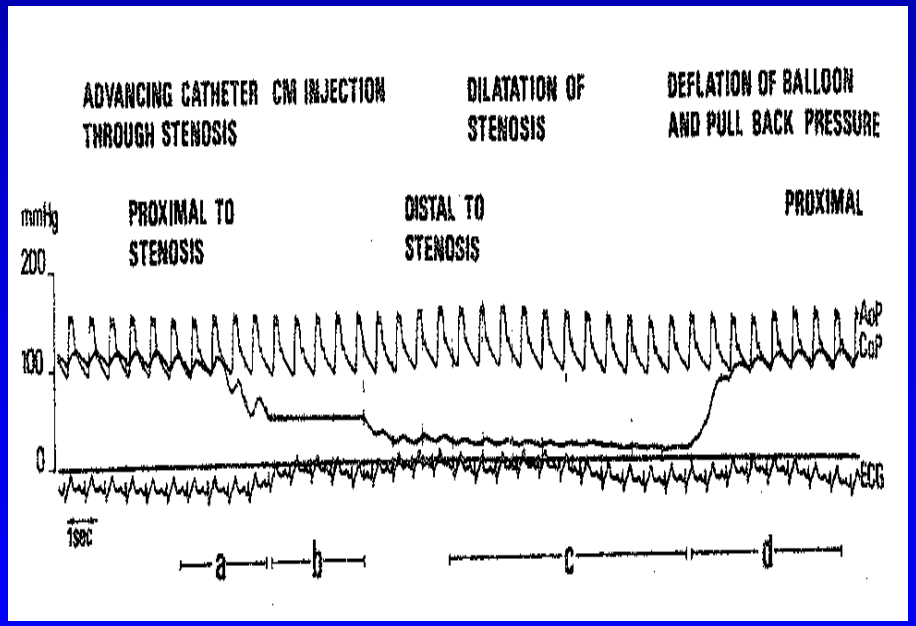
But....they were limited by

- 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***
  (overestimation of gradients)





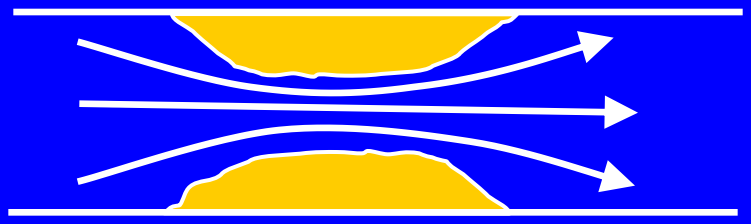
But....they were limited by

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

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

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

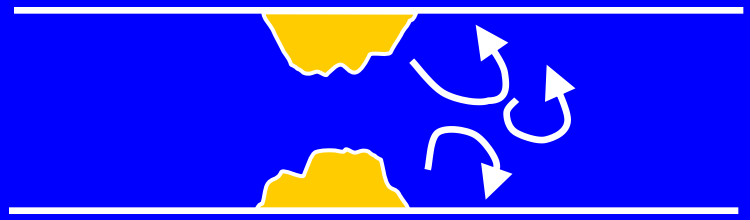
f = friction coefficient



Moderate gradient at rest

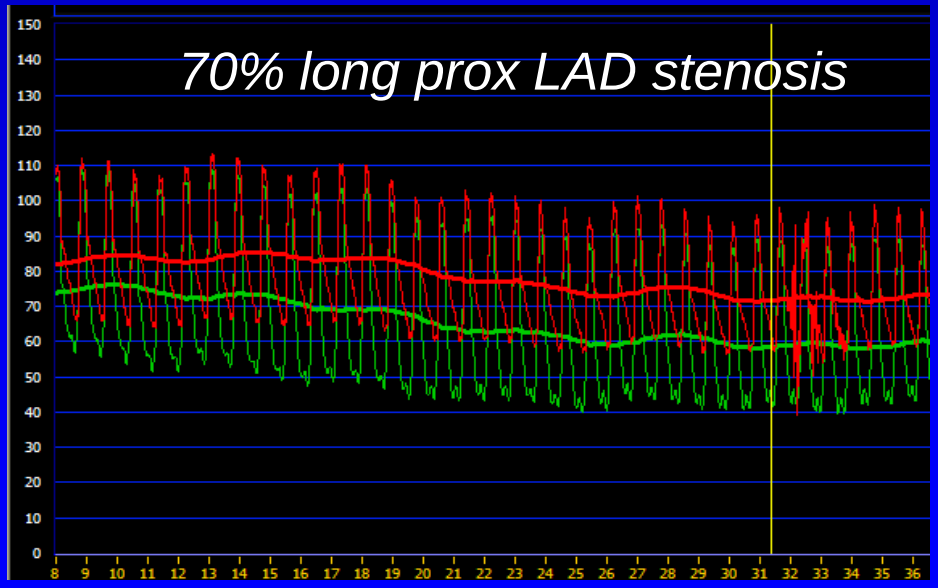
Moderate increment at hyperemia

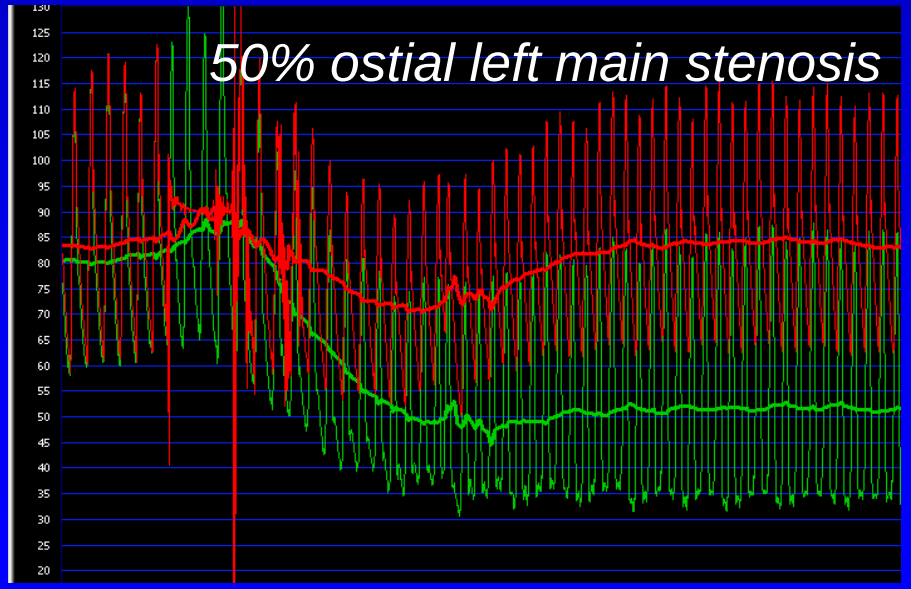
S = separation coefficient



Small gradient at rest

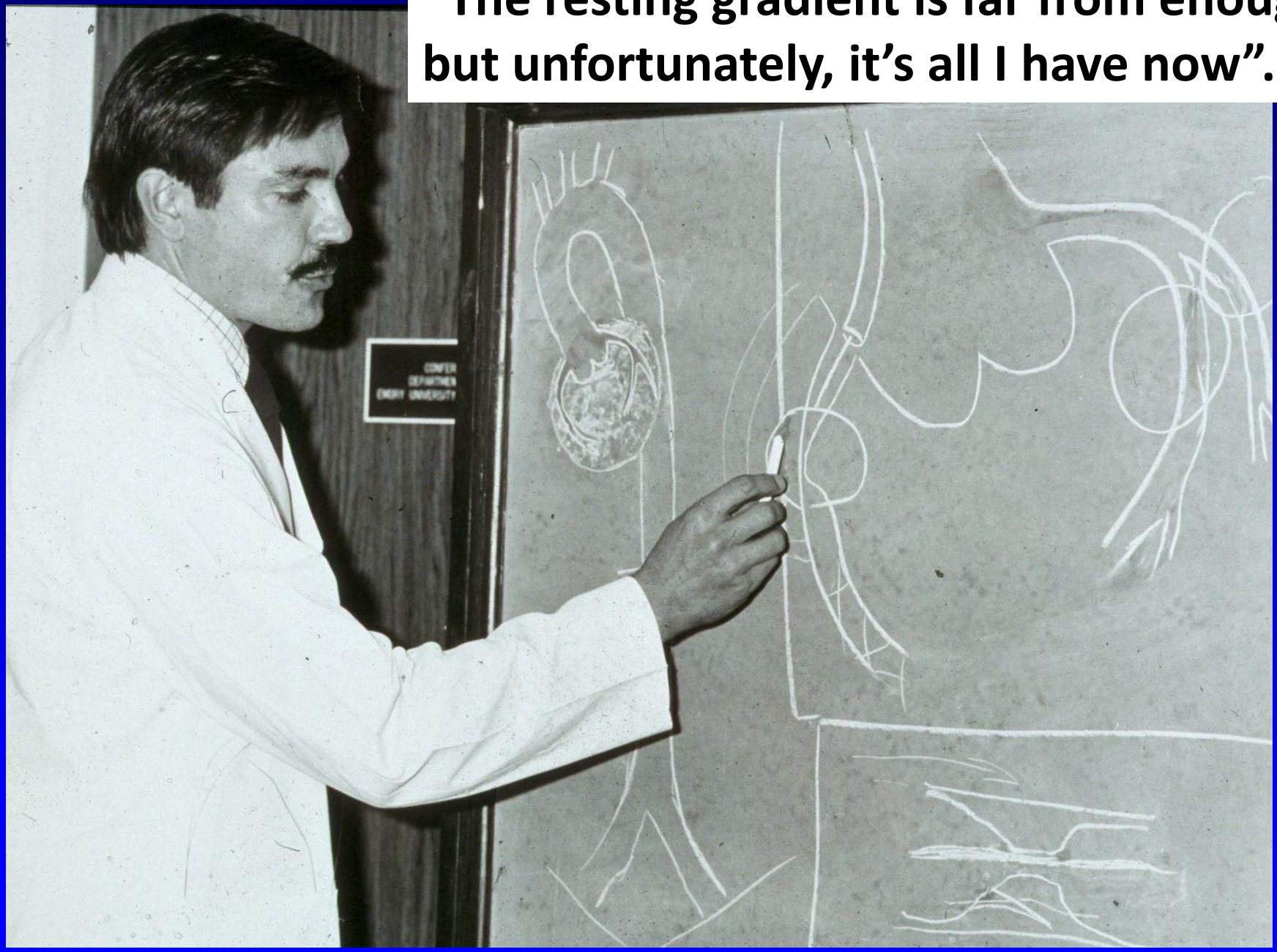
Large gradient at hyperemia





→ **resting gradient cannot predict hyperemic gradient**

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



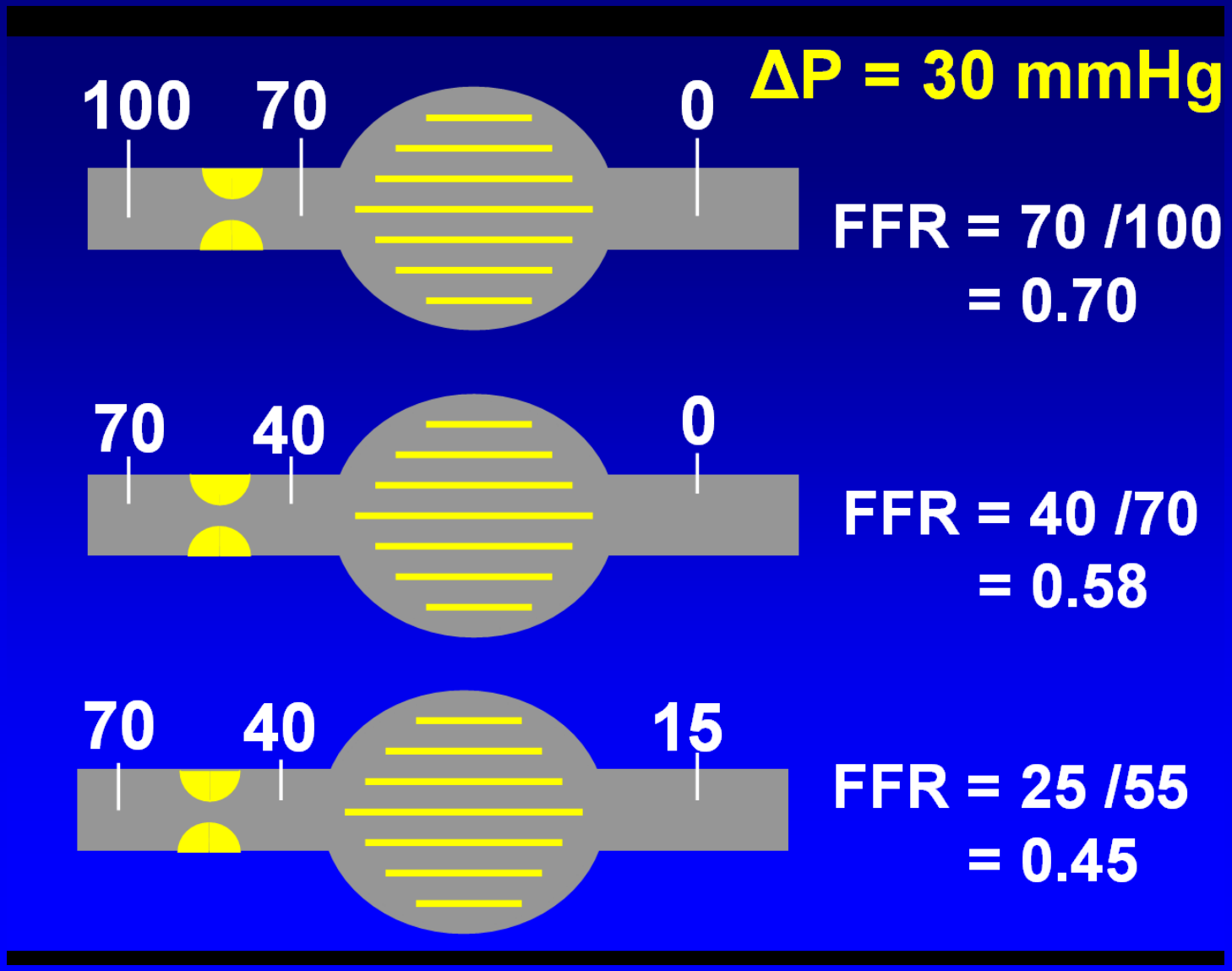
But....they were limited by

- 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 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**

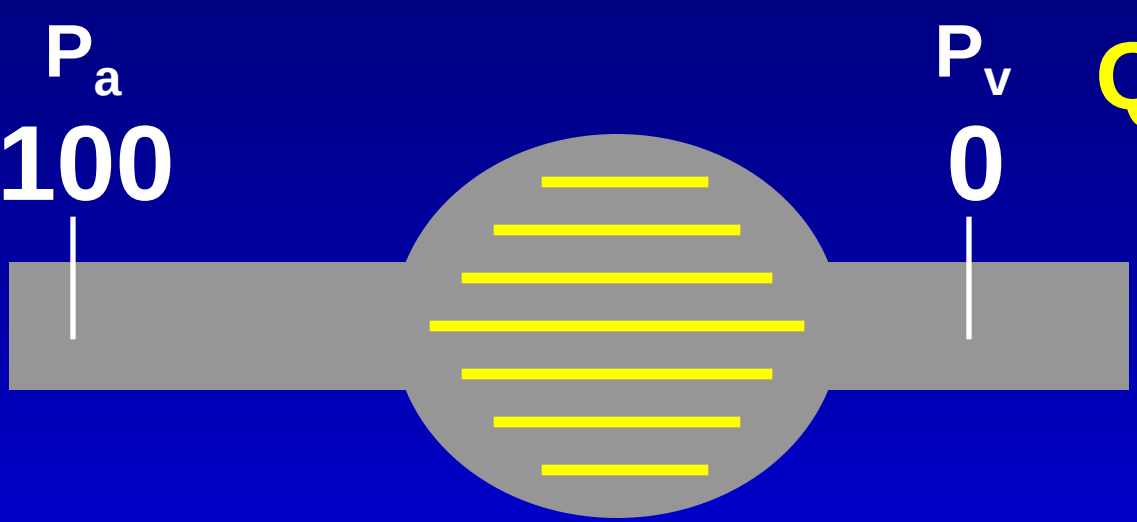
FRACTIONAL FLOW RESERVE:

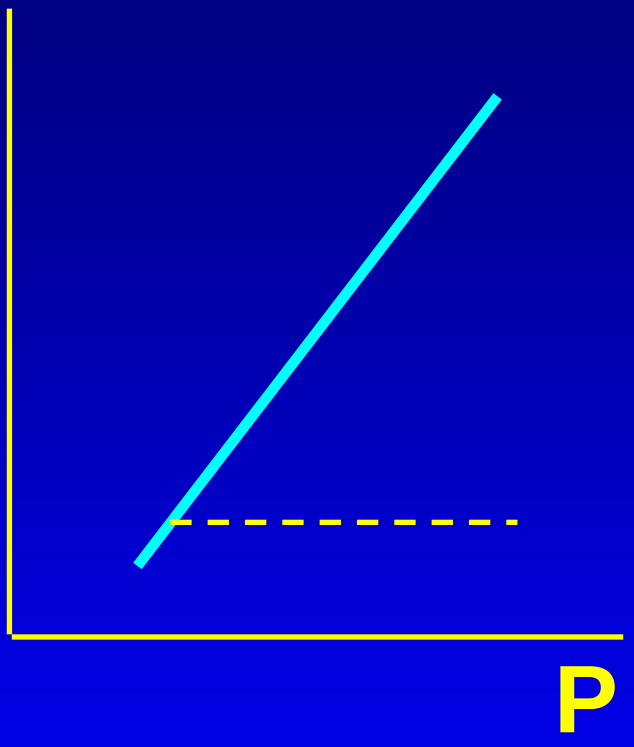
The index FFR (***Fractional Flow Reserve***)
is based upon the two following principles:

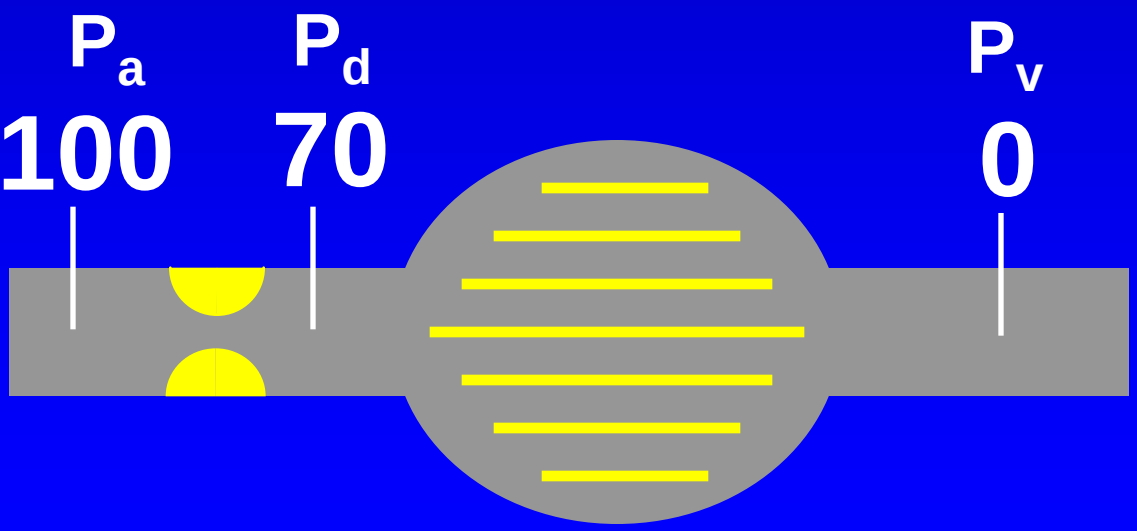
- *It is not resting flow, but **maximum achievable flow** which determines the functional capacity (exercise tolerance) of a patient*

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

During Maximal Vasodilatation







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

$$= 0.70$$

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

P_a = mean aortic pressure at maximum hyperemia

P_d = mean distal coronary pressure at maximum hyperemia

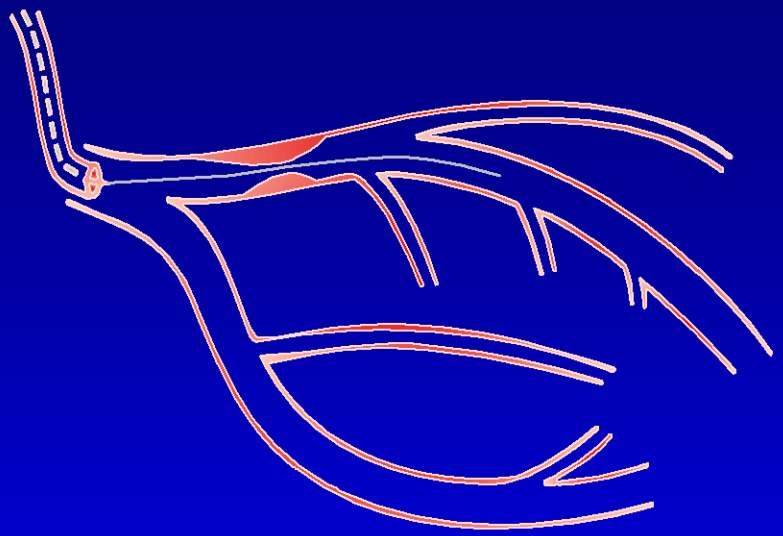
FFR = 0.6 means:

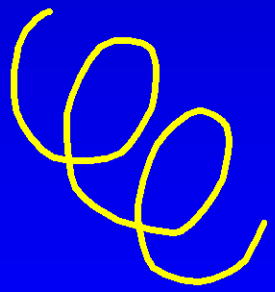
"Due to this particular stenosis, maximum achievable blood flow to the myocardium supplied by this artery, is only 60 % of what it would be if this coronary artery were completely normal"

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"

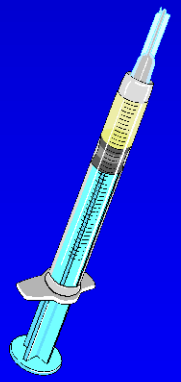
Application in catherization laboratory





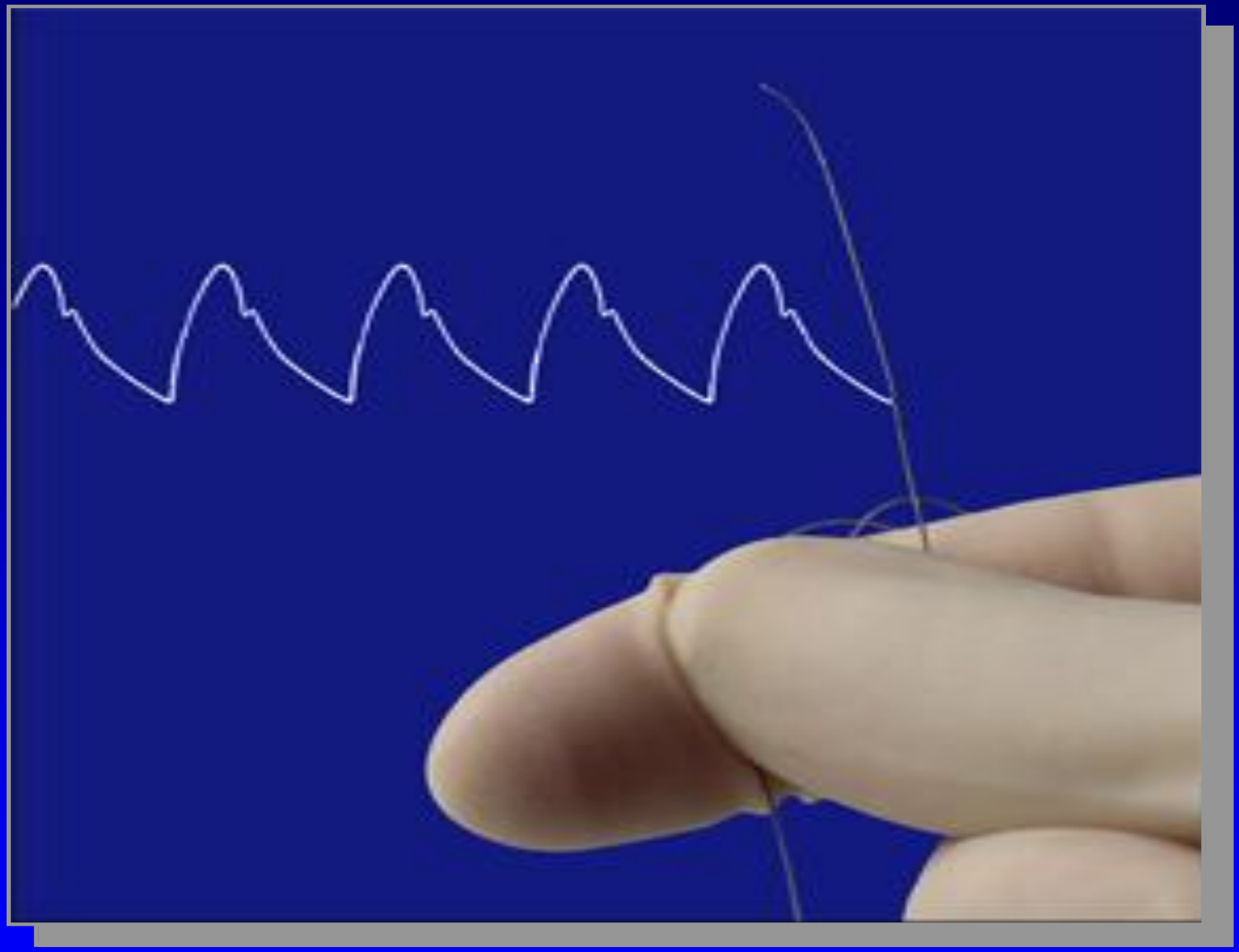
pressure wire

+



hyperemic stimulus

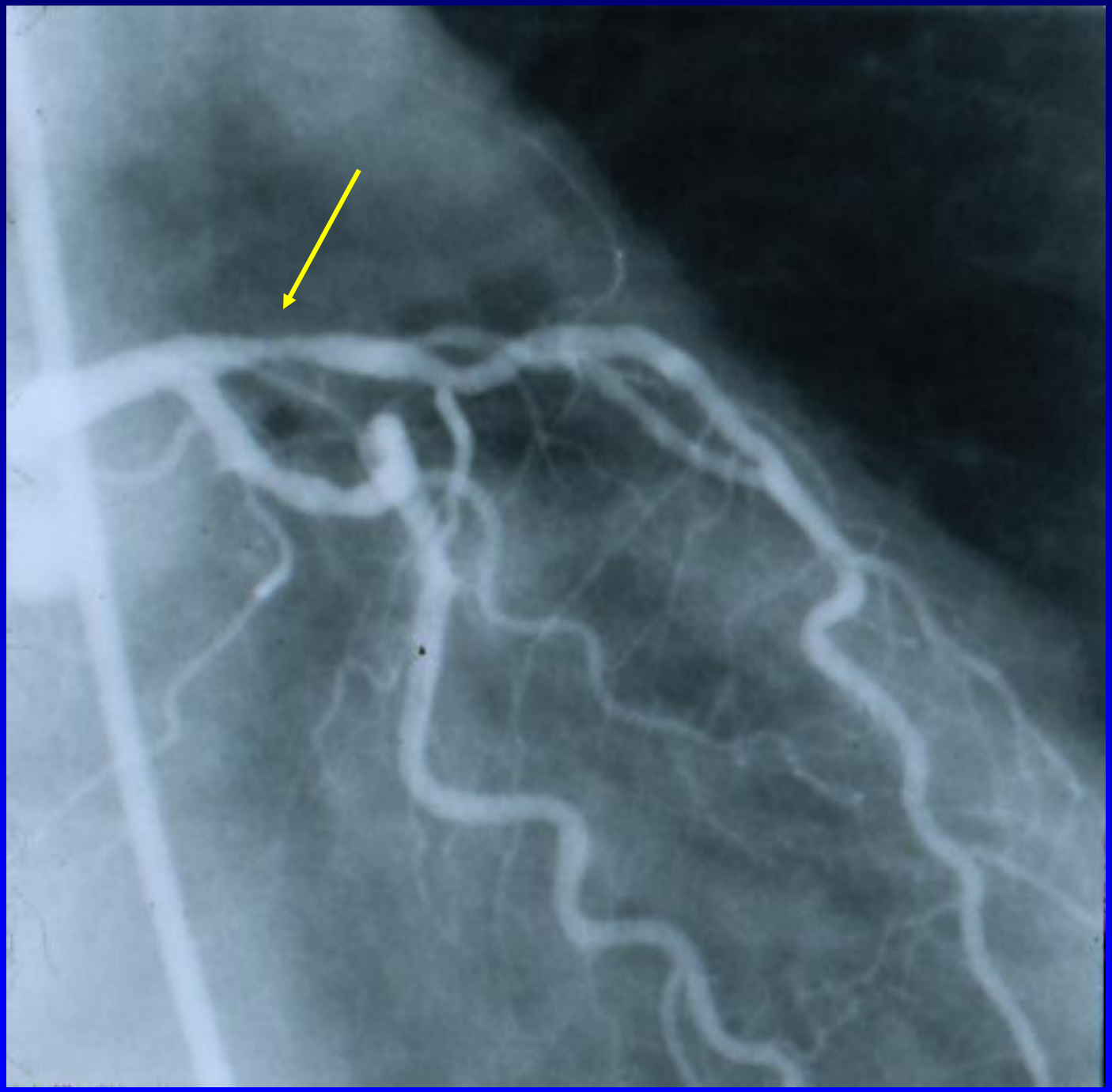
= **FFRmyo**



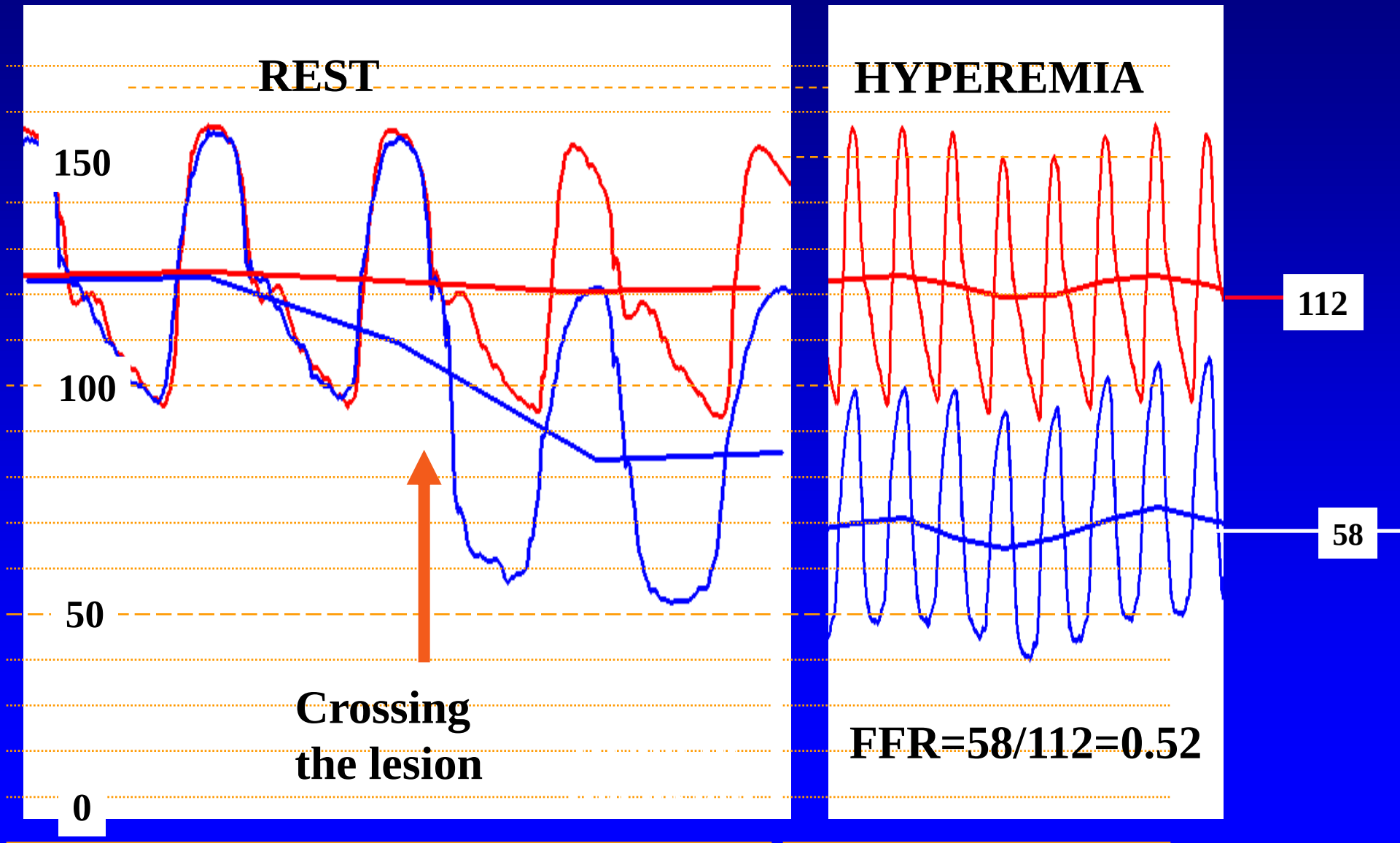
0.014 sensor-tipped PTCA guidewire (St Jude Medical & Volcano)

***CLINICAL PRACTICE*:**

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

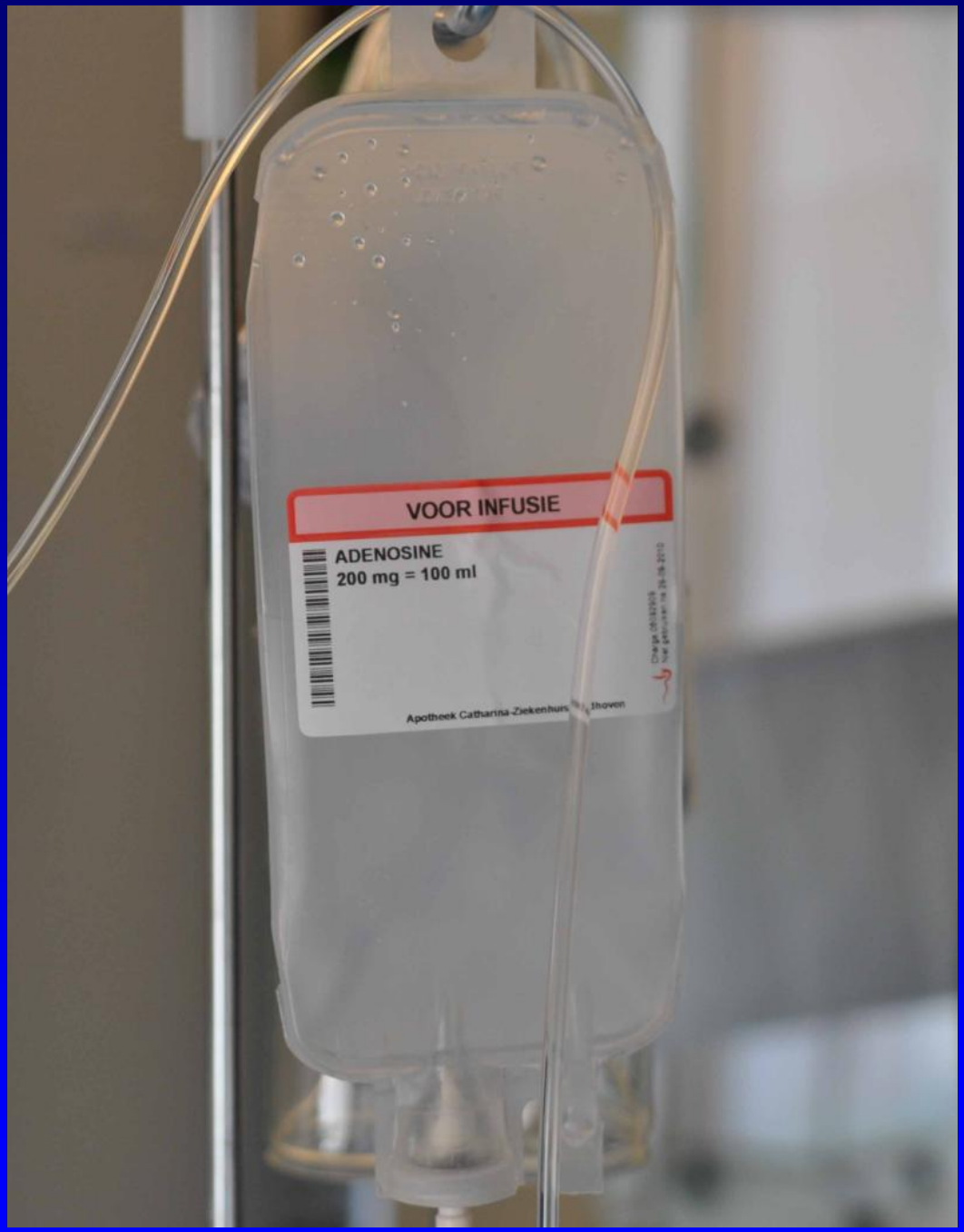


Fractional Flow Reserve in Clinical Practice



A FEW WORDS ABOUT HYPEREMIA

(next speaker, Bernard De Bruyne)



Adenosine for
i.v. infusion

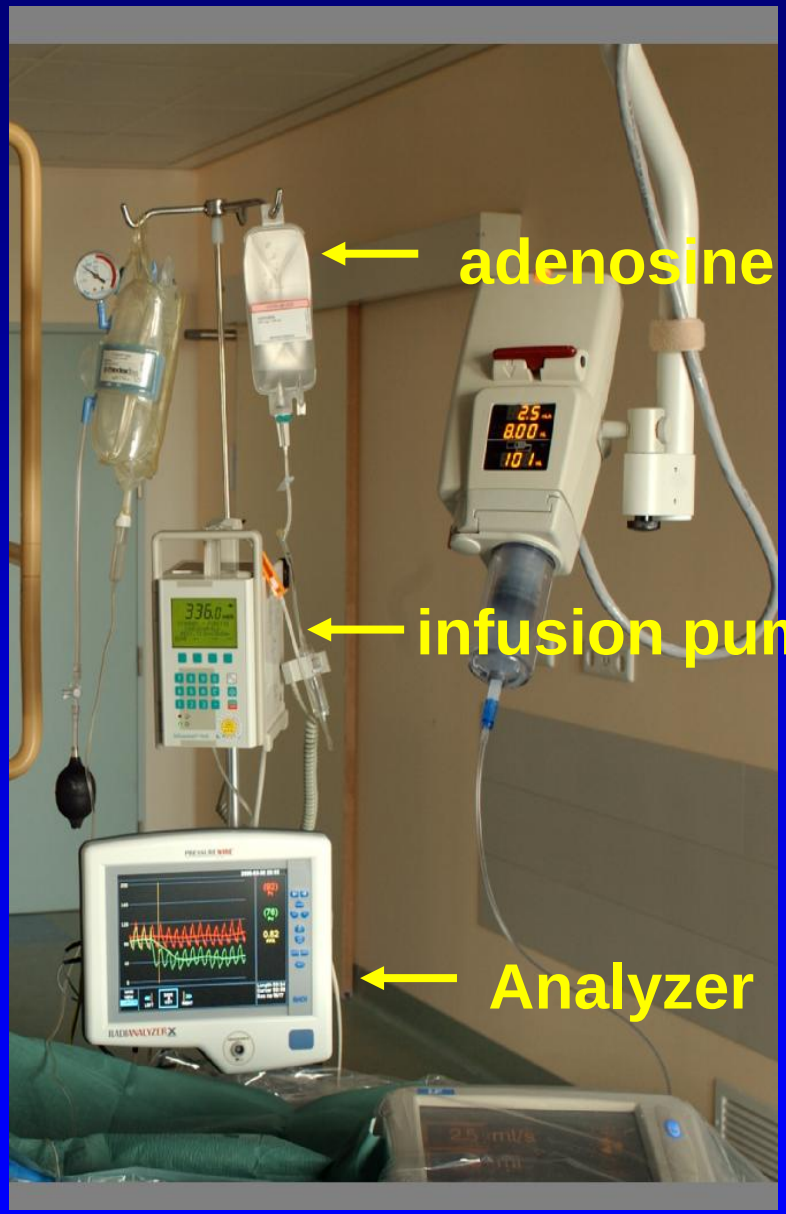
(standard bag
200 mg = 100 ml)

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)



- *no preparation in the lab*
- *no difficult calculations*
- *always the same dilution*
- *no risk of dosage error*
- *no loss of time*

MAXIMUM HYPEREMIA IS IMPORTANT !

NOTE:

- sometimes, periodic fluctuations are present during i.v. adenosine induced steady state hyperemia
- this is related to the speed of metabolization of adenosine (patient-dependent) and the breathing pattern
- *always take the lowest value of FFR*

(key papers: De Bruyne, Circulation 2003;107:1877-1883
McGeoch, CCI 2008;71:198-204

Is it necessary to use hyperemia ?

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

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

  → cut-off point around 0.85 with accuracy ≥ 90% compared to FFR cut-off point of 0.80

(A.Jeremias, N. Johnson, Saturday morning)

Advantages of Pd/Pa *contrast* (cFFR) compared to iFR or Pd/Pa at "rest"

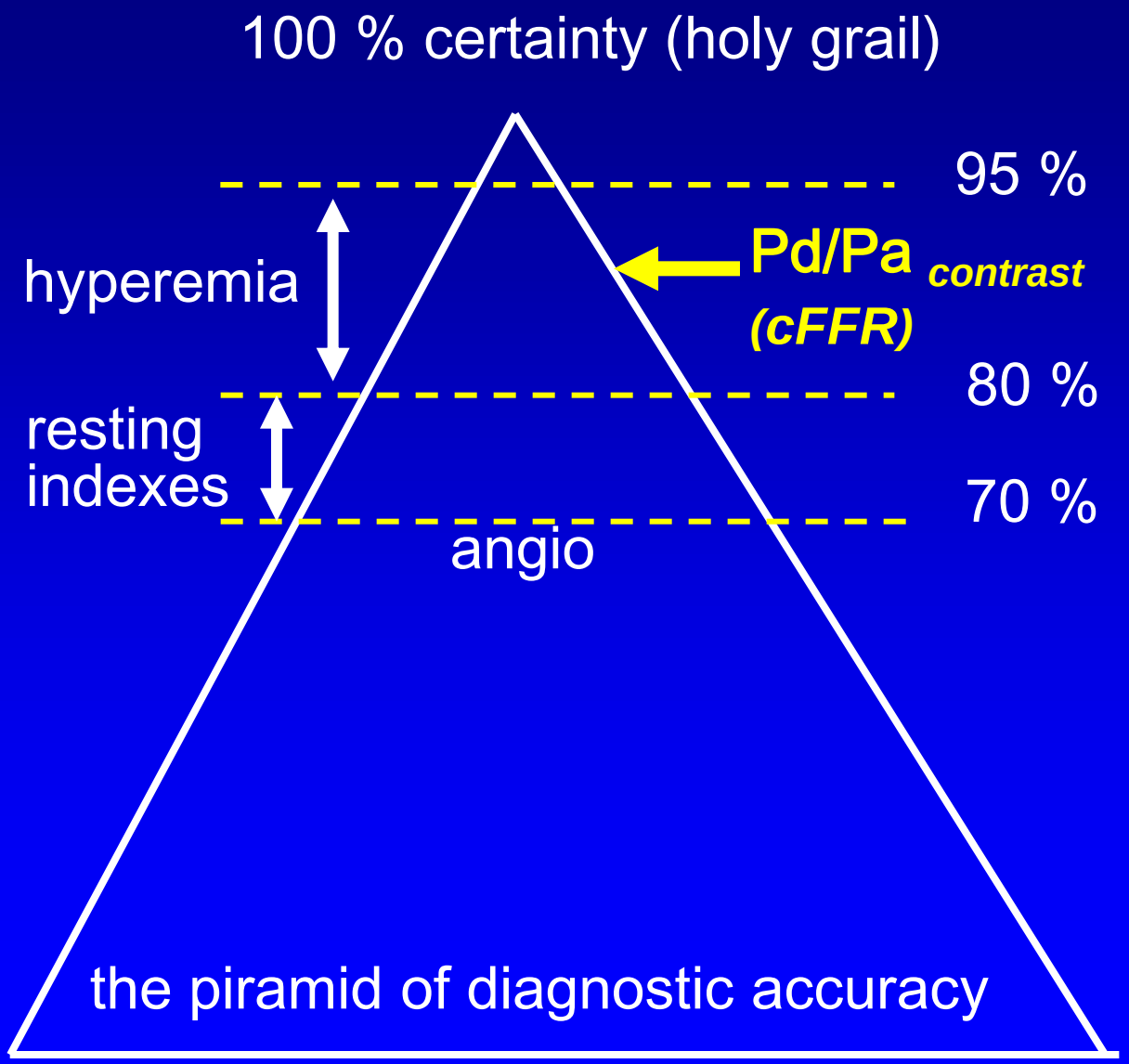
- no ECG needed; easier to perform
- no specific software needed,
  can be used with every pressure wire &interface
- no particular steady state needed
  (resting conditions or hyperemia)
- ***more accurate than those resting indexes***

Correct Classification of Ischemic Stenosis

FFR

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

angiography



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

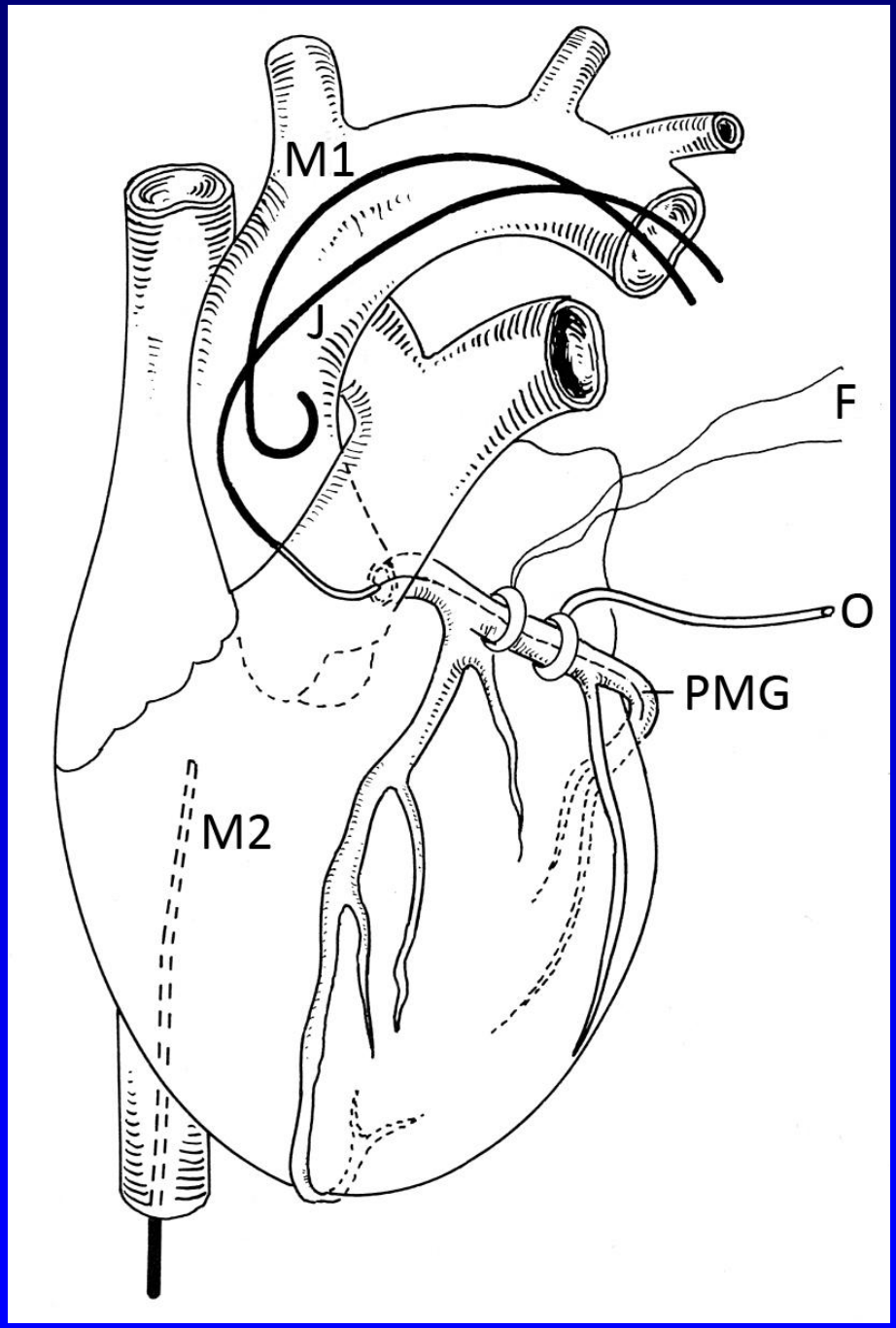
- sound scientific basis and experimental validation

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

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)

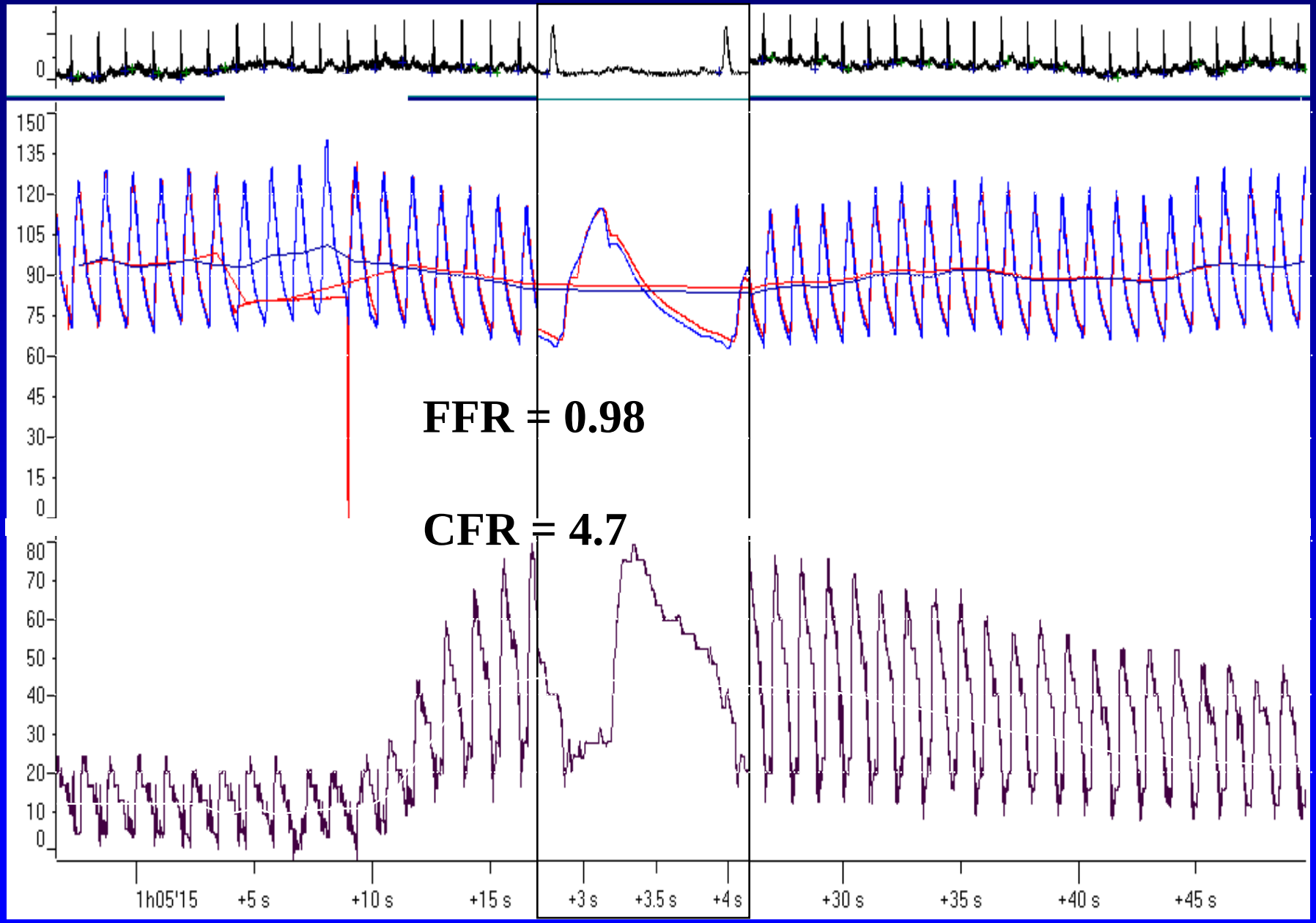
Pijls, Circulation 1995;92: 183-193

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

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

→ prospective multitesting Bayesian approach

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

How to search for the threshold of a new index ?

In most studies:

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

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

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

But……in another population, another ROC and another "best cut-off point" and "accuracy" will be found !!!

Author	Meeting or Citation	Date	N	iFR cutoff*
Davies	TCT	2011 November	157	none**
Sen	JACC 59:1392	2011 December		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 ?

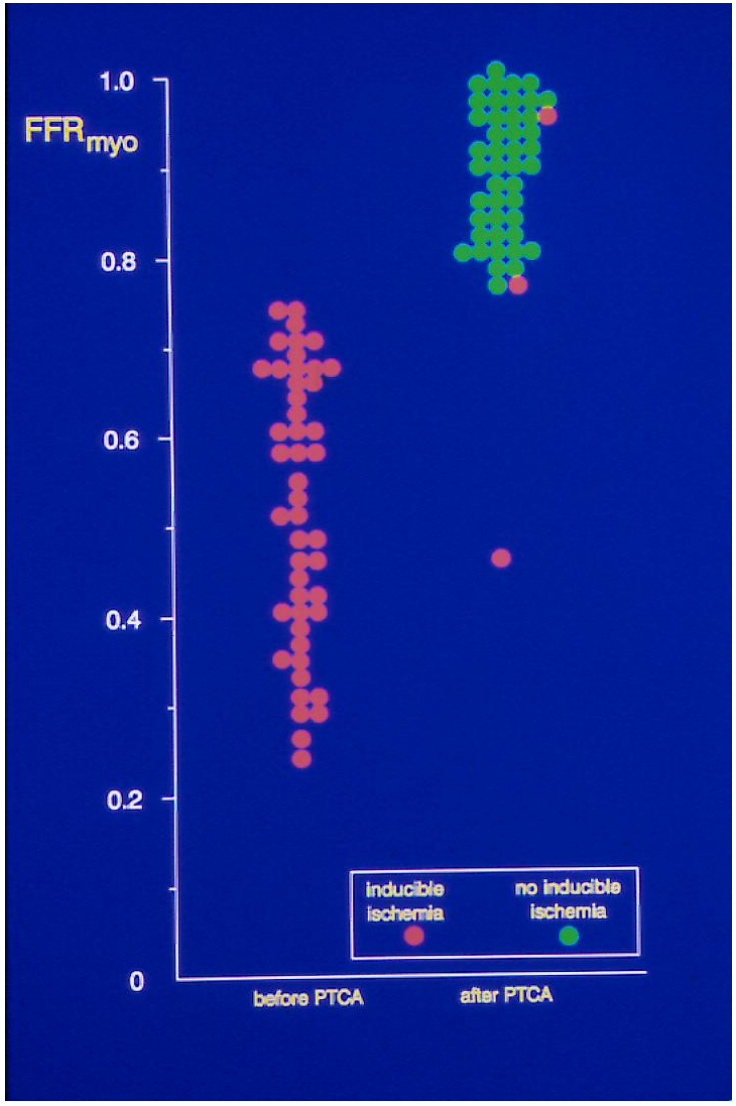
The right way to go is a 2-step approach:

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**

Validation of FFR in humans (step 1)



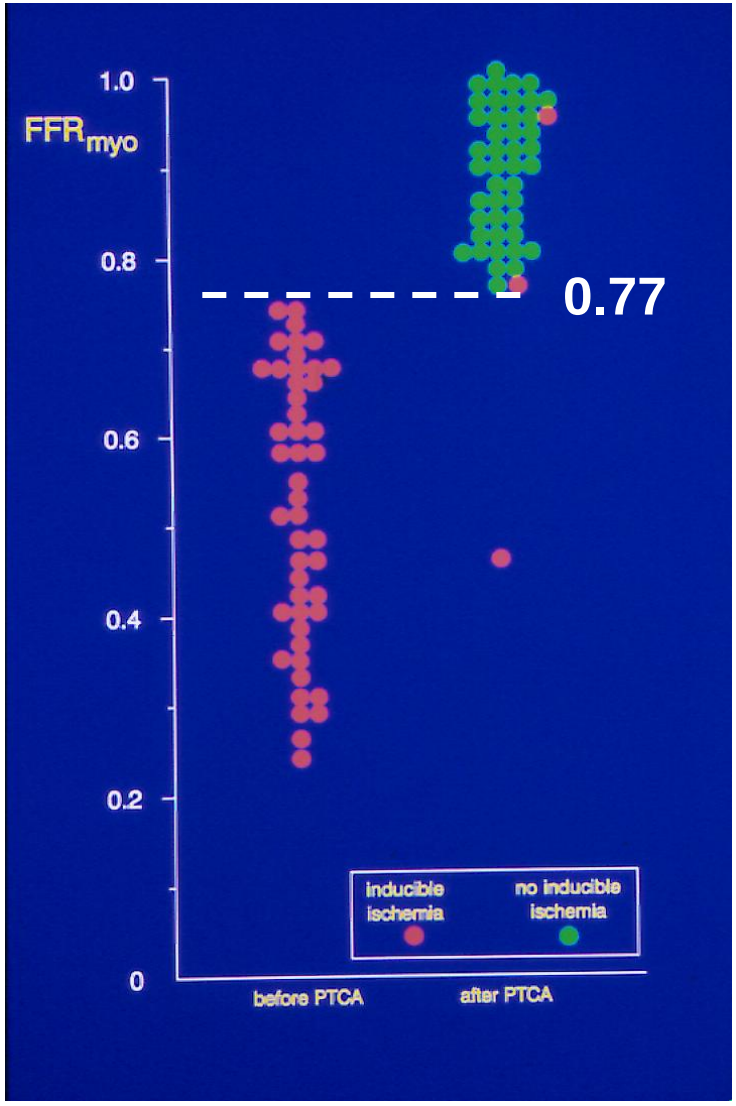
Proper validation of any index needs ***2 steps:***

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

Validation of FFR in humans (step 1)



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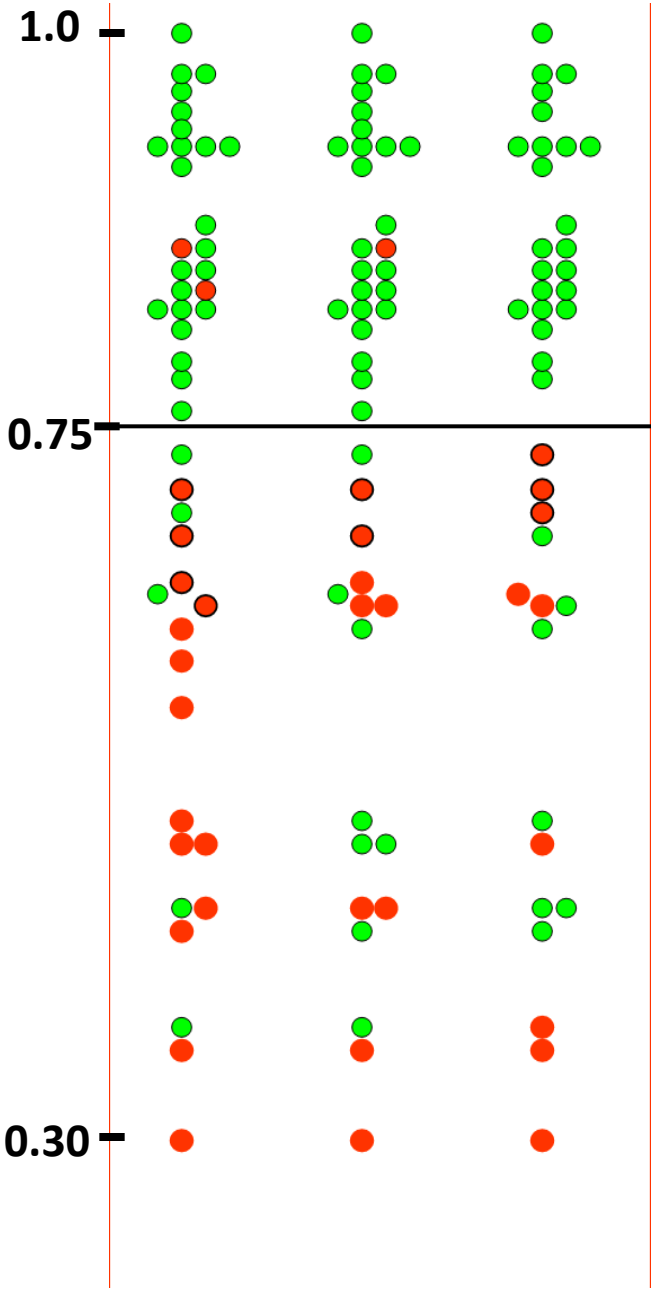


Testing of FFR versus True Gold Standard

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**.
(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

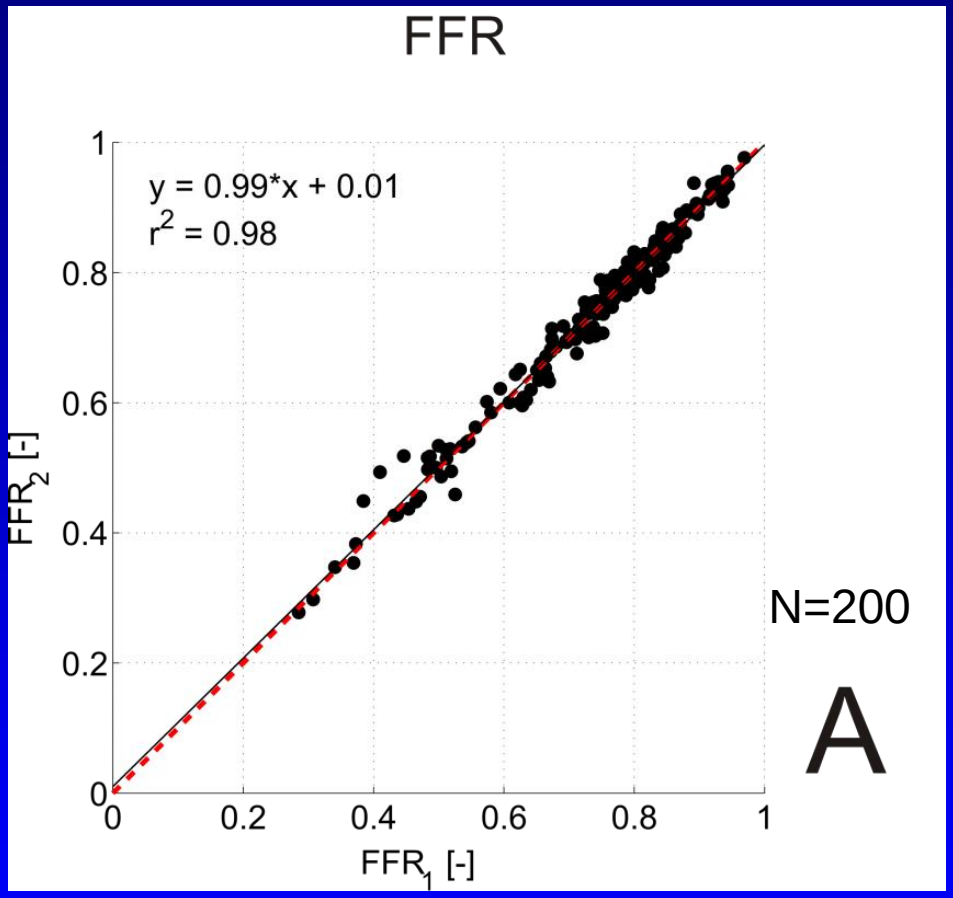
Let's have a closer look to FFR

Prerequisites for a reliable index for decision making

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

} tomorrow

Reproducibility of FFR



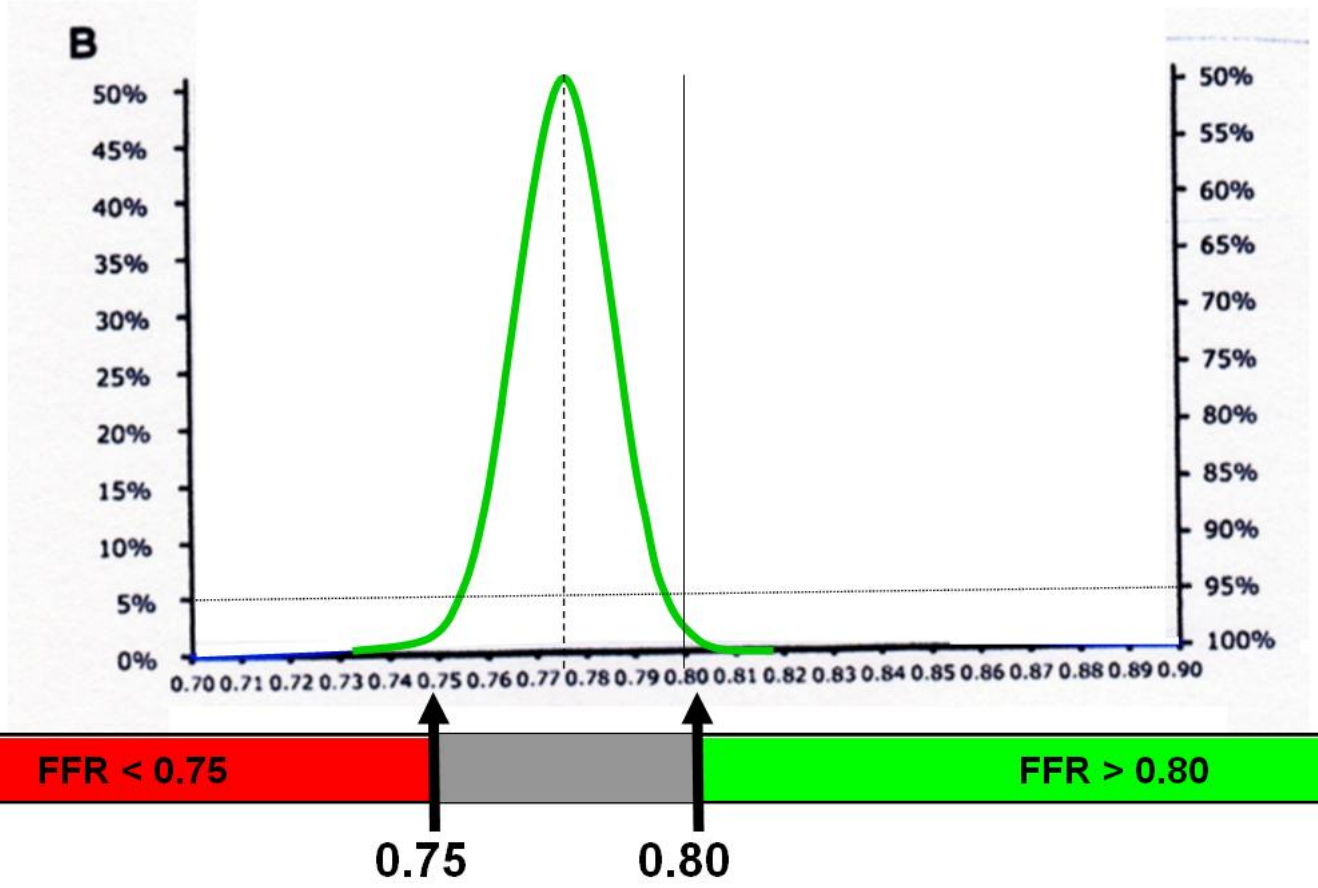
VERIFY study, Berry et al, JACC 2013 (published februari 2013)

(all-comers during one month)

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

Probability that treatment decision will change if the respective index measurement is repeated

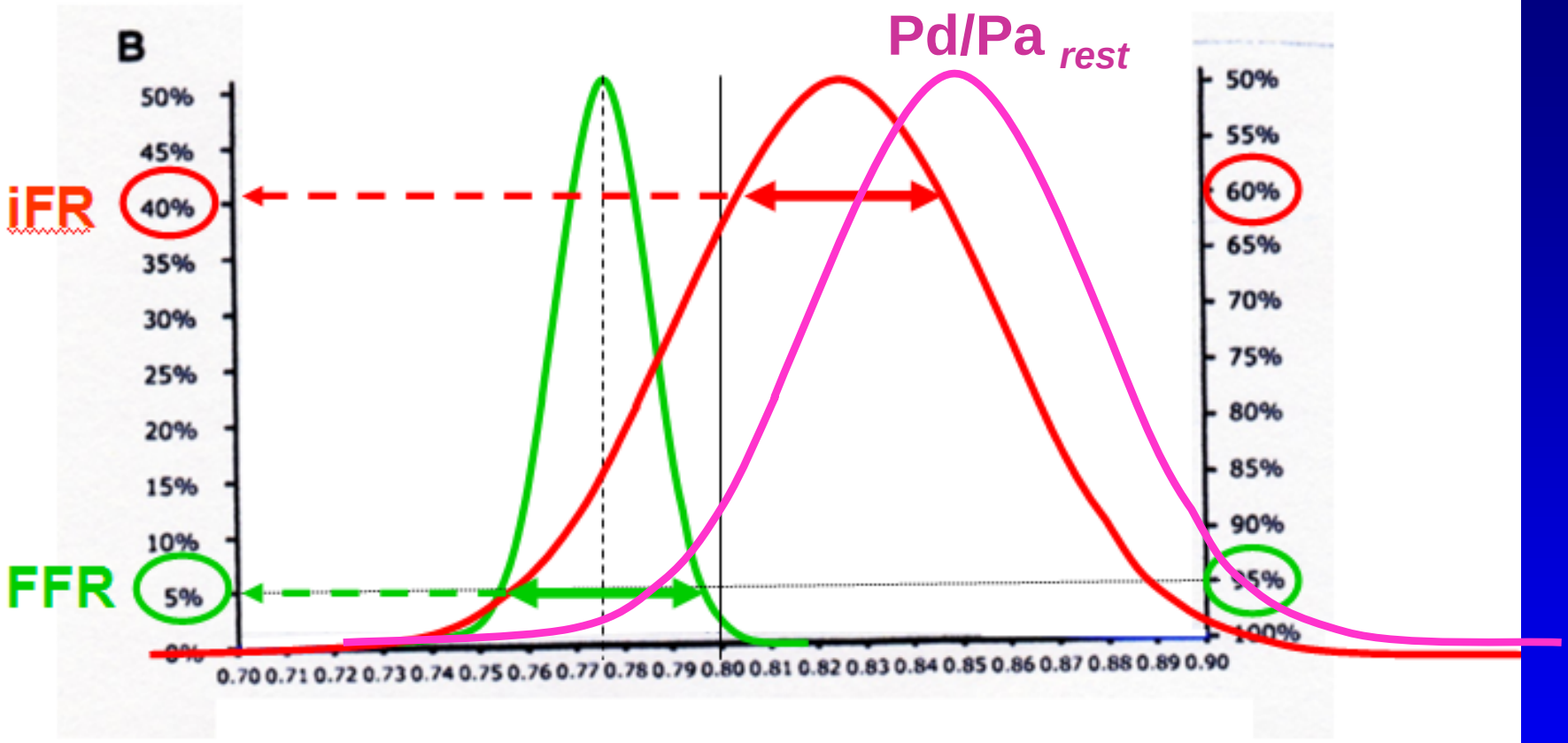
Classification certainty of single measurement



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

Probability that treatment decision will change if the respective index measurement is repeated

Classification certainty of single measurement

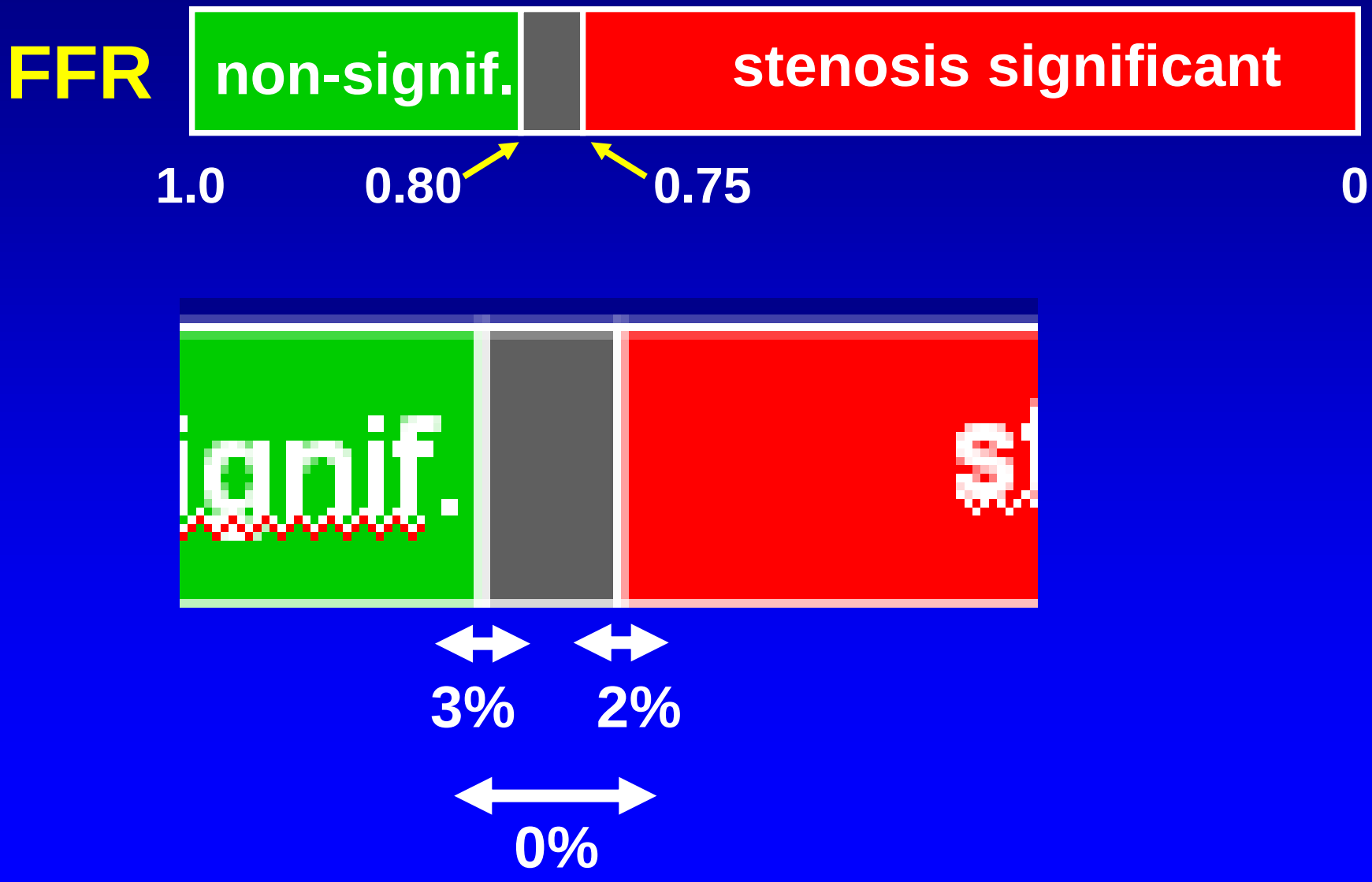


FFR, VERIFY study

iFR, ADVISE study

Pd/Pa *rest* VERIFY study

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

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PRACTICAL PERFORMANCE OF FFR - MEASUREMENT

Mr R, born 22-01-1968 (46-year-old

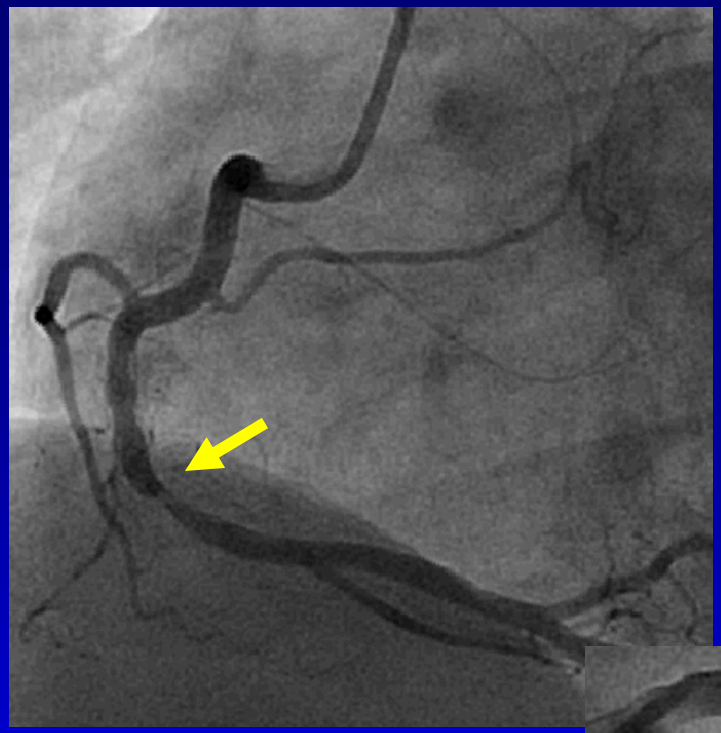
- admission on jan 25th, 2014 with acute lateral wall MI
- PPCI of occluded diagonal branch

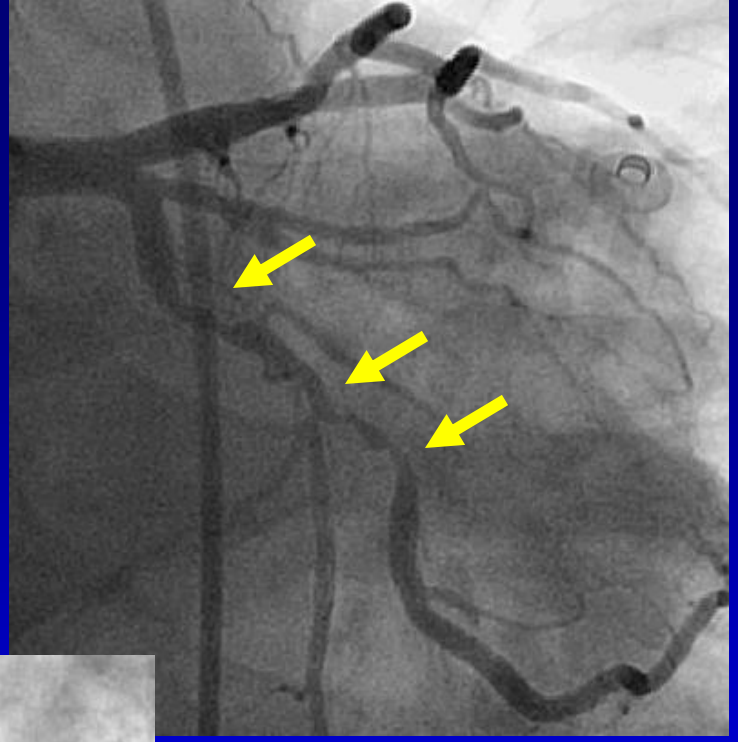
- Concomittant 3-vessel disease:
  - LAD : 50%
  - LCX : long tandem lesion 50-70% + 70-90%
  - RCA : 50-70%

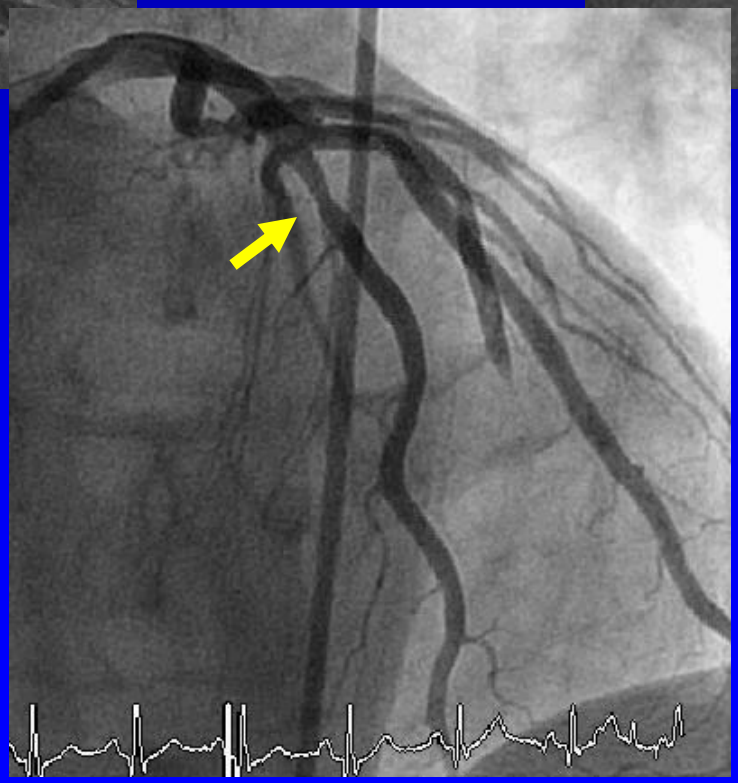
- Syntax score: 22

- Heartteam: CABG or FFR-guided MVD PCI

⟶ ***choice for FFR guided PCI, as pilot for FAME-3***







70% RCA
50% LAD
90% long LCX

Nitroglycerine

Note !

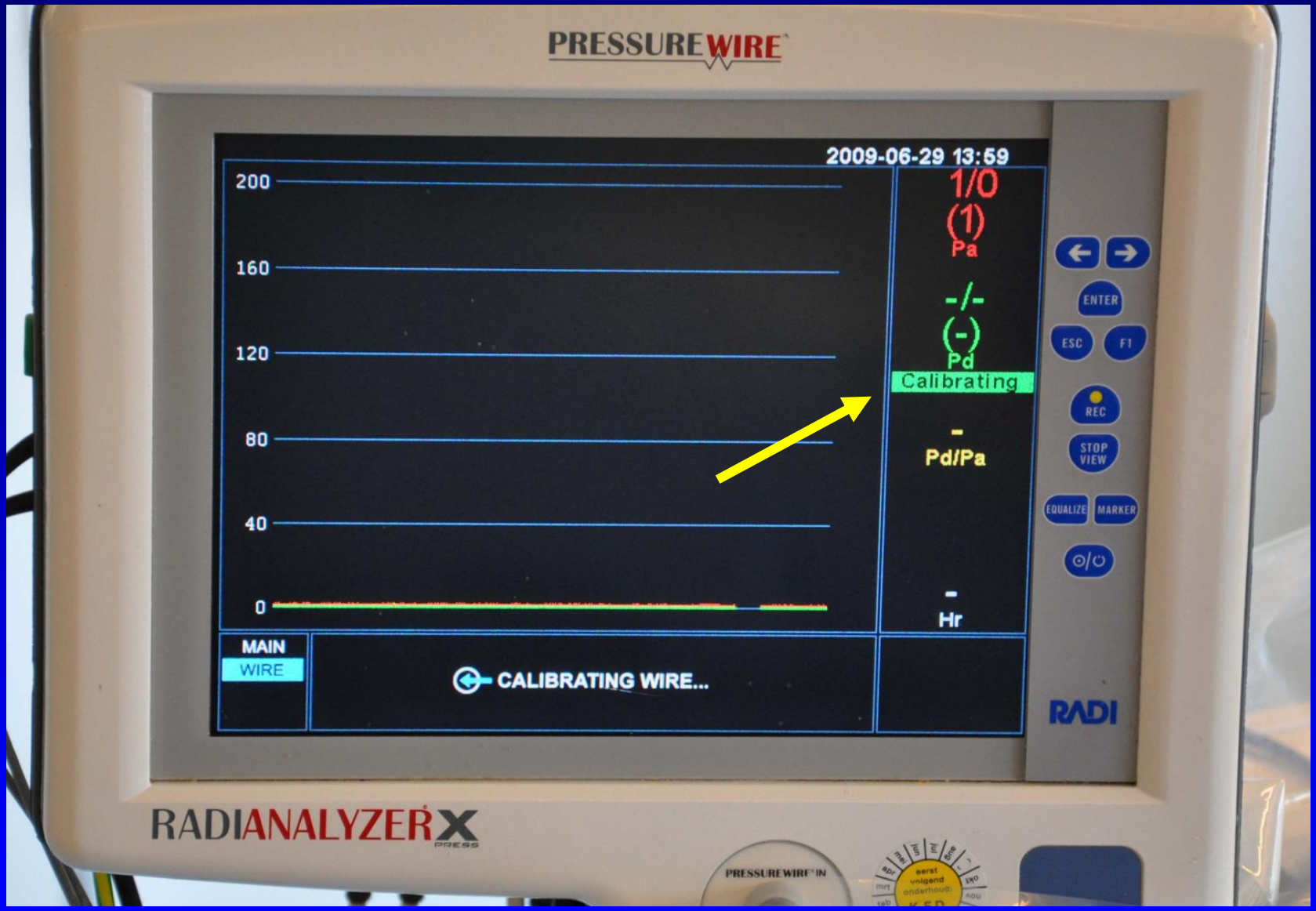
As in any intracoronary manipulation, before entering the coronary circulation, administer *200-300 µg NTG i.c.*

200 – 300 µg NTG i.c.

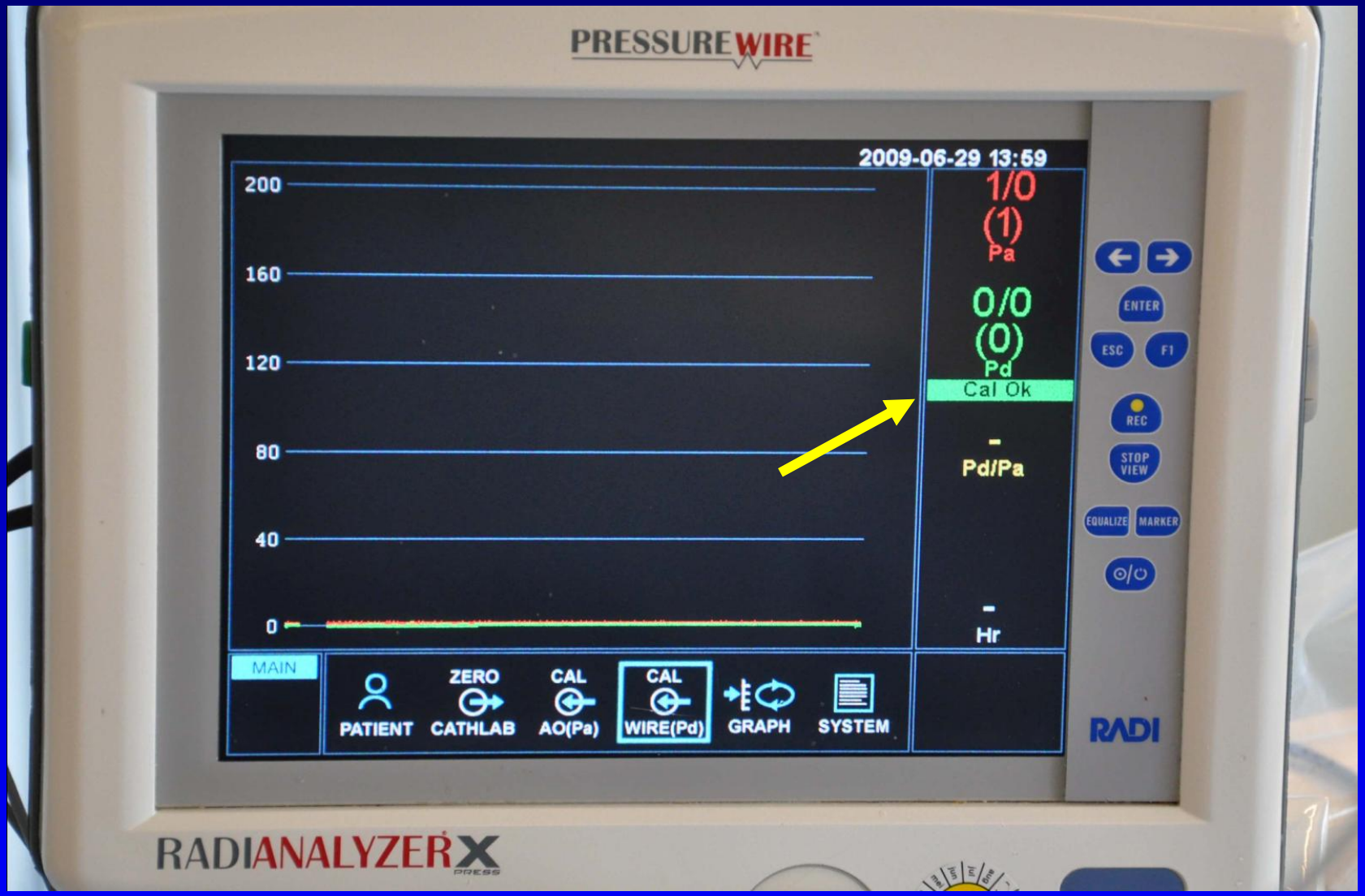
Unpacking of the Pressure Wire

Flushing the Pressure Wire

Connecting the Pressure Wire to Analyzer



Calibrating Pressure Wire



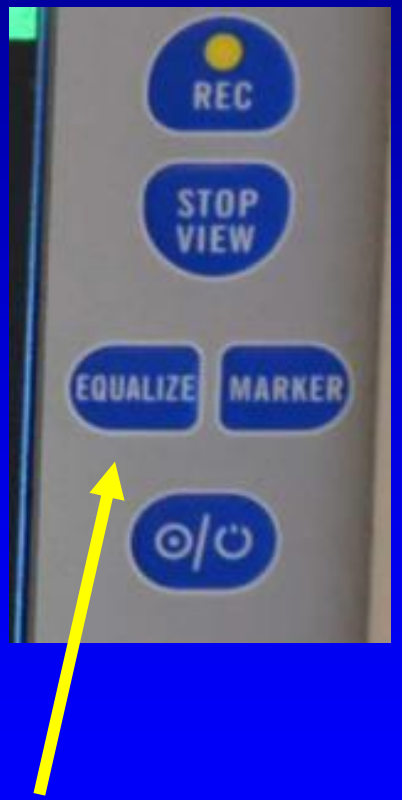
Pressure Wire Calibrated: Ok

Pressure Wire introduced into Y-connector

Shaping of the tip of the PW

Introducing the PW into the Guiding Catheter

start with verification of equal signals when sensor is located at tip of the guiding catheter and equalize



NOTE:

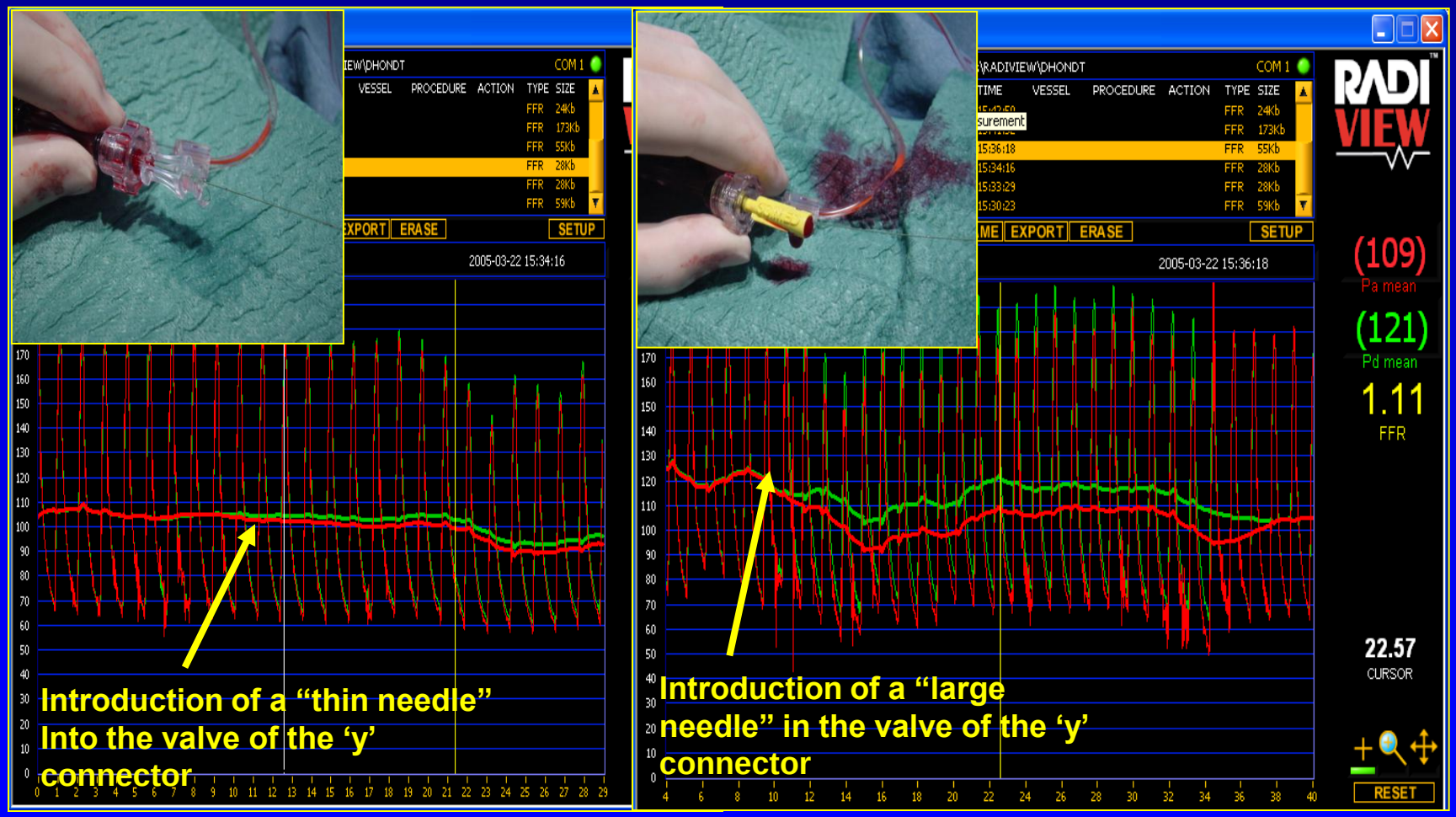
introducer needle in or out !?!

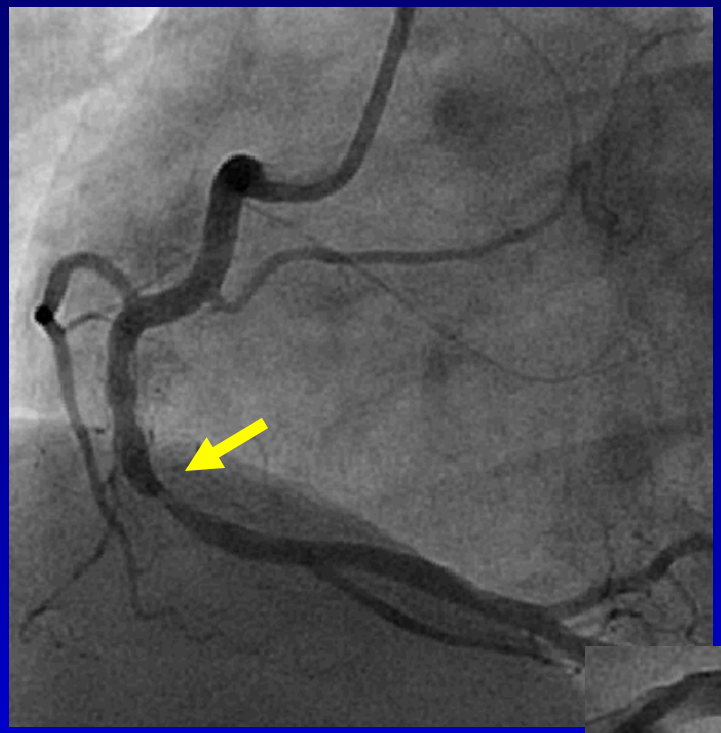
→ ***doesn't matter as long as you realize what you are doing***

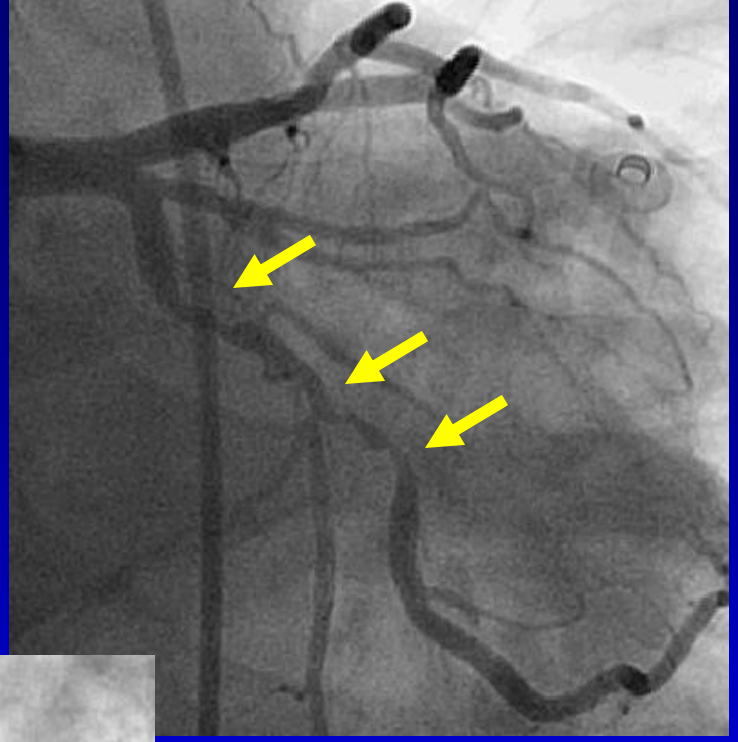
1. ***Know your needle***

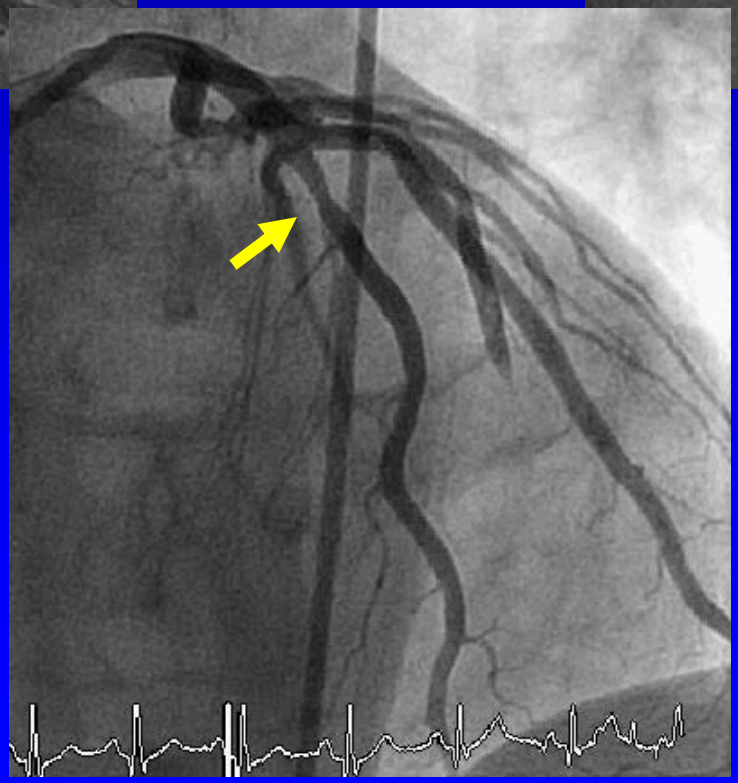
2. ***Realize that some apparent "drift" at the end is not drift per se but can be caused by the presence of the introducer when doing the initial measurement and absence of the (removed) introducer at the end***

Introducer effect *(mistake in live case in PCR 2010)*

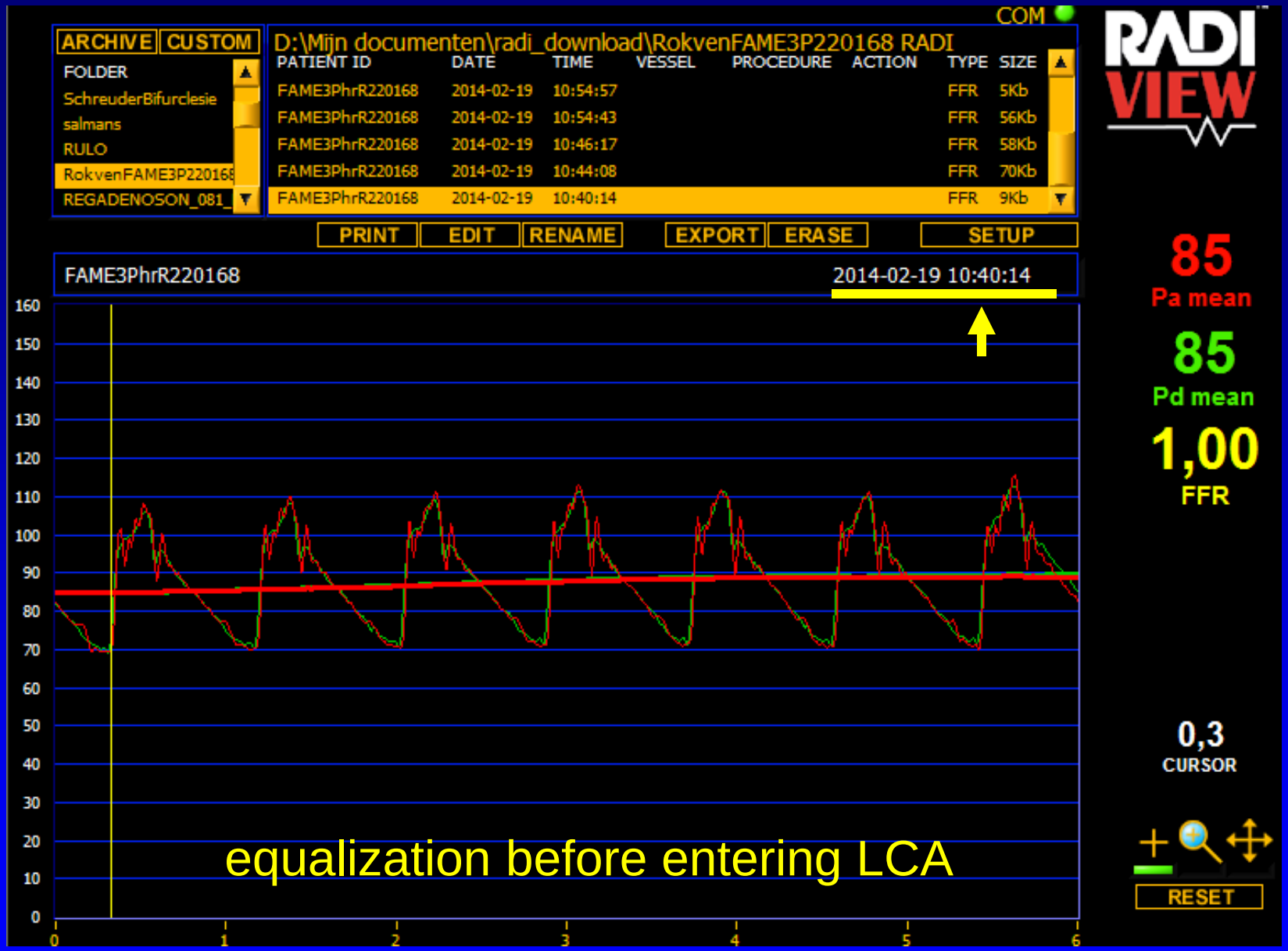








70% RCA
50% LAD
90% long LCX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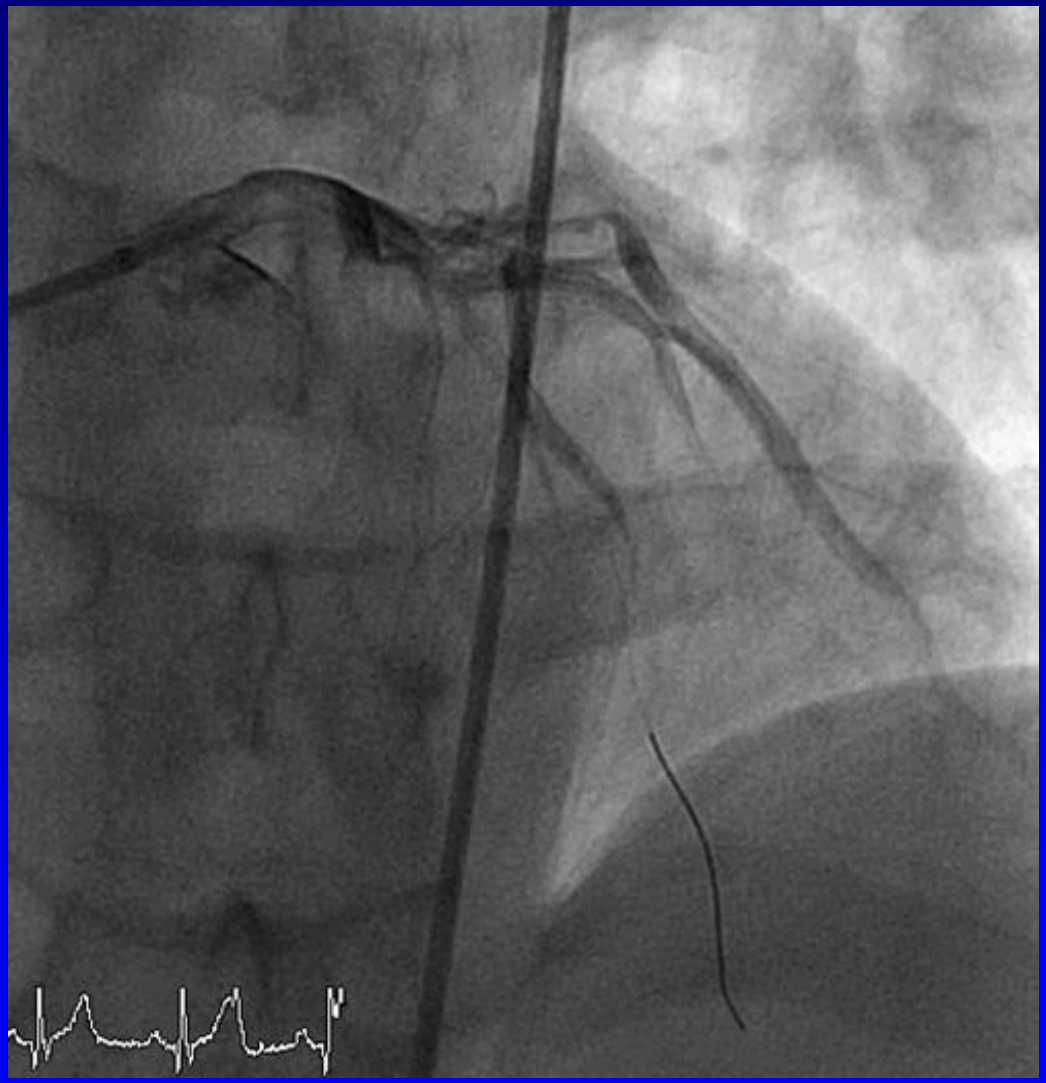
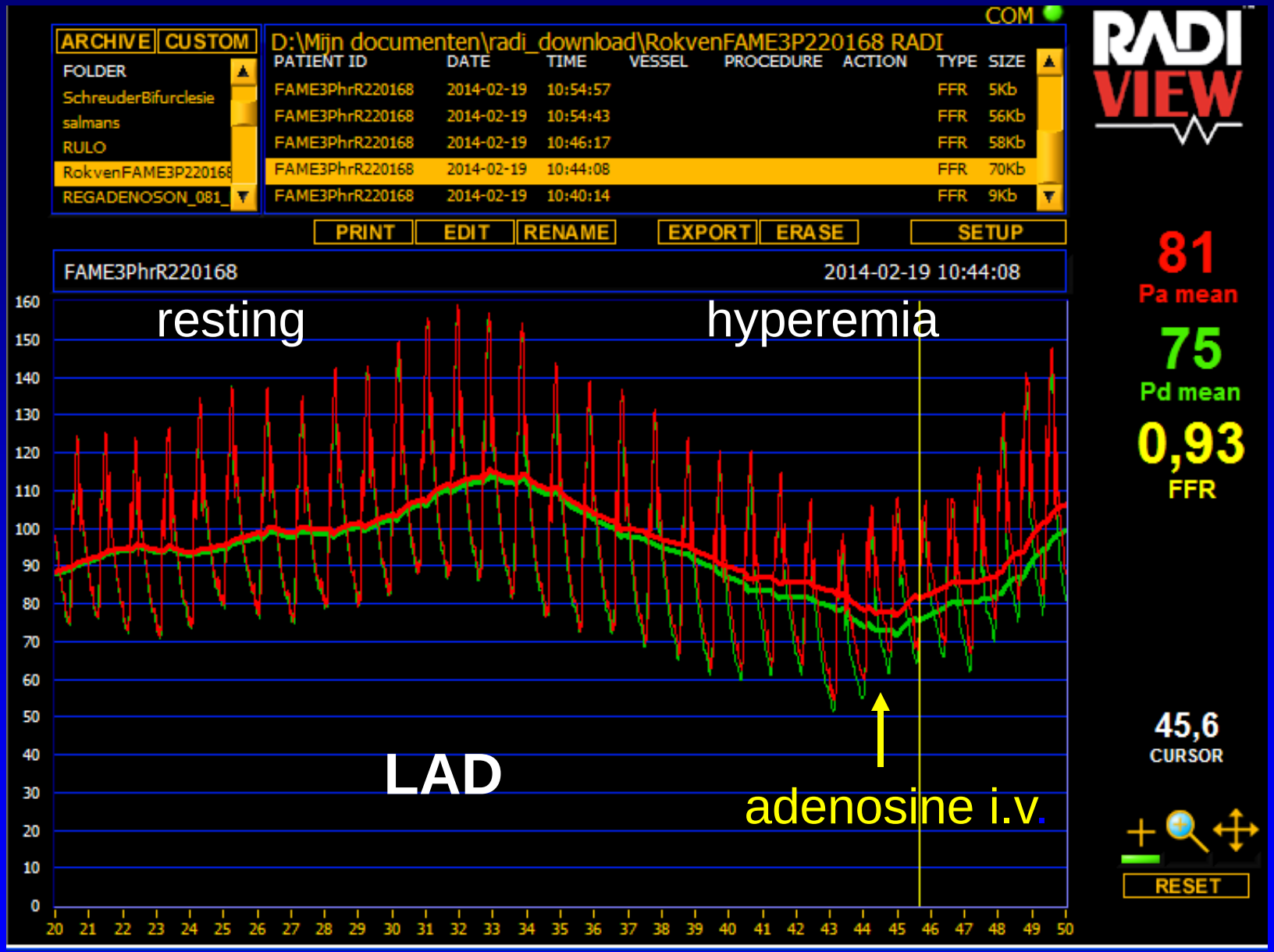
PATIENT ID DATE TIME VESSEL PROCEDURE ACTION TYPE SIZE
FAME3PhrR220168 2014-02-19 10:54:57 FFR 5Kb
FAME3PhrR220168 2014-02-19 10:54:43 FFR 56Kb
FAME3PhrR220168 2014-02-19 10:46:17 FFR 58Kb
FAME3PhrR220168 2014-02-19 10:44:08 FFR 70Kb
FAME3PhrR220168 2014-02-19 10:40:14 FFR 9Kb
PRINT
EDIT
RENAME
EXPORT
ERASE
SETUP
FAME3PhrR220168
2014-02-19 10:40:14
RADI VIEW
85
Pa mean
85
Pd mean
1,00
FFR
0,3
CURSOR
RESET
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
equalization before entering LCA



PressureWire in LAD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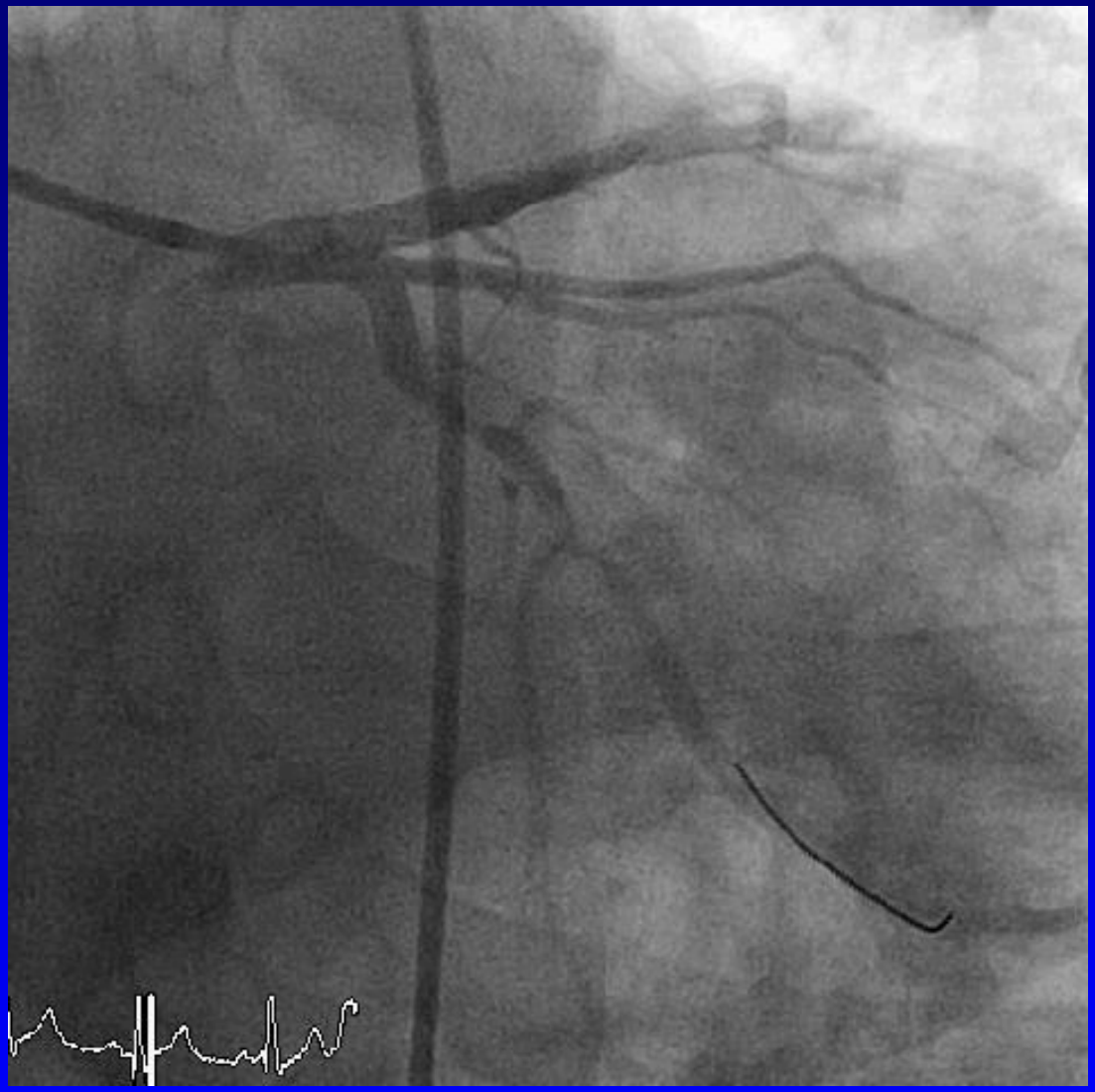
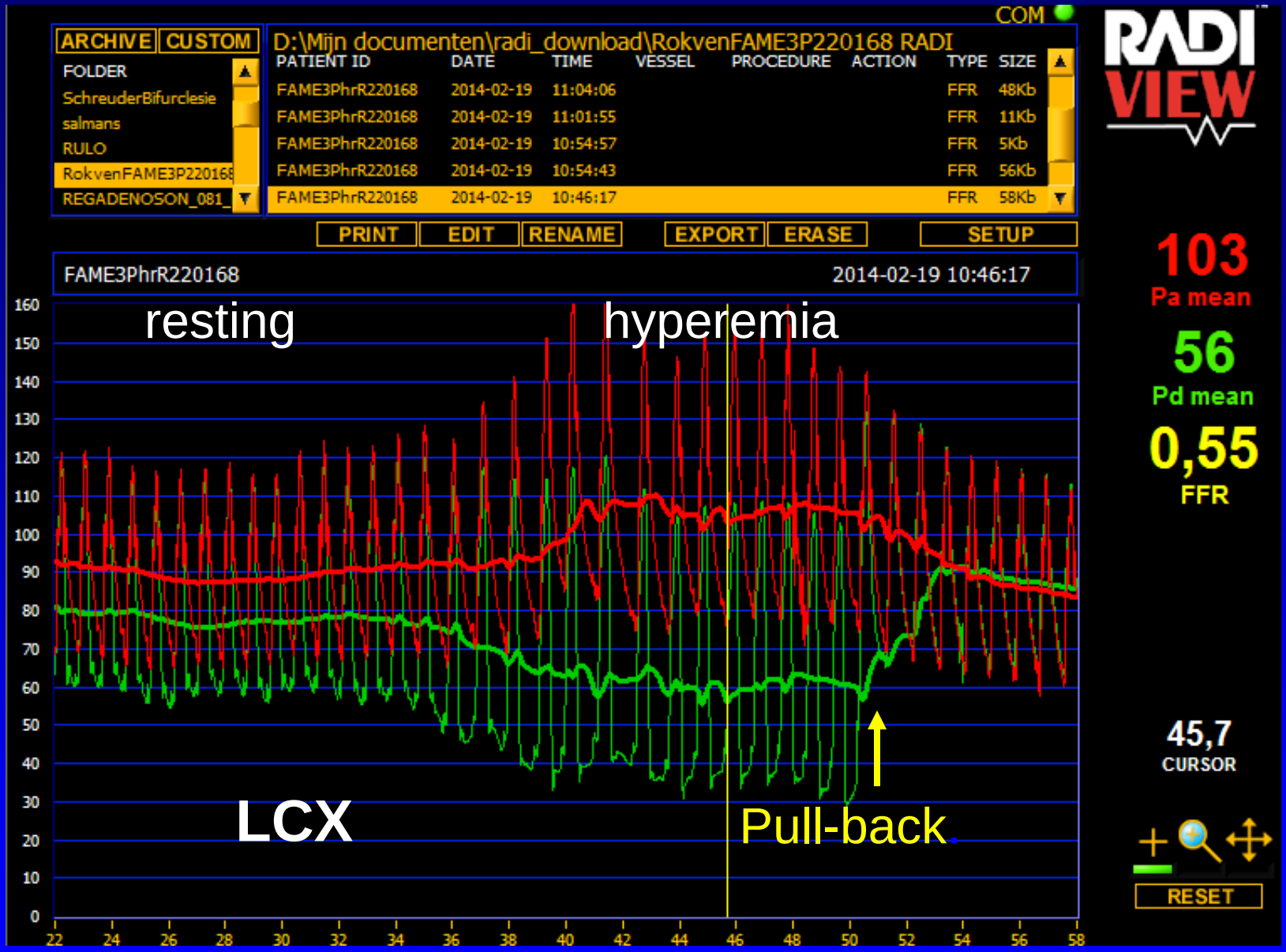
FAME3PhrR220168 2014-02-19 10:54:43 FFR 56Kb
FAME3PhrR220168 2014-02-19 10:46:17 FFR 58Kb
FAME3PhrR220168 2014-02-19 10:44:08 FFR 70Kb
FAME3PhrR220168 2014-02-19 10:40:14 FFR 9Kb
PRINT
EDIT
RENAME
EXPORT
ERASE
SETUP
RADI VIEW
FAME3PhrR220168
2014-02-19 10:44:08
resting
hyperemia
LAD
adenosine i.v.
81
Pa mean
75
Pd mean
0,93
FFR
45,6
CURSOR
RESET
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50



PressureWire in LCX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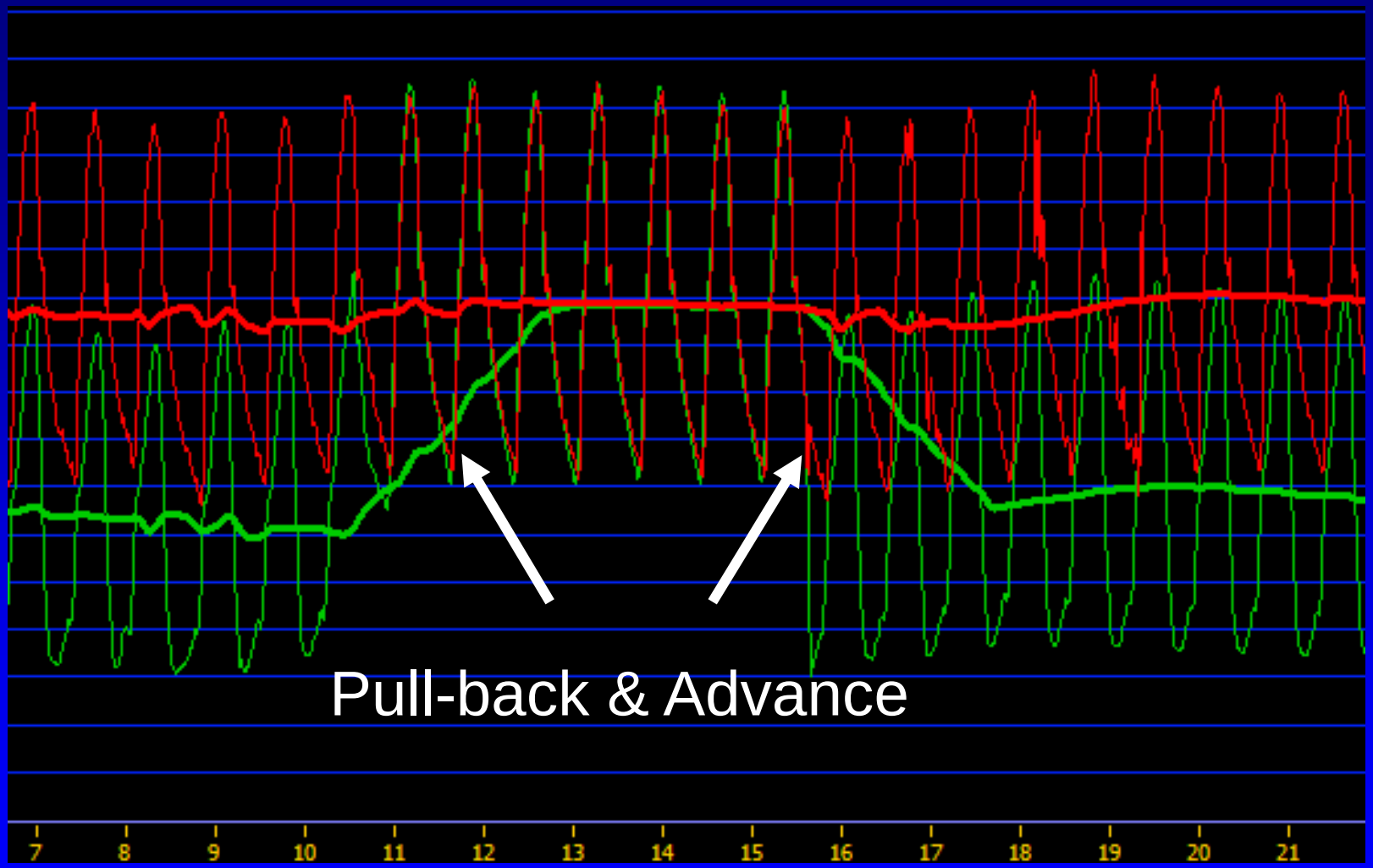
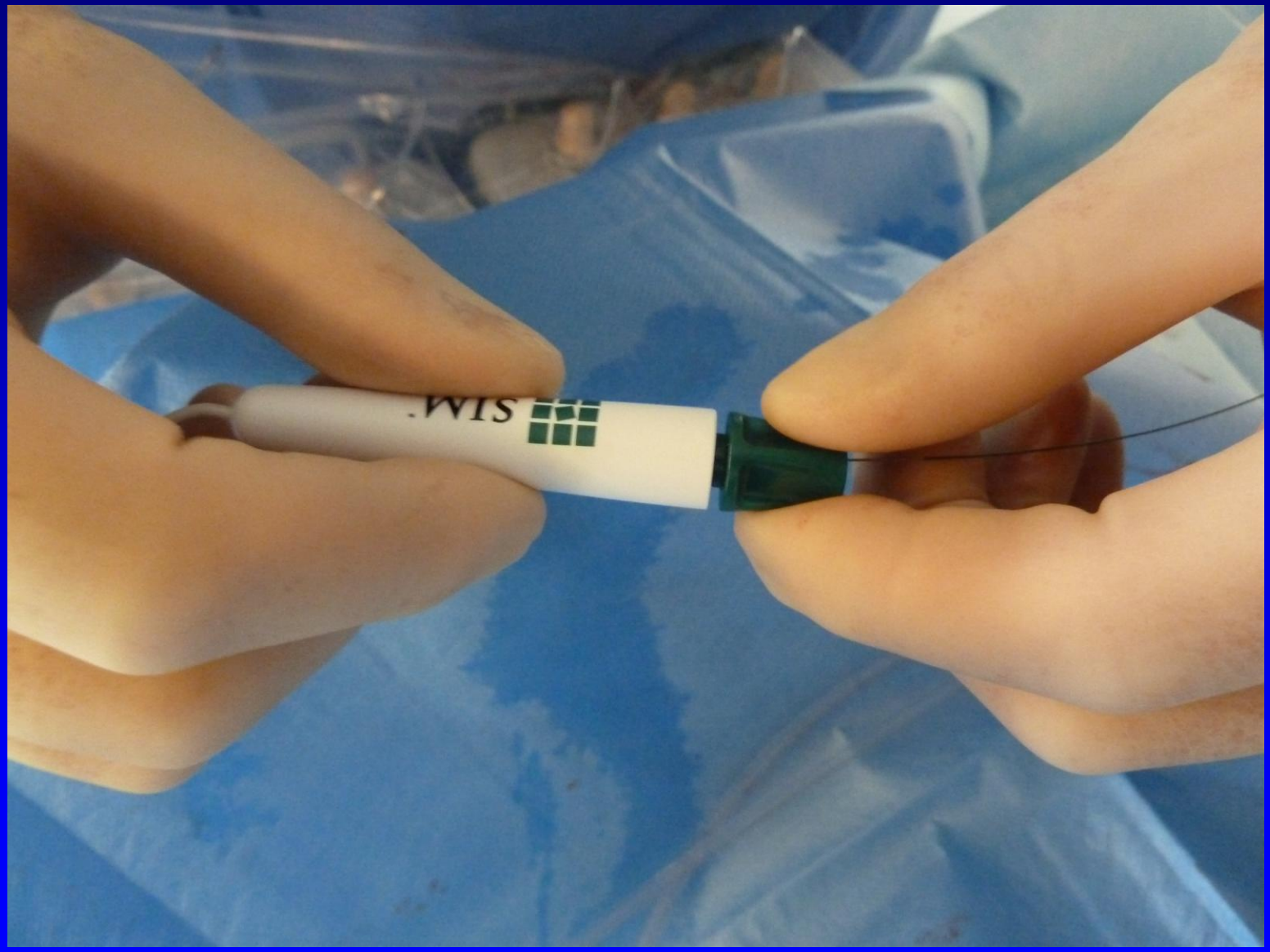
PATIENT ID DATE TIME VESSEL PROCEDURE ACTION TYPE SIZE
FAME3PhrR220168 2014-02-19 11:04:06 FFR 48Kb
FAME3PhrR220168 2014-02-19 11:01:55 FFR 11Kb
FAME3PhrR220168 2014-02-19 10:54:57 FFR 5Kb
FAME3PhrR220168 2014-02-19 10:54:43 FFR 56Kb
FAME3PhrR220168 2014-02-19 10:46:17 FFR 58Kb
PRINT
EDIT
RENAME
EXPORT
ERASE
SETUP
RADI VIEW
FAME3PhrR220168
2014-02-19 10:46:17
resting
hyperemia
LCX
Pull-back
103
Pa mean
56
Pd mean
0,55
FFR
45,7
CURSOR
RESET

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

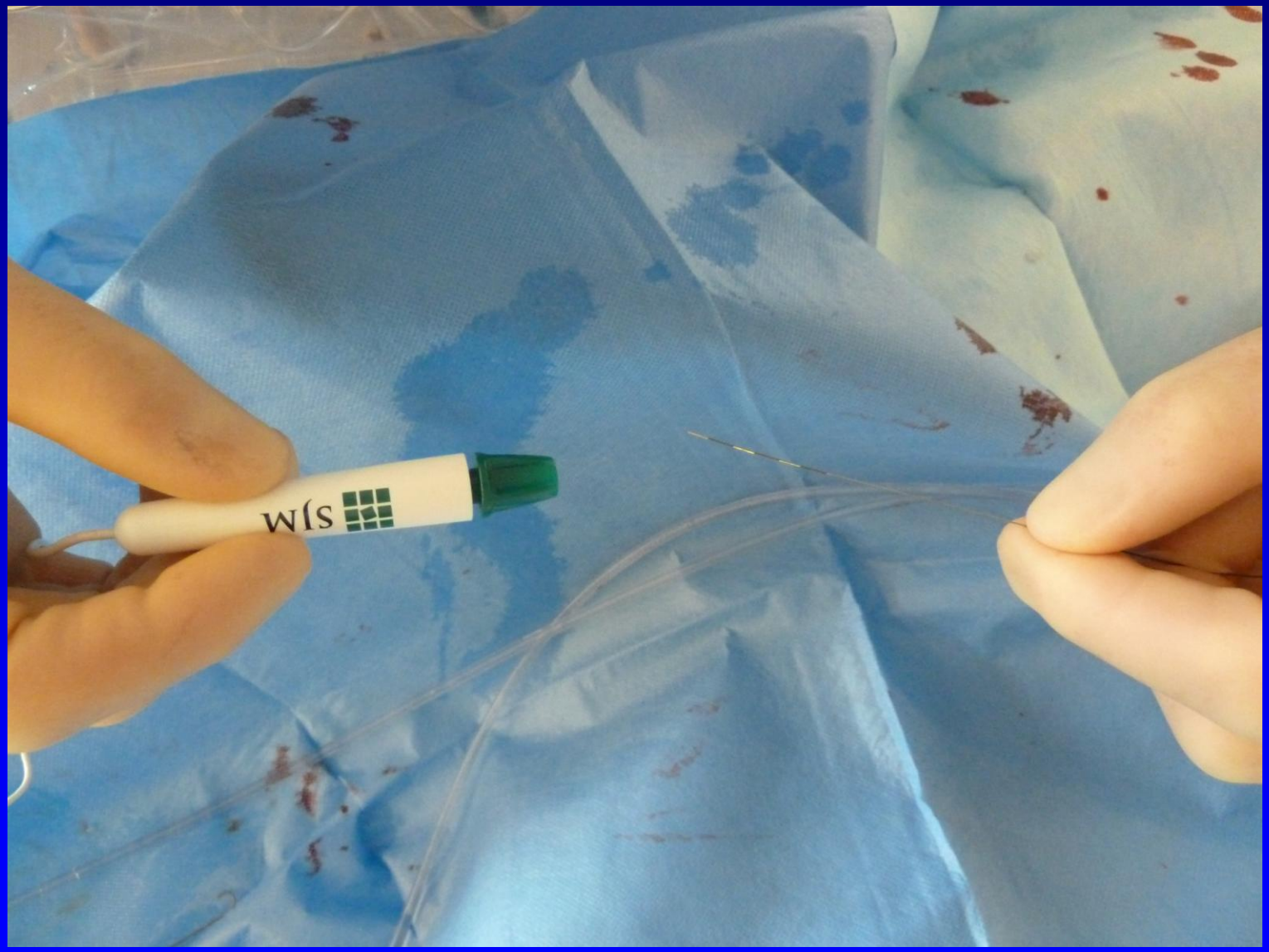


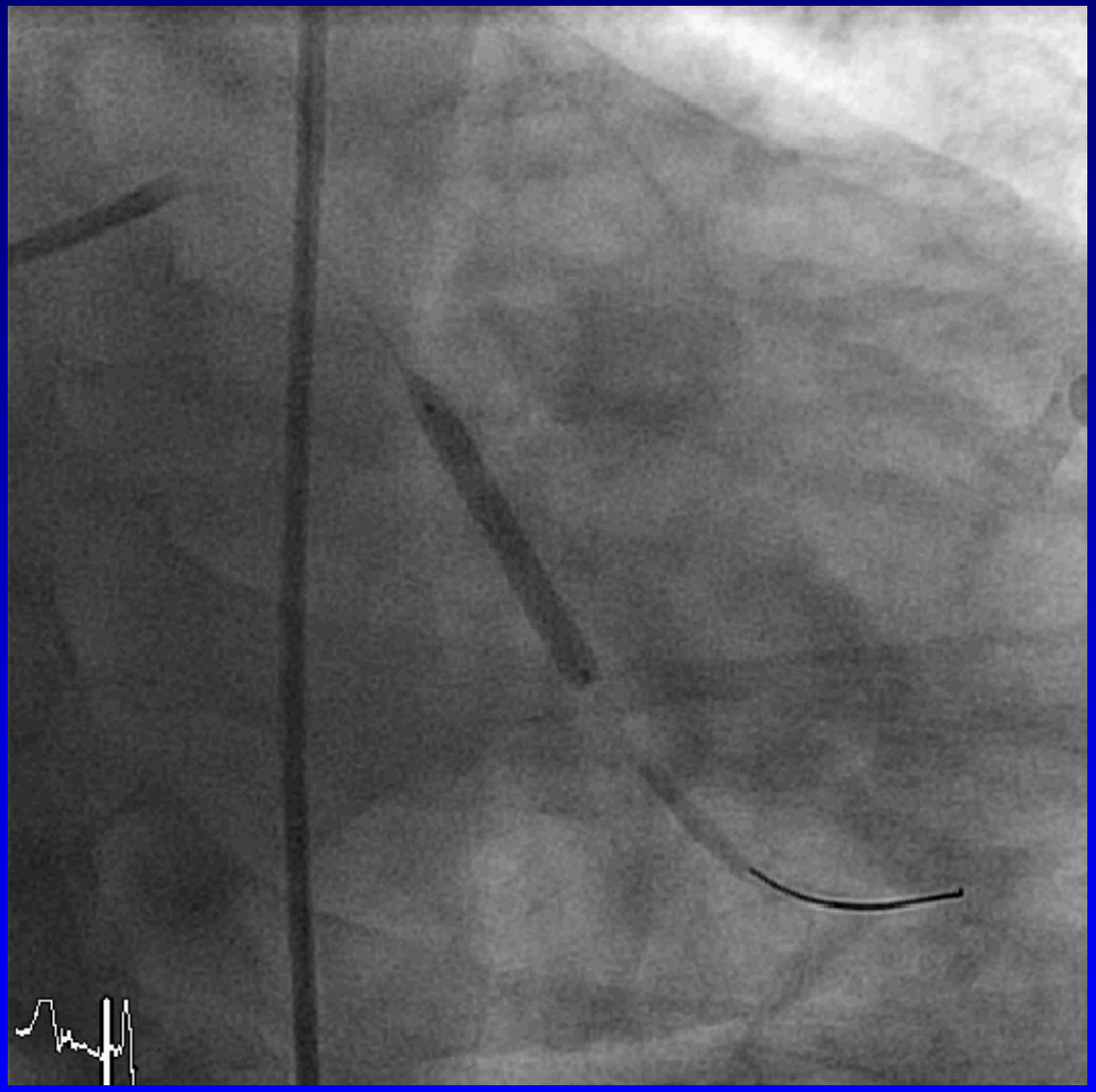
Pull-back recording for detailed spatial information about distribution of lesions along the complete artery

If you need to treat, disconnect pressure wire

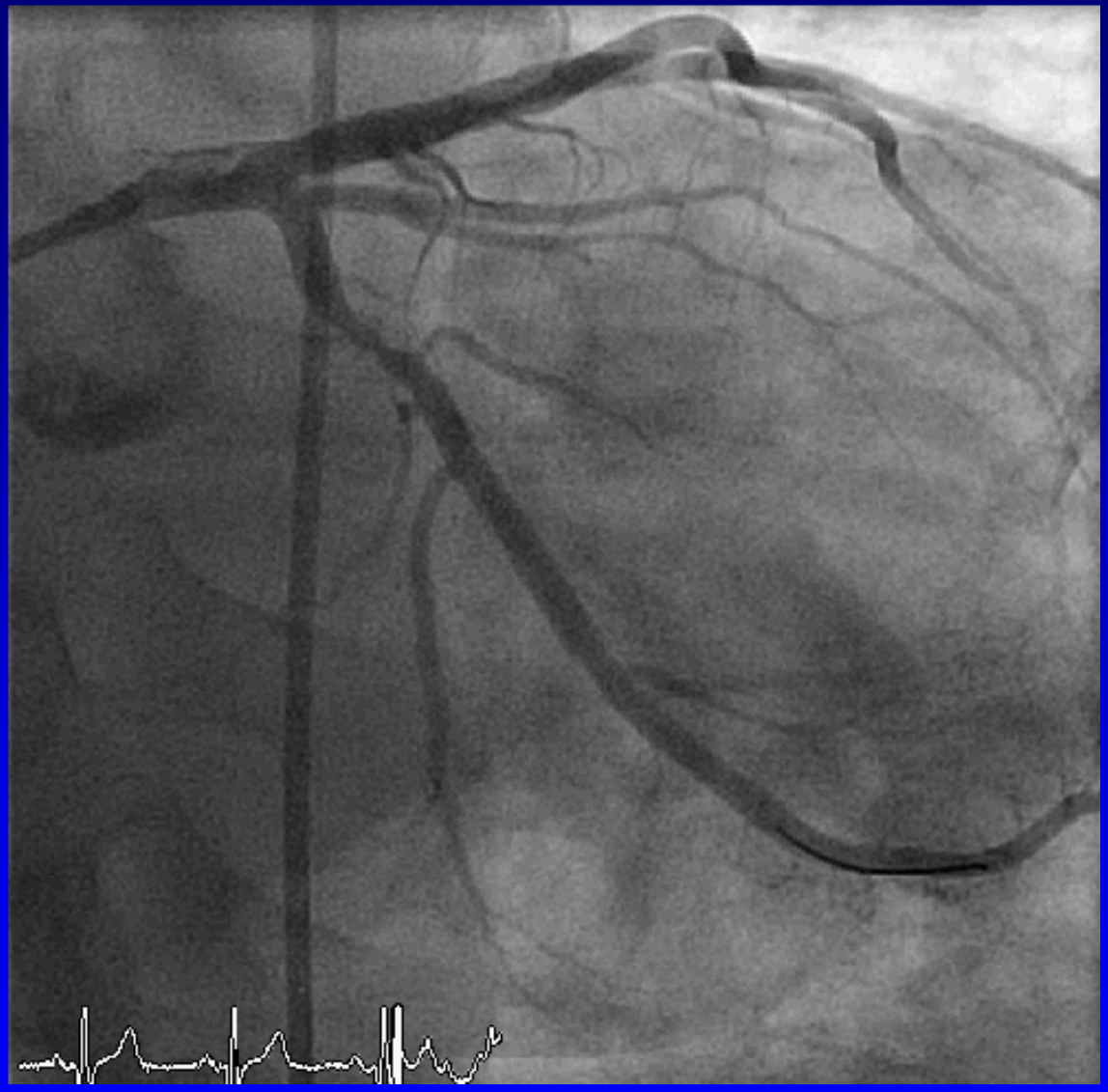


disconnecting the pressure wire…….

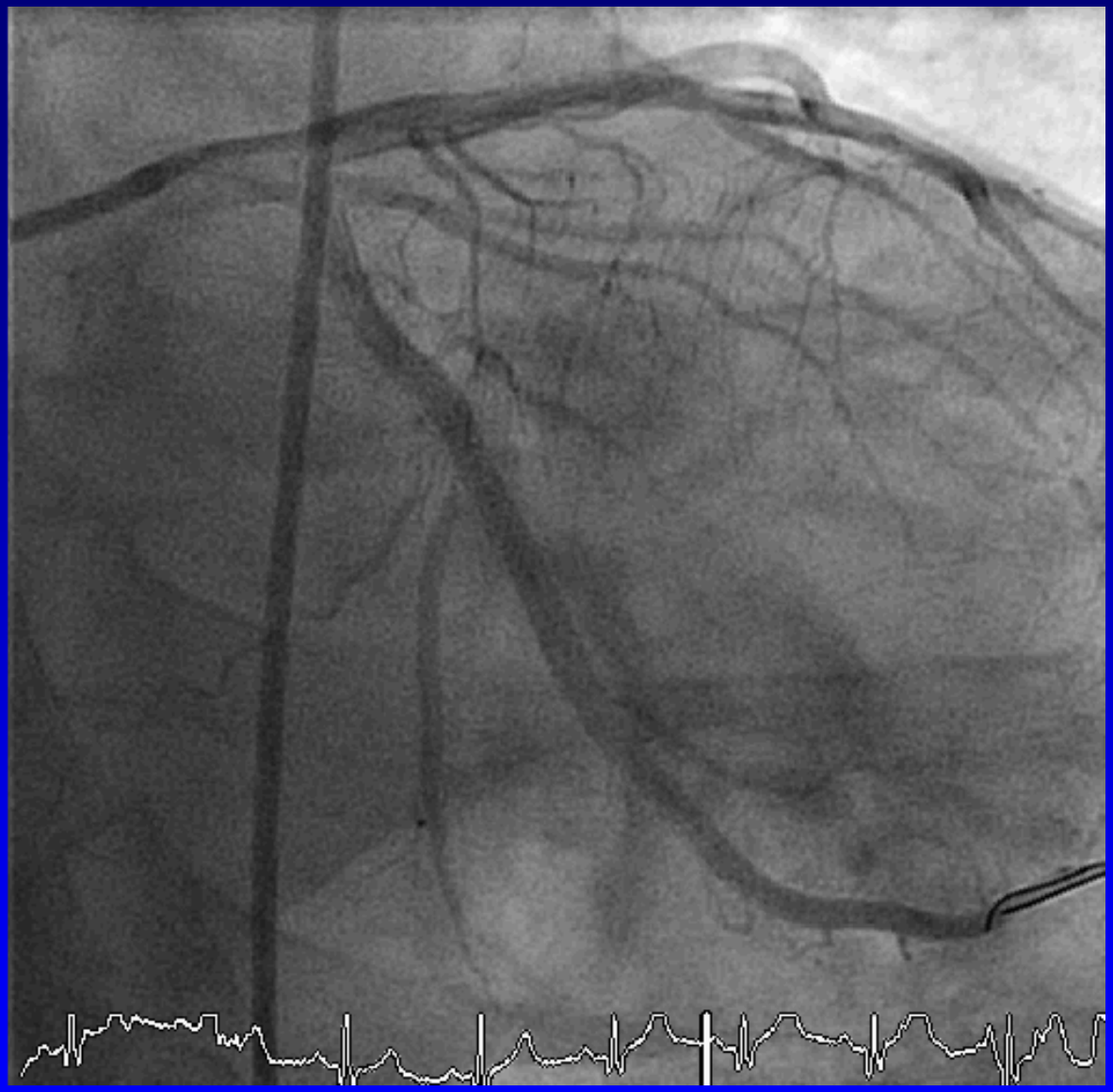




first stent in LCX (3.0x22)

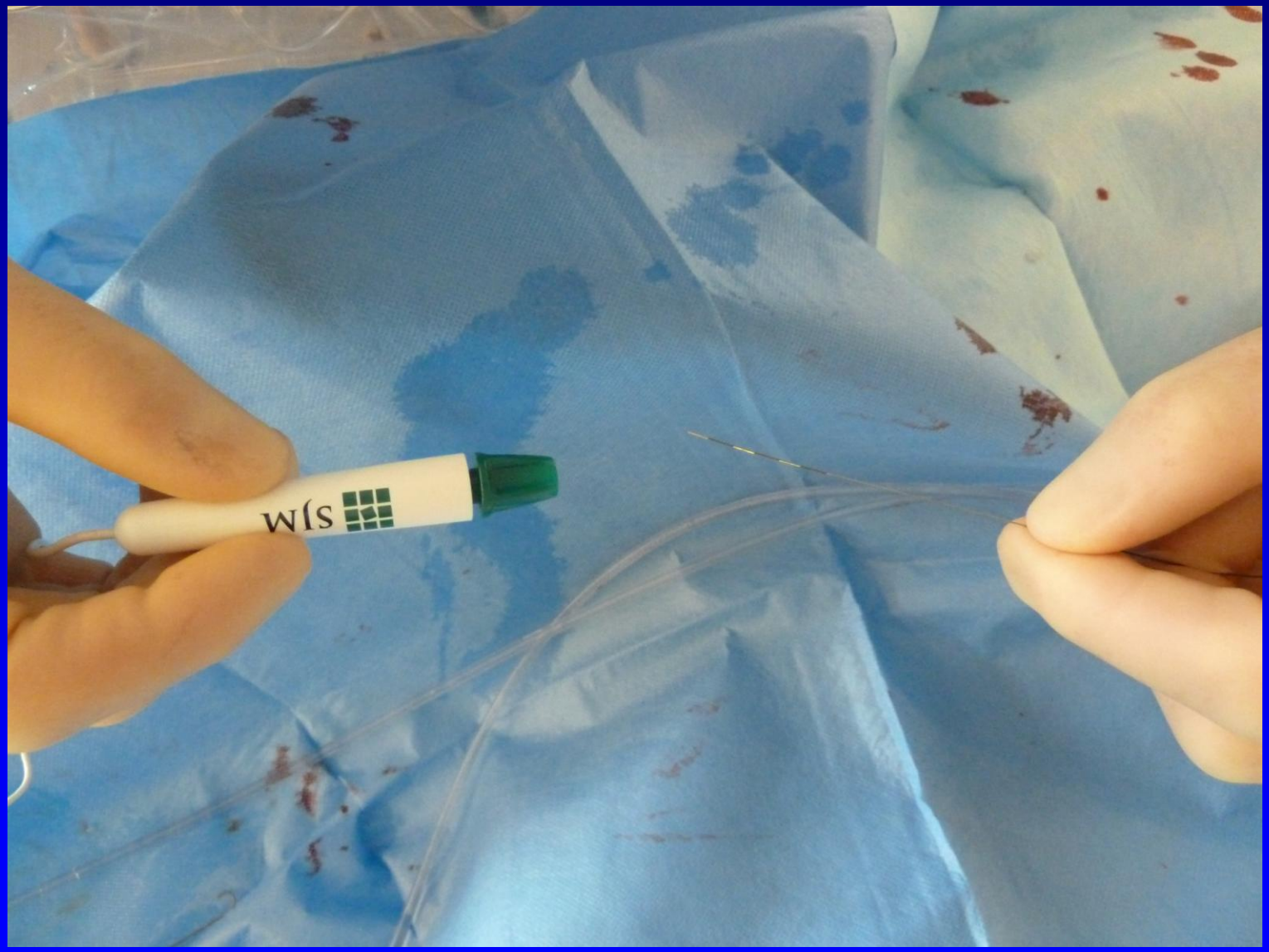


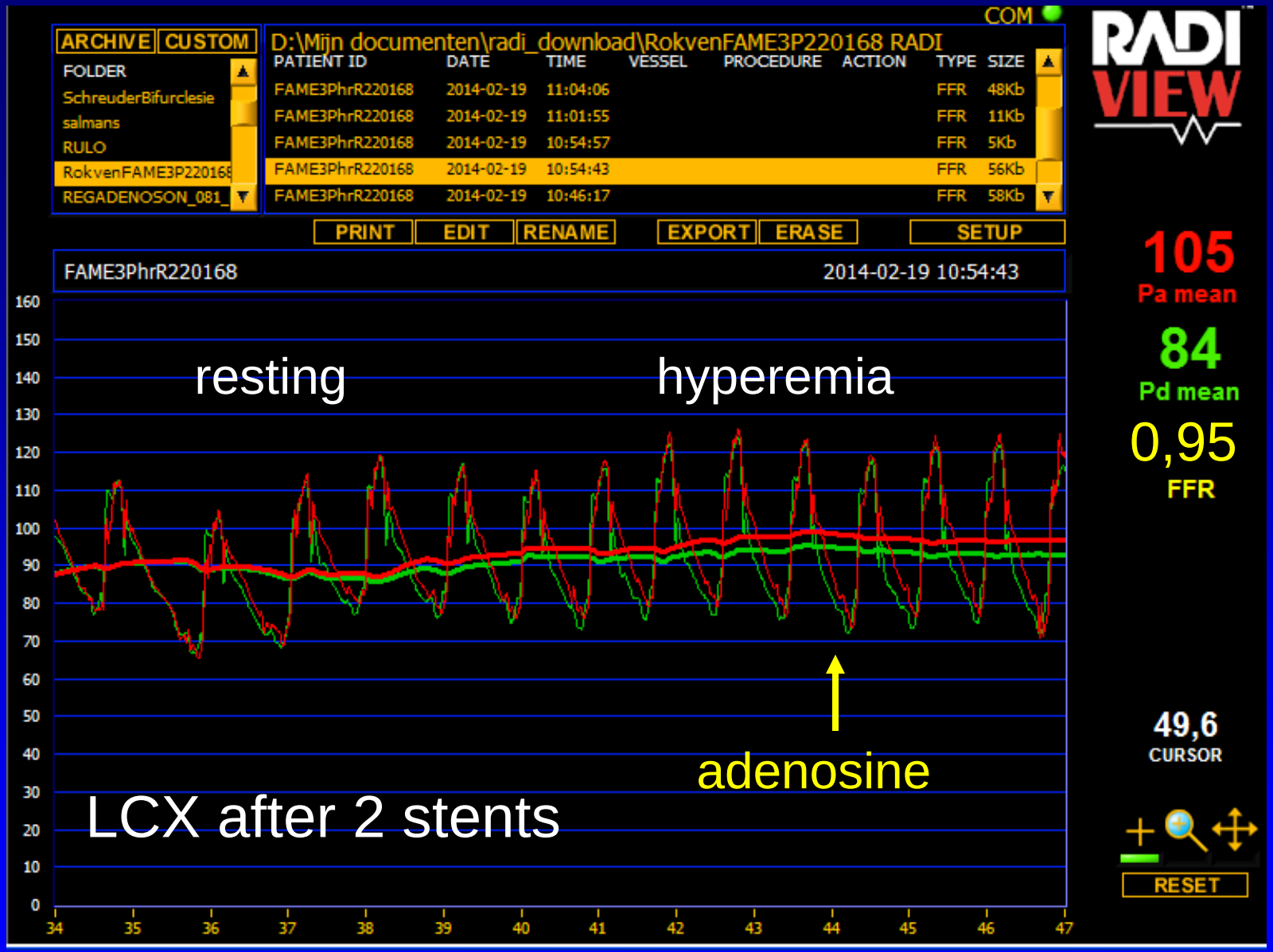
LCX after first stent



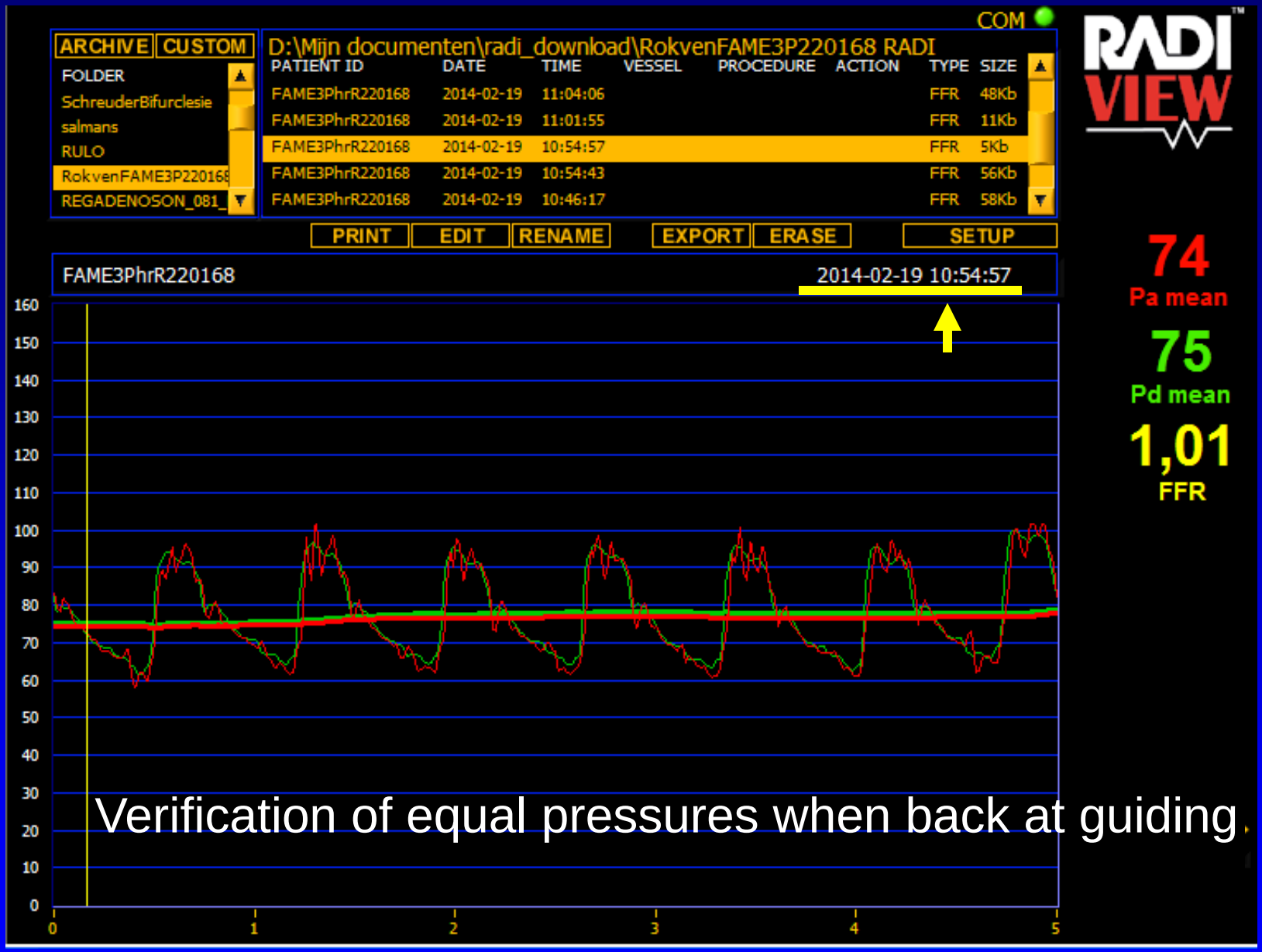
LCX after second stent

For post-stent FFR → simply connect the pressure wire

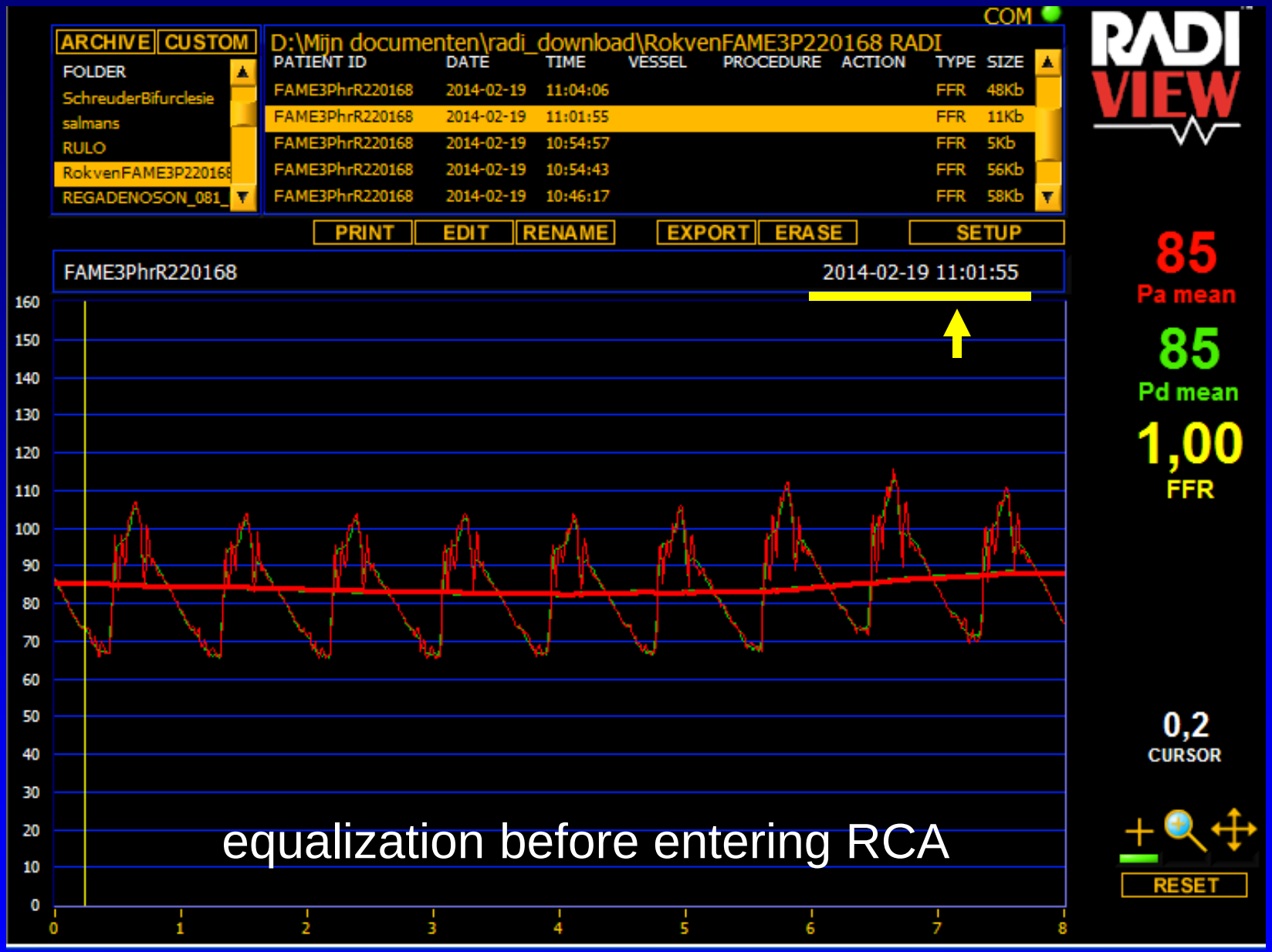




Post-stent FFR measurement to evaluate result



Verification of equal pressures when back at guiding.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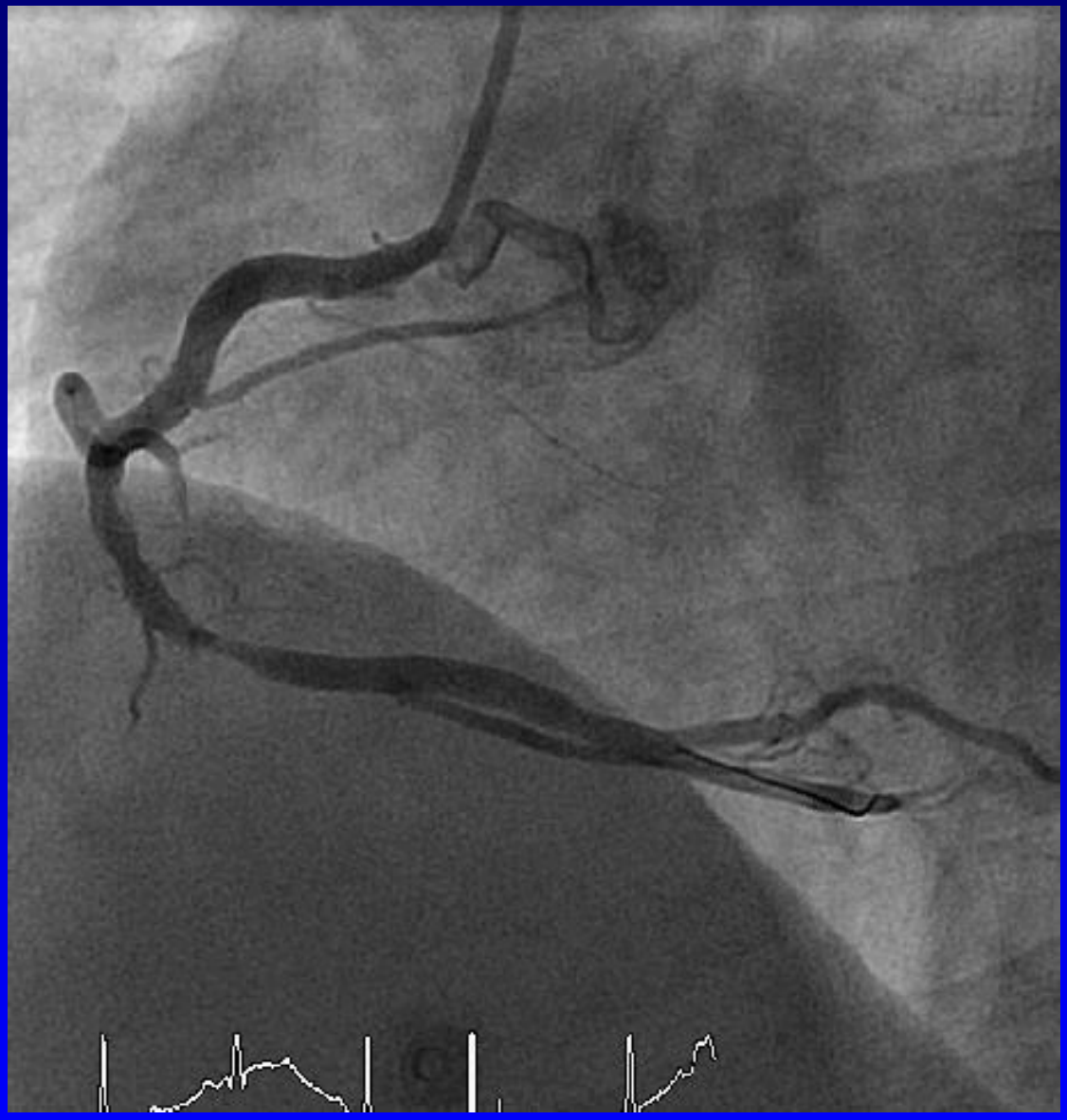
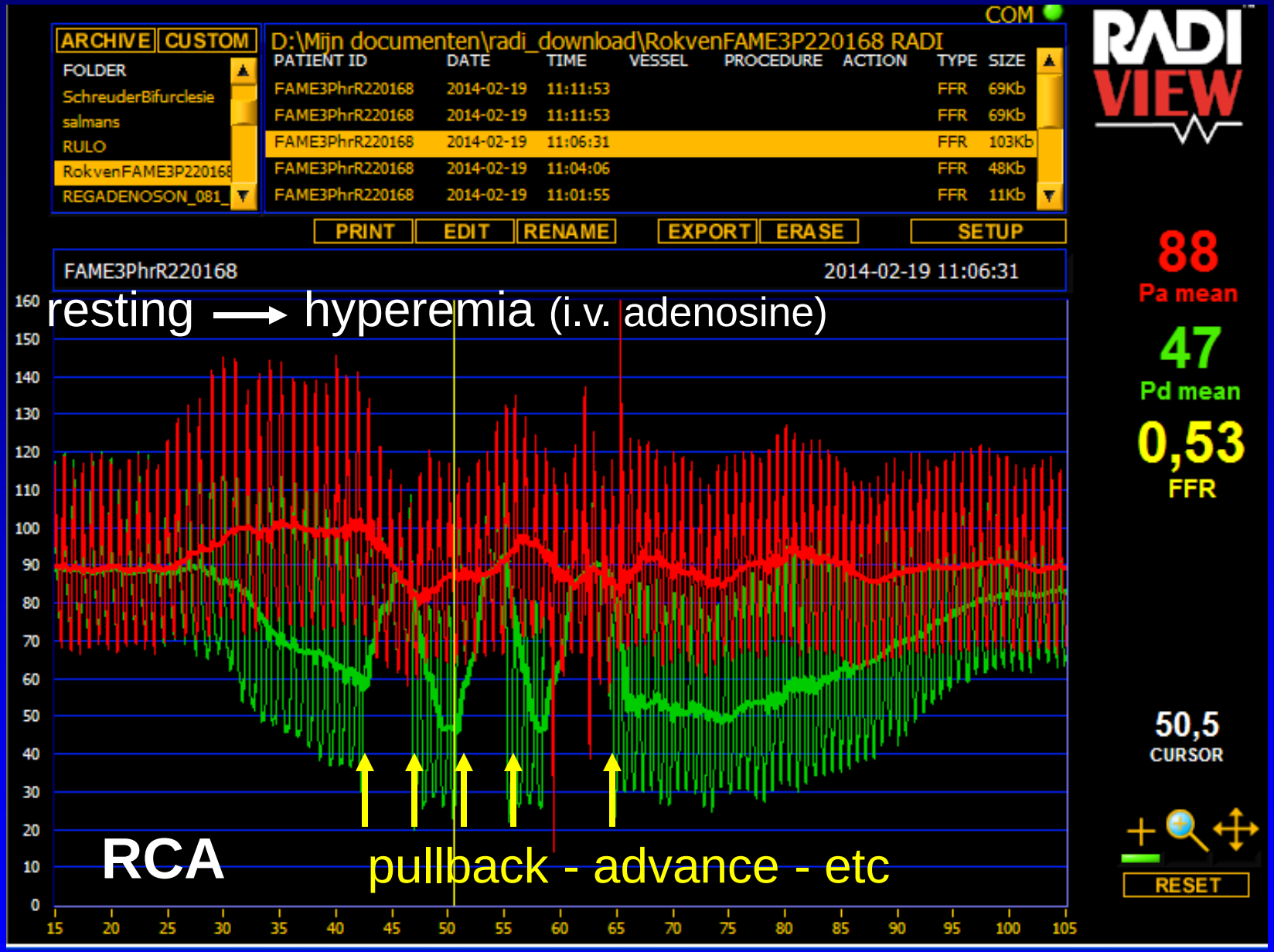
PATIENT ID DATE TIME VESSEL PROCEDURE ACTION TYPE SIZE
FAME3PhrR220168 2014-02-19 11:04:06 FFR 48Kb
FAME3PhrR220168 2014-02-19 11:01:55 FFR 11Kb
FAME3PhrR220168 2014-02-19 10:54:57 FFR 5Kb
FAME3PhrR220168 2014-02-19 10:54:43 FFR 56Kb
FAME3PhrR220168 2014-02-19 10:46:17 FFR 58Kb
PRINT
EDIT
RENAME
EXPORT
ERASE
SETUP
FAME3PhrR220168
2014-02-19 11:01:55
RADI VIEW
85
Pa mean
85
Pd mean
1,00
FFR
0,2
CURSOR
RESET
equalization before entering RCA



PressureWire in RCA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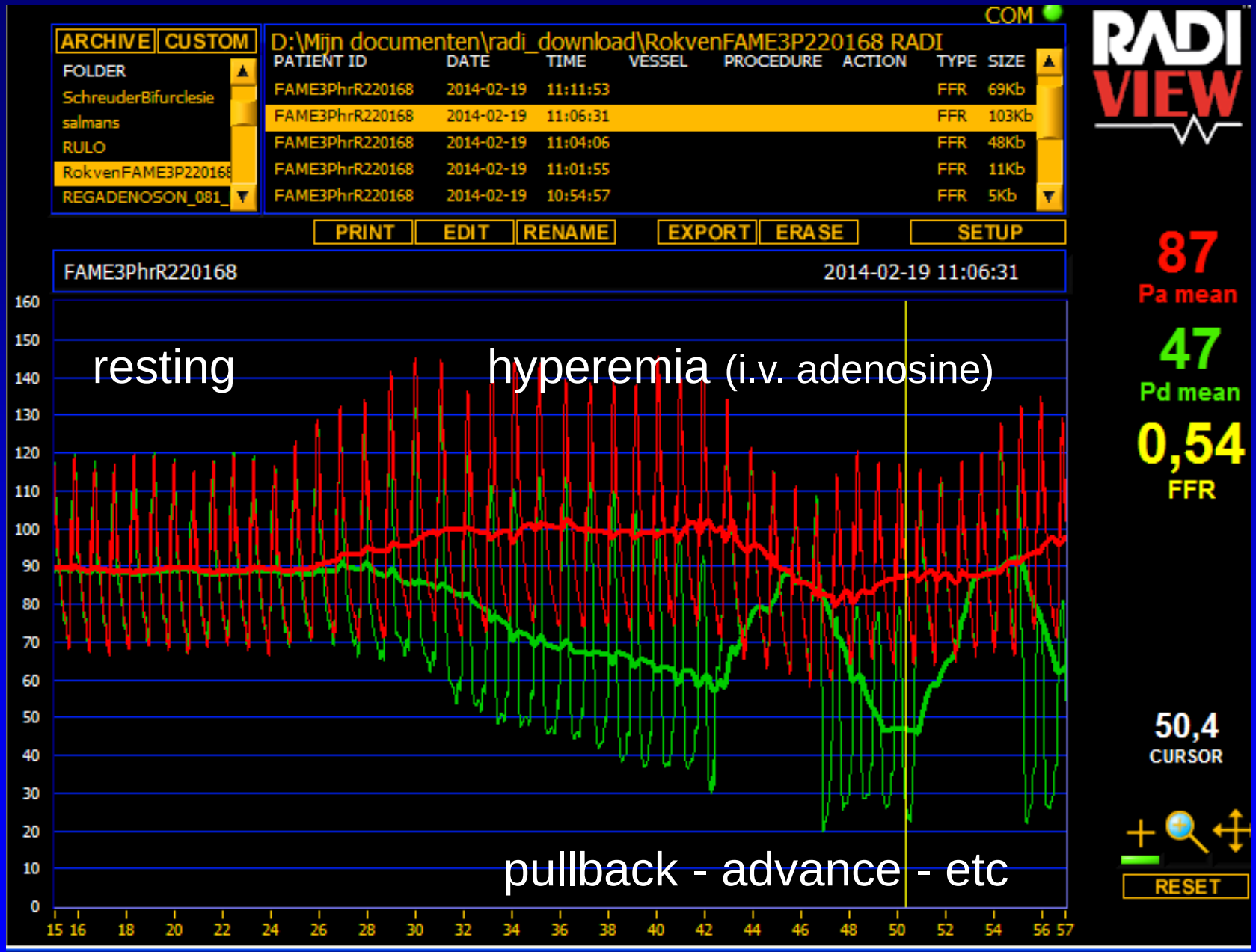
PATIENT ID DATE TIME VESSEL PROCEDURE ACTION TYPE SIZE
FAME3PhrR220168 2014-02-19 11:11:53 FFR 69Kb
FAME3PhrR220168 2014-02-19 11:11:53 FFR 69Kb
FAME3PhrR220168 2014-02-19 11:06:31 FFR 103Kb
FAME3PhrR220168 2014-02-19 11:04:06 FFR 48Kb
FAME3PhrR220168 2014-02-19 11:01:55 FFR 11Kb
PRINT
EDIT
RENAME
EXPORT
ERASE
SETUP
FAME3PhrR220168
2014-02-19 11:06:31
resting ⟶ hyperemia (i.v. adenosine)
RADI VIEW
88
Pa mean
47
Pd mean
0,53
FFR
50,5
CURSOR
RESET
RCA
pullback - advance - etc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FAME3PhrR220168 2014-02-19 11:06:31 FFR 103Kb
FAME3PhrR220168 2014-02-19 11:04:06 FFR 48Kb
FAME3PhrR220168 2014-02-19 11:01:55 FFR 11Kb
FAME3PhrR220168 2014-02-19 10:54:57 FFR 5Kb
PRINT
EDIT
RENAME
EXPORT
ERASE
SETUP
FAME3PhrR220168
2014-02-19 11:06:31
RADI VIEW
87
Pa mean
47
Pd mean
0,54
FFR
50,4
CURSOR
RESET
resting
hyperemia (i.v. adenosine)
pullback - advance - etc
160
150
140
130
120
110
100
90
80
70
60
50
40
30
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10
0
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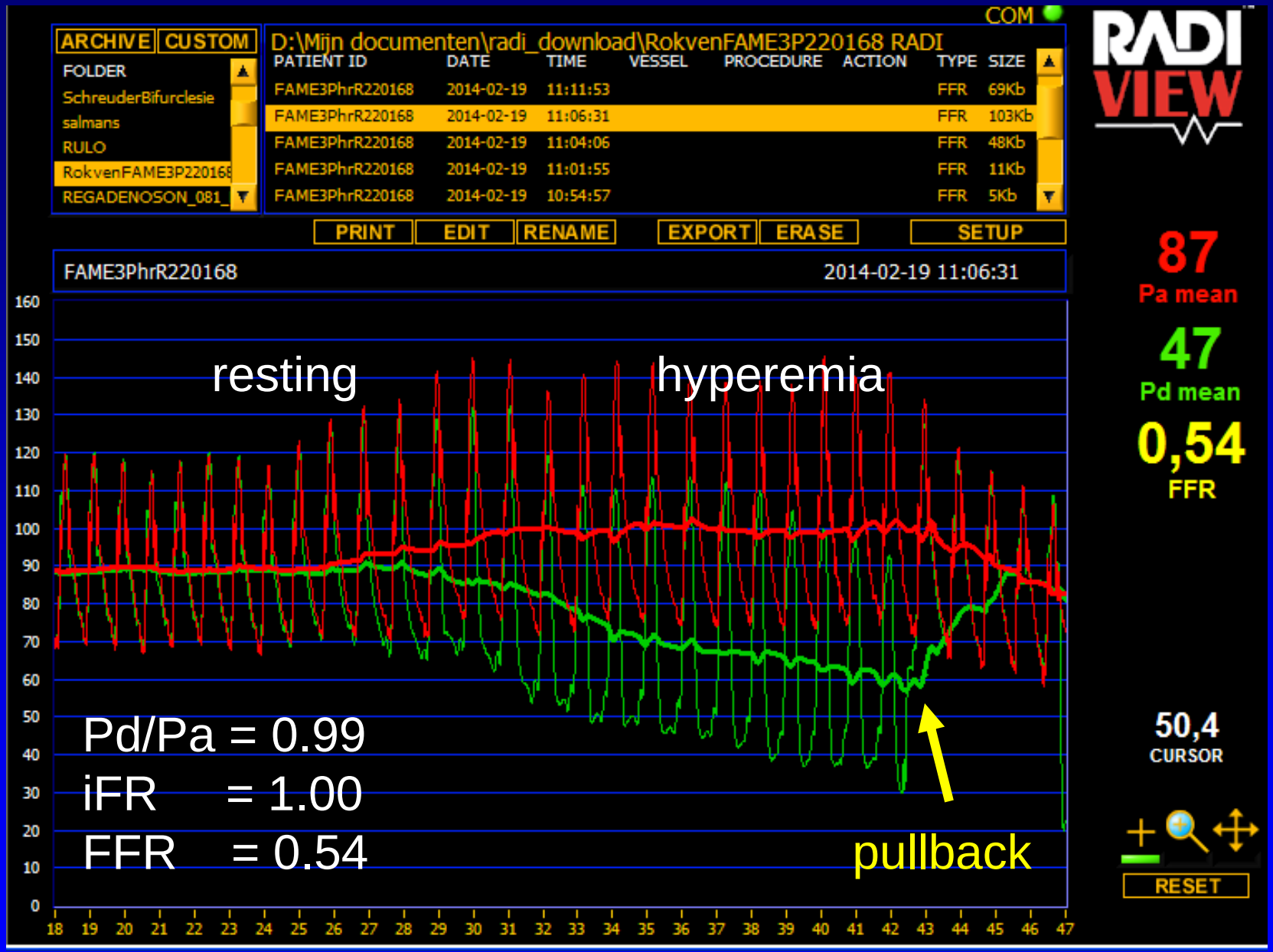
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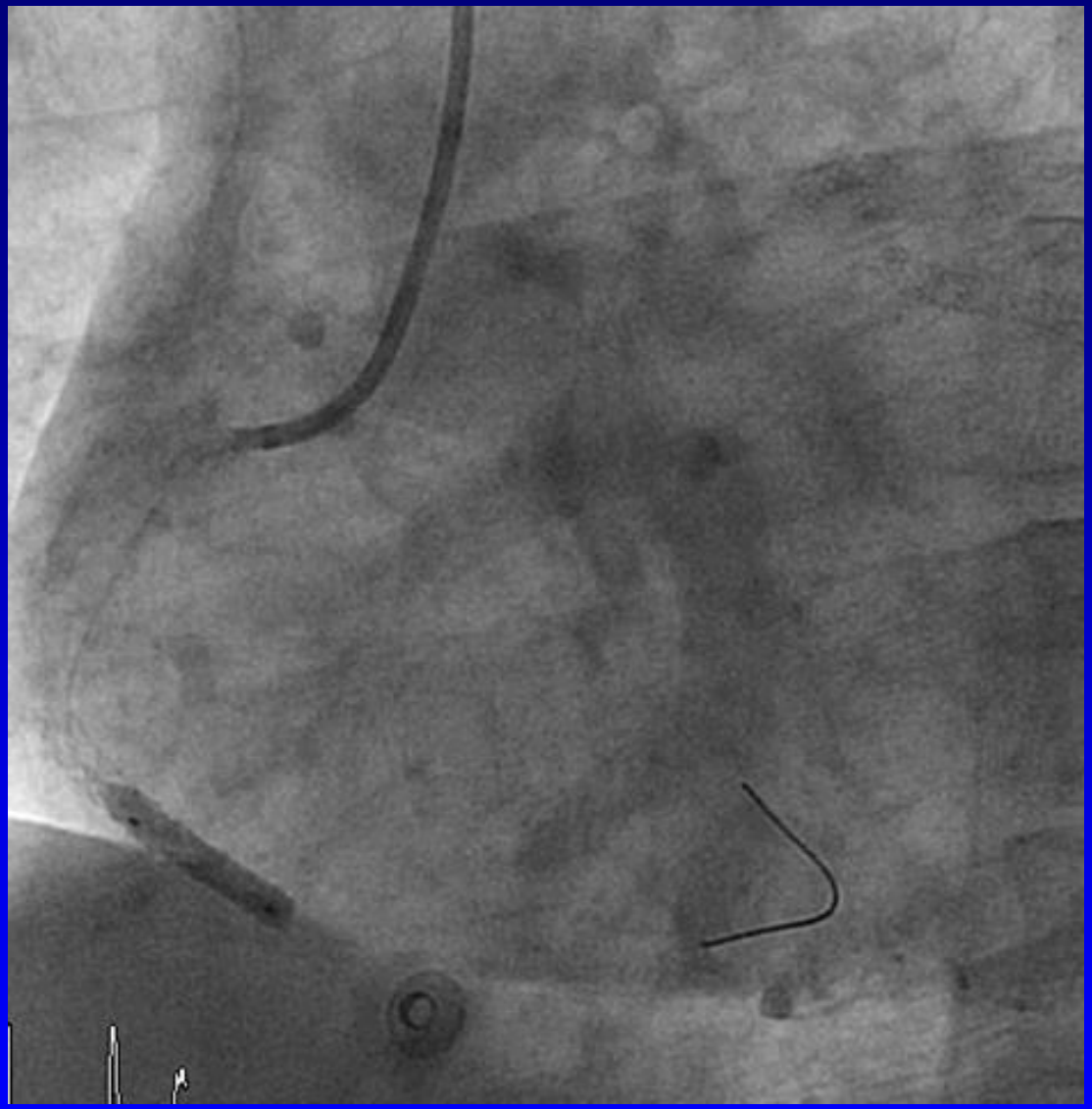
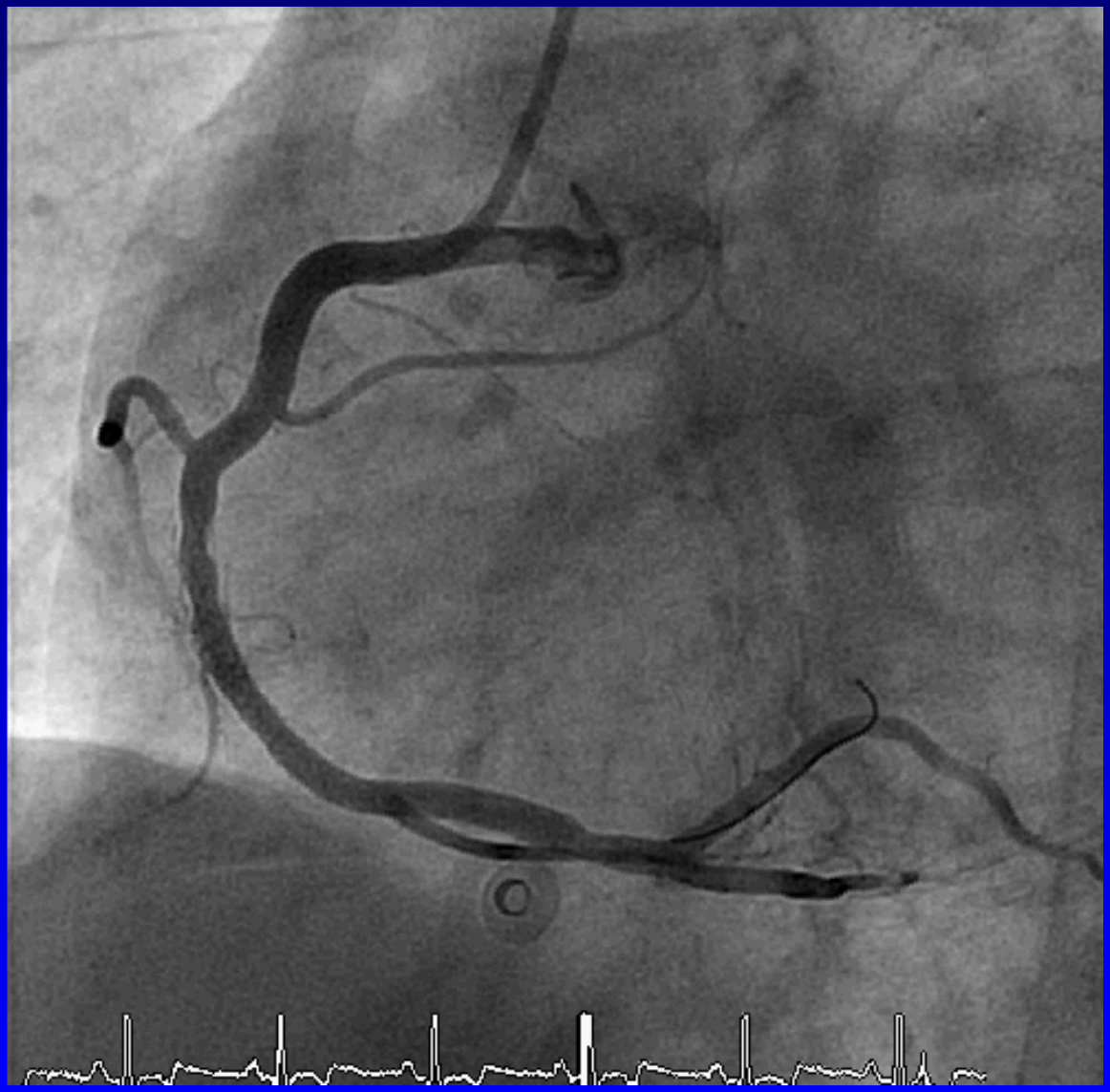
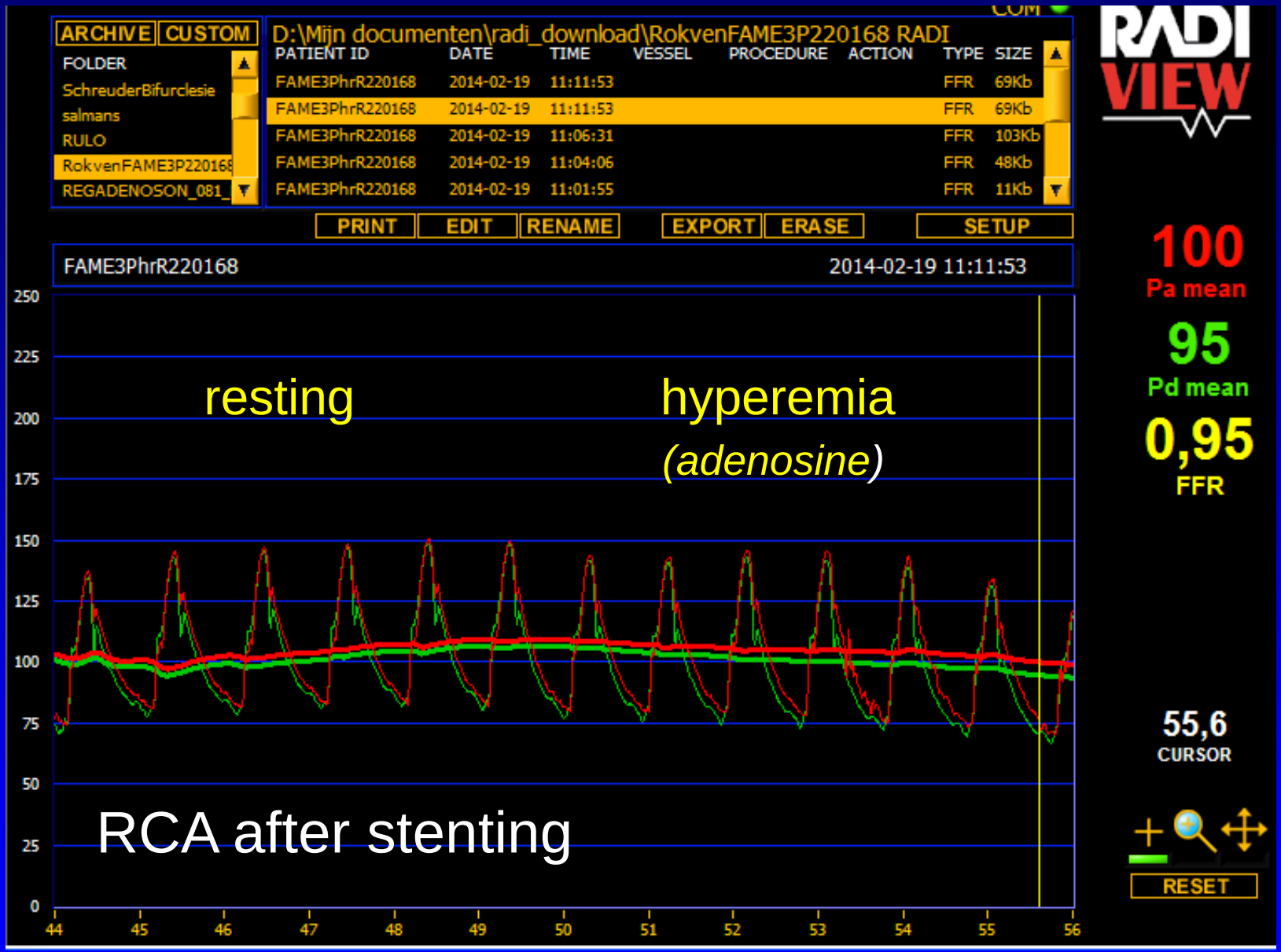
FAME3PhrR220168 2014-02-19 11:06:31 FFR 103Kb
FAME3PhrR220168 2014-02-19 11:04:06 FFR 48Kb
FAME3PhrR220168 2014-02-19 11:01:55 FFR 11Kb
FAME3PhrR220168 2014-02-19 10:54:57 FFR 5Kb
PRINT
EDIT
RENAME
EXPORT
ERASE
SETUP
RADI VIEW
FAME3PhrR220168
2014-02-19 11:06:31
resting
hyperemia
Pd/Pa = 0.99
iFR = 1.00
FFR = 0.54
pullback
87
Pa mean
47
Pd mean
0,54
FFR
50,4
CURSOR
RESET
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47



Stent in RCA (3,5x 18)



RCA after stenting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PATIENT ID DATE TIME VESSEL PROCEDURE ACTION TYPE SIZE
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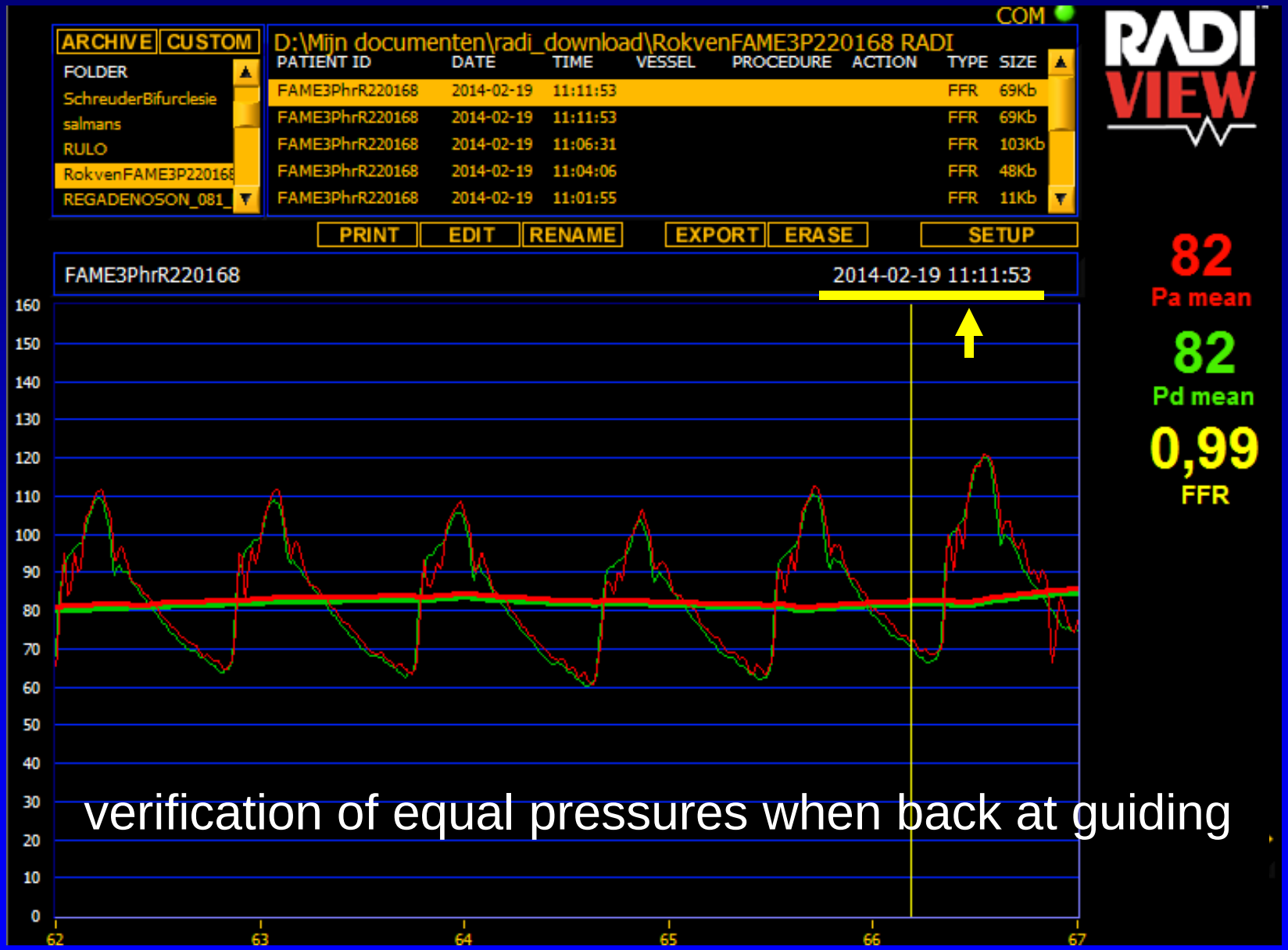
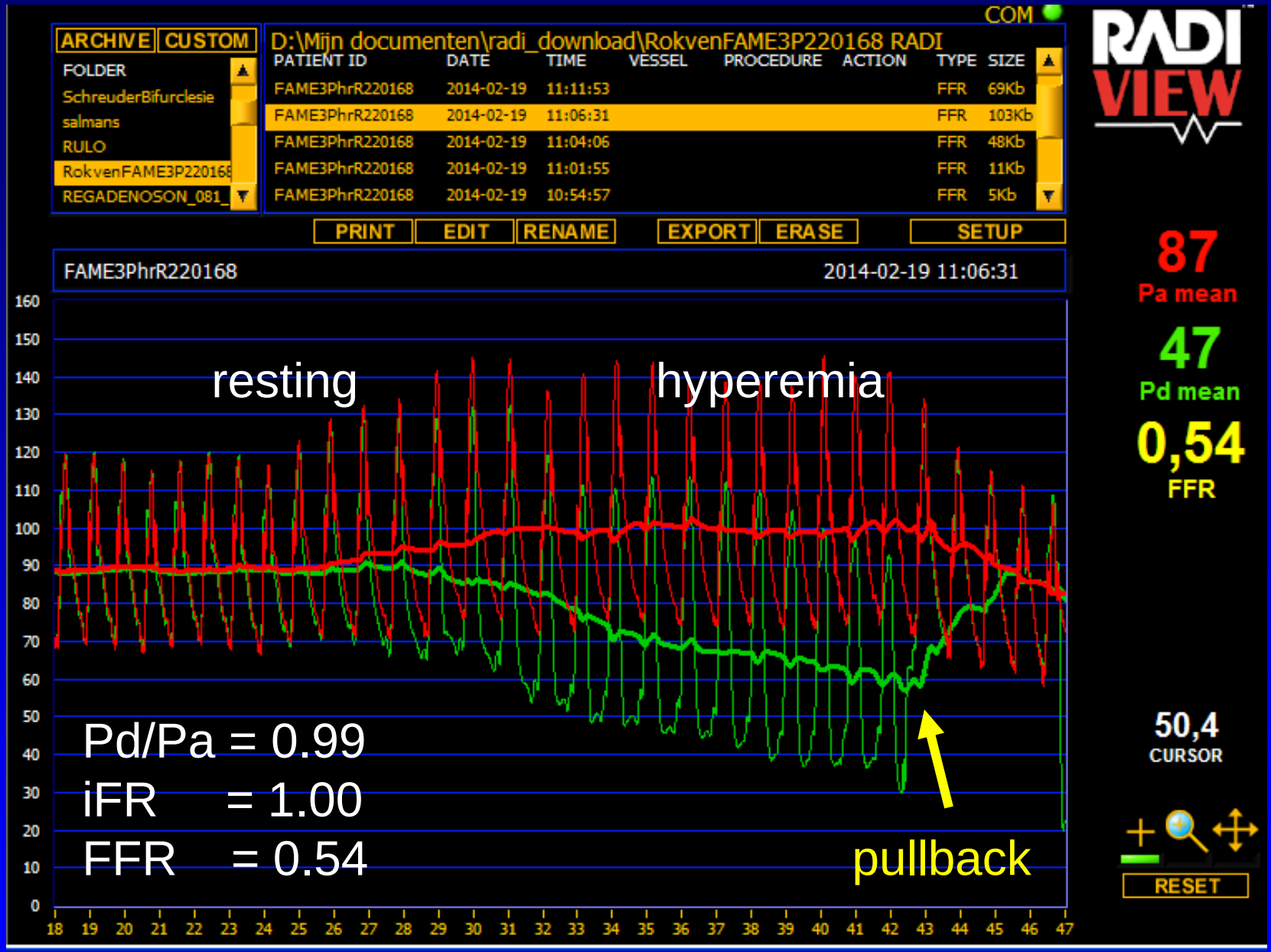
FAME3PhrR220168 2014-02-19 11:11:53 FFR 69Kb
FAME3PhrR220168 2014-02-19 11:06:31 FFR 103Kb
FAME3PhrR220168 2014-02-19 11:04:06 FFR 48Kb
FAME3PhrR220168 2014-02-19 11:01:55 FFR 11Kb
PRINT
EDIT
RENAME
EXPORT
ERASE
SETUP
FAME3PhrR220168
2014-02-19 11:11:53
resting
hyperemia
(adenosine)
RCA after stenting
RADI VIEW
100
Pa mean
95
Pd mean
0,95
FFR
55,6
CURSOR
RESET



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 → *saturday morning session*

In many complex angiographic conditions, FFR can be assessed as regular:

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

} *tomorrow morning*

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

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**	**B**
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**

ESC-EACTS Guidlines for Myocardial Revascularisation, August 30, 2010

Starting – up FFR measurements in your Lab:

- study the principles and understand the concept
- be prepared to rely upon your brains, rather than on the angio: what you measure is more reliable than what you see
- involve your nurses/technicians/residents and convince your fellow staff members
- do not just an occasional patient with a mild stenosis once in a week, but use the PW consistently in 10 or 20 consecutive cases during 1 or 2 weeks

HOW TO START A FFR PROGRAM IN YOUR CATH-LAB

If you decide to measure FFR, ***do it always in the same way and be consistent in your decision:***

FFR > 0.80 ⟶ no stent indicated, medical treatment
FFR < 0.75 ⟶ stent, if technically feasible

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

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

“FFR never lies”

(key paper: Koolen, Cathet Cardiovasc Interv 2008: 72:248-256)

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

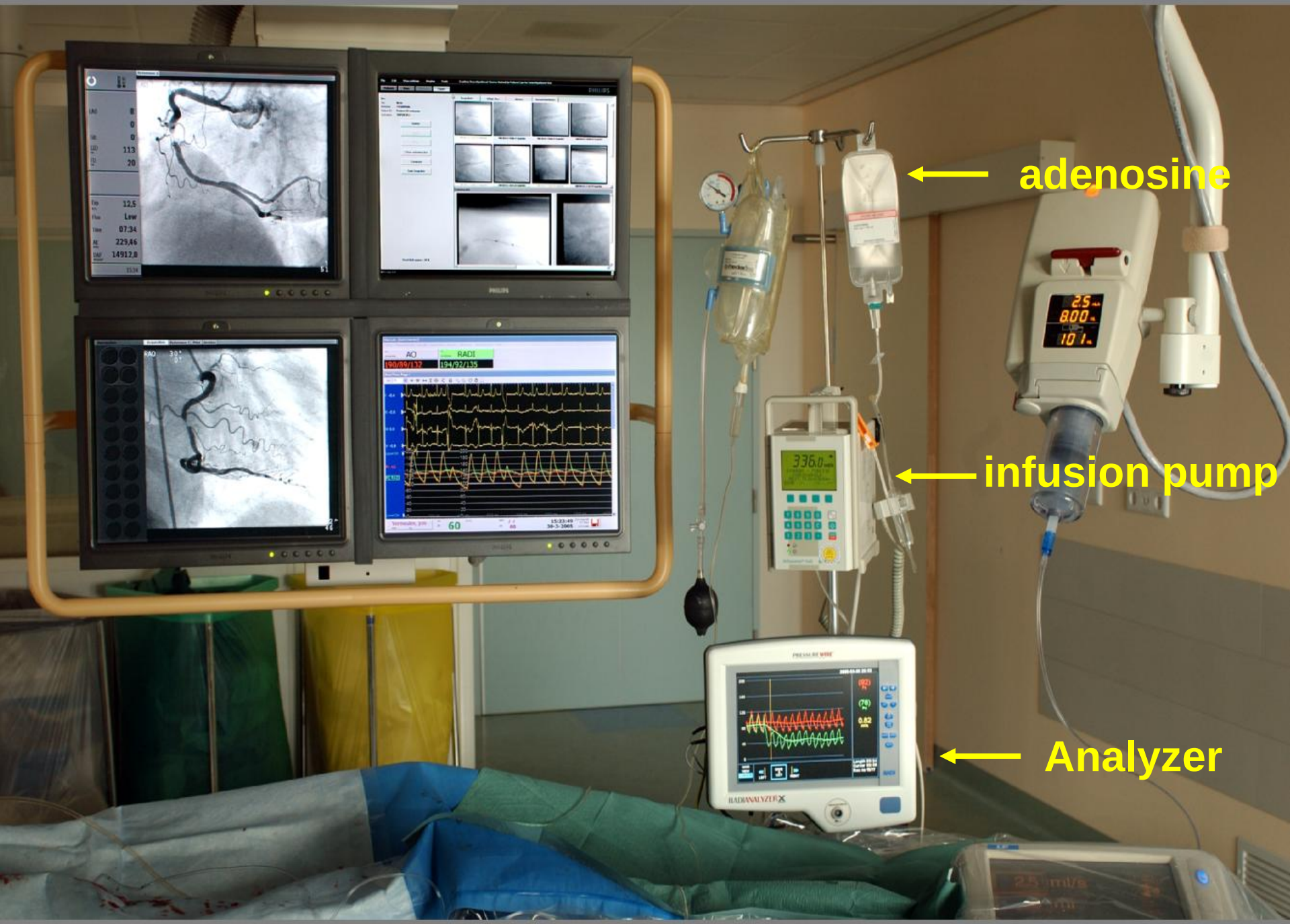
therefore, train your nurses and make them understand the principles, practice, and great advantages of FFR

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
Analyzer

Catharina Hospital, Eindhoven, NL

1800 FFR cases per year

EINDE

FFR: The Pressure Pull-back Curve

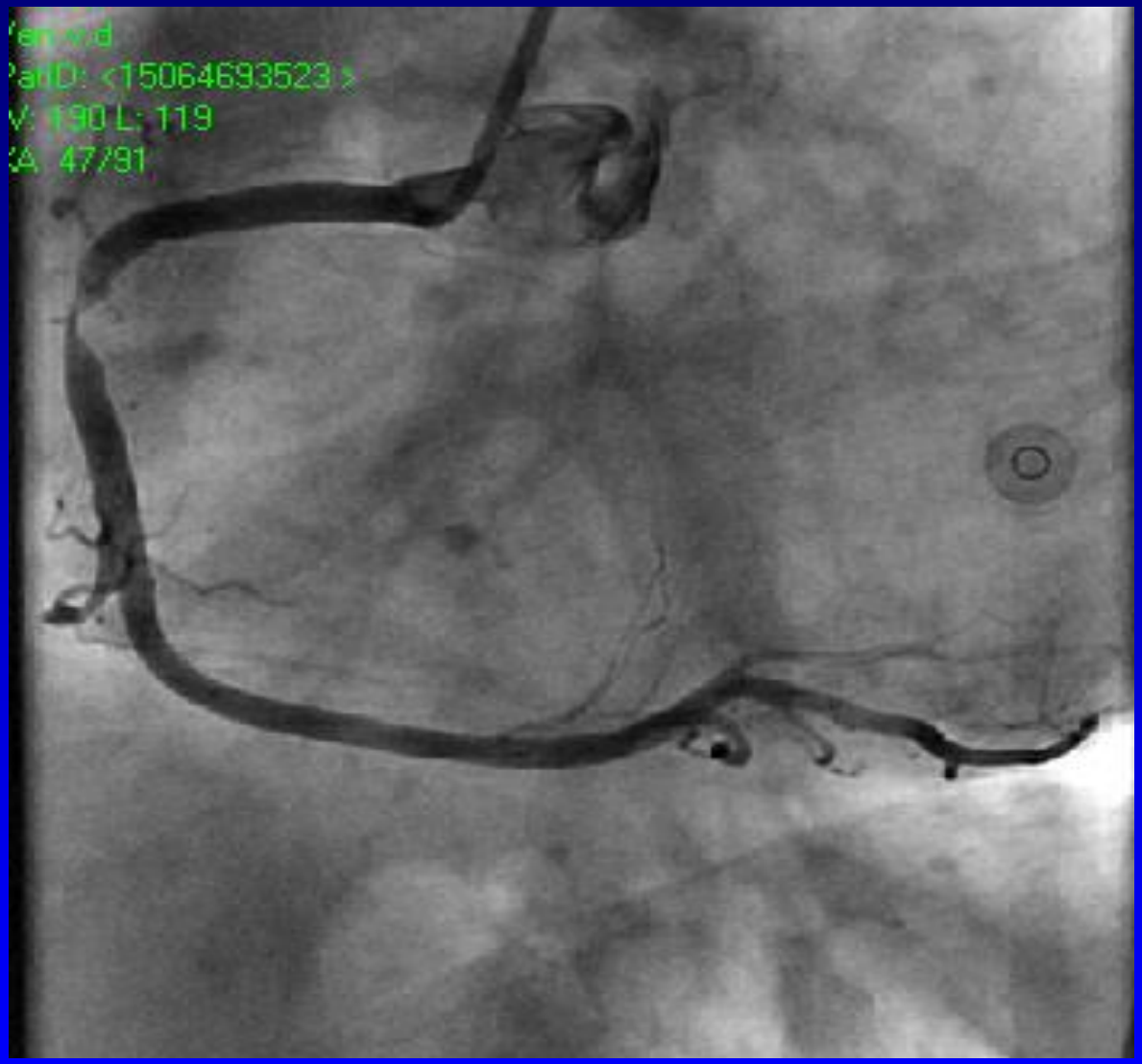
Pressure pull-back curve at maximum hyperemia:

- place sensor in distal coronary artery
- induce sustained maximum hyperemia by i.v. adenosine, or i.c. papaverine or peripheral bolus of regadenoson
- pull back the sensor slowly under fluoroscopy
- the individual contribution of every segment and spot to the extent of disease can be studied in this way

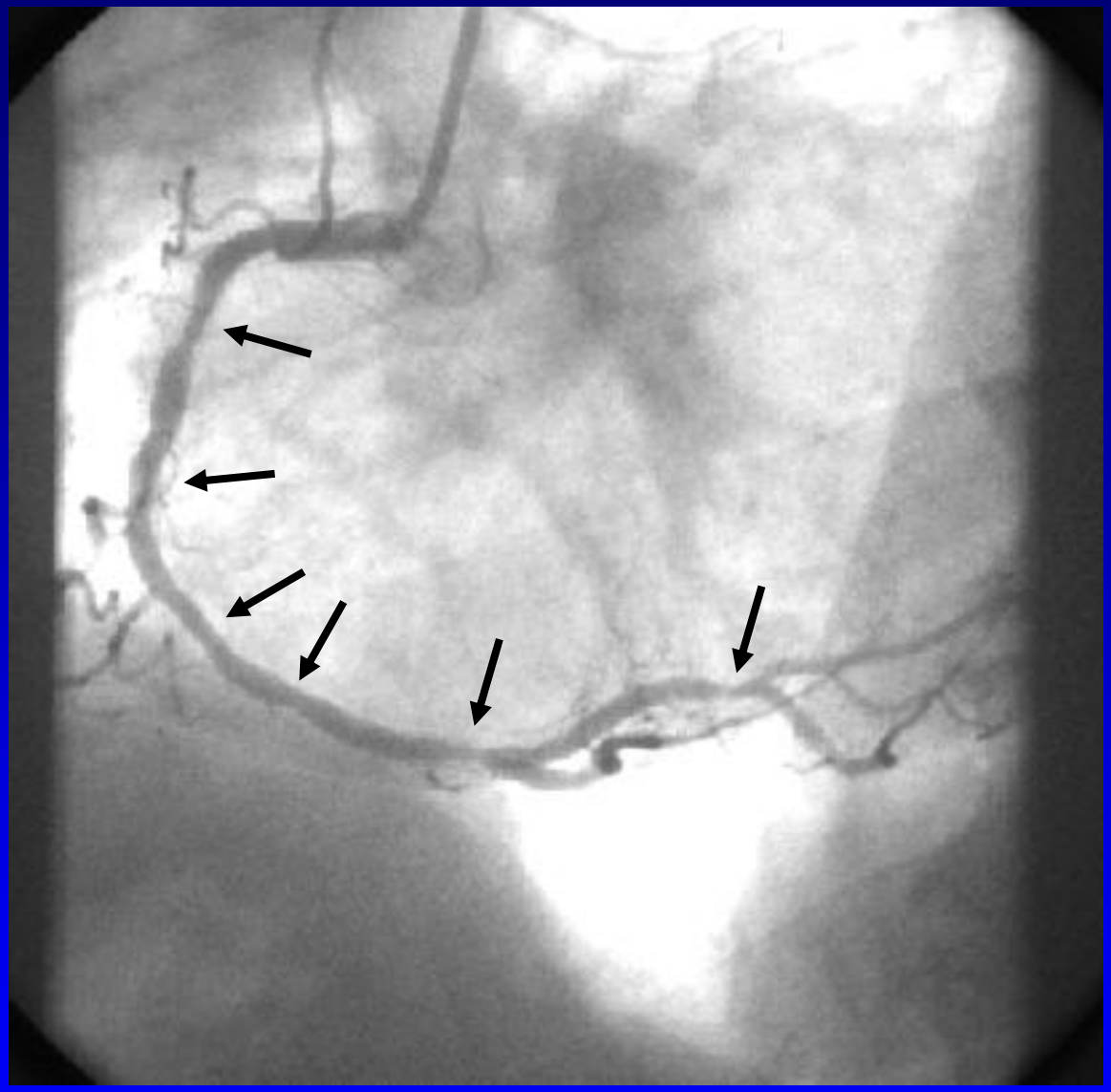
Coronary pressure is unique in this respect and such detailed spatial information cannot be obtained by any other invasive or non-invasive method

pressure pullback recording at hyperemia

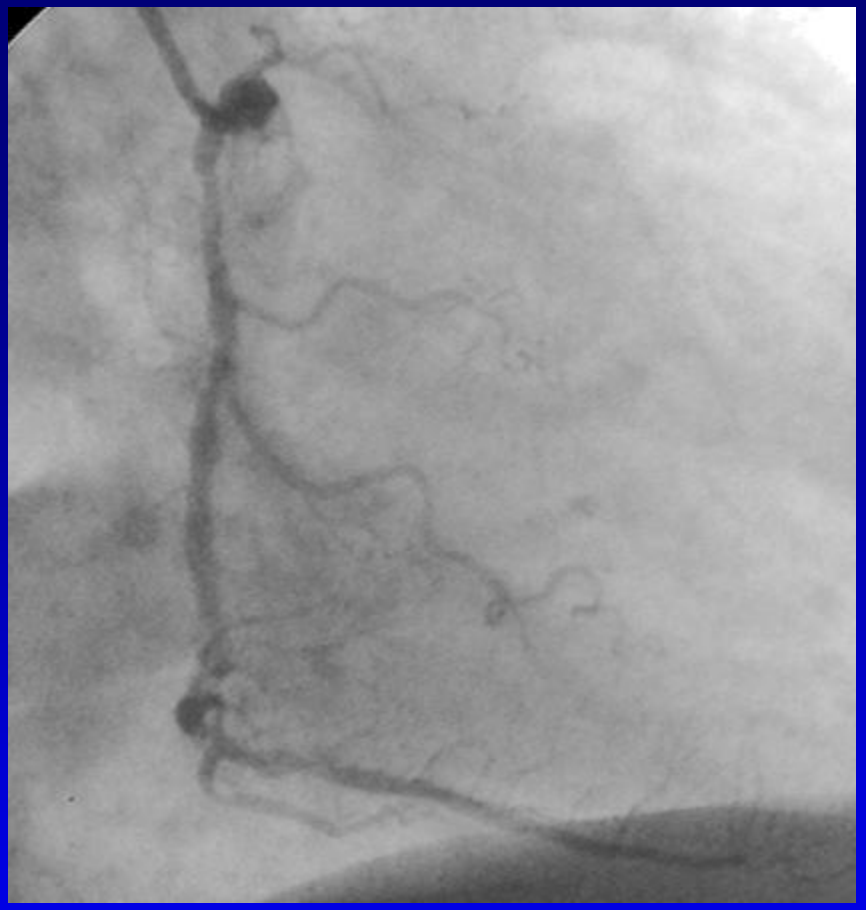
Male 58-y-old



Typical chest pain; positive MIBI-Spect inferior wall

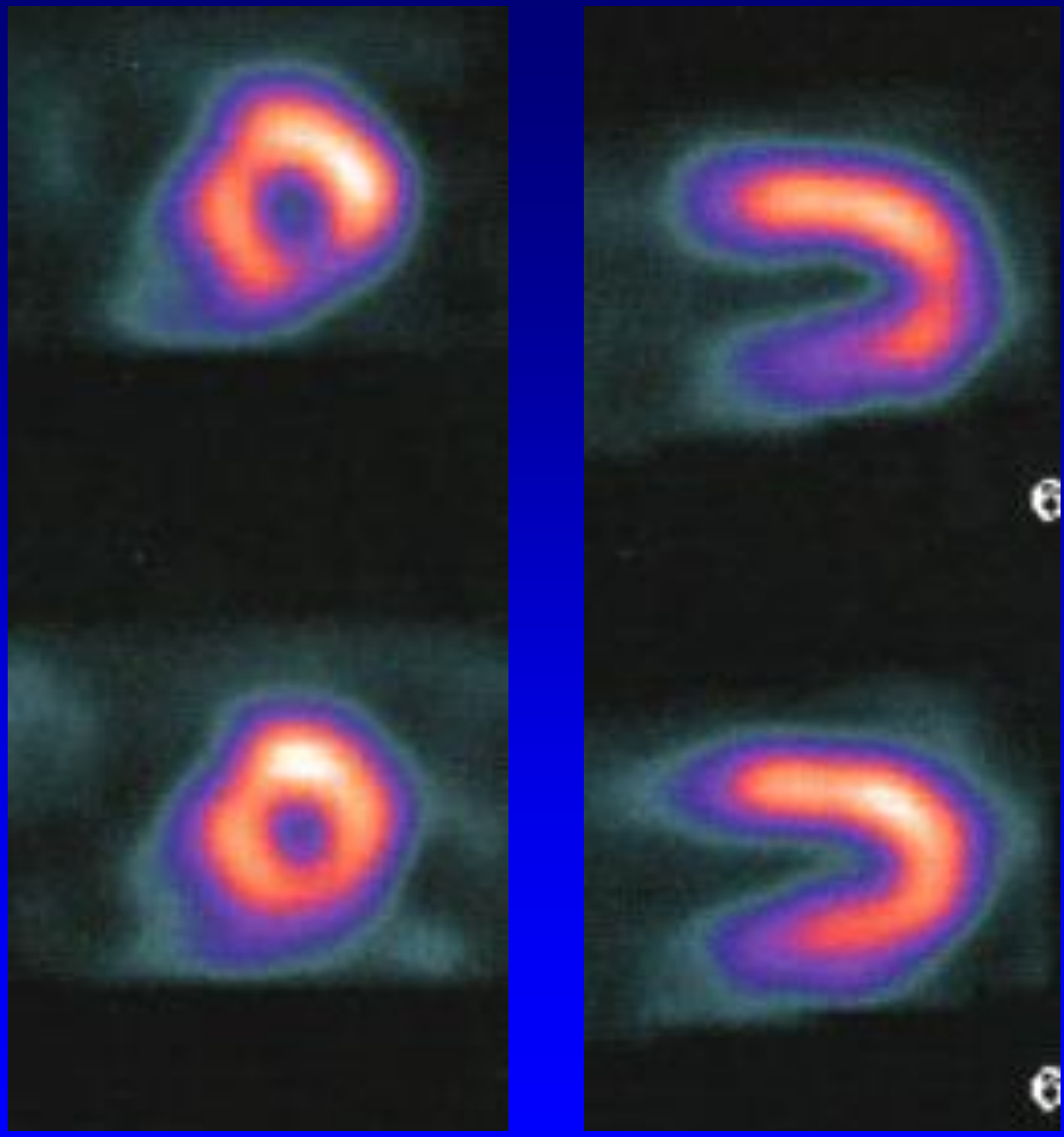


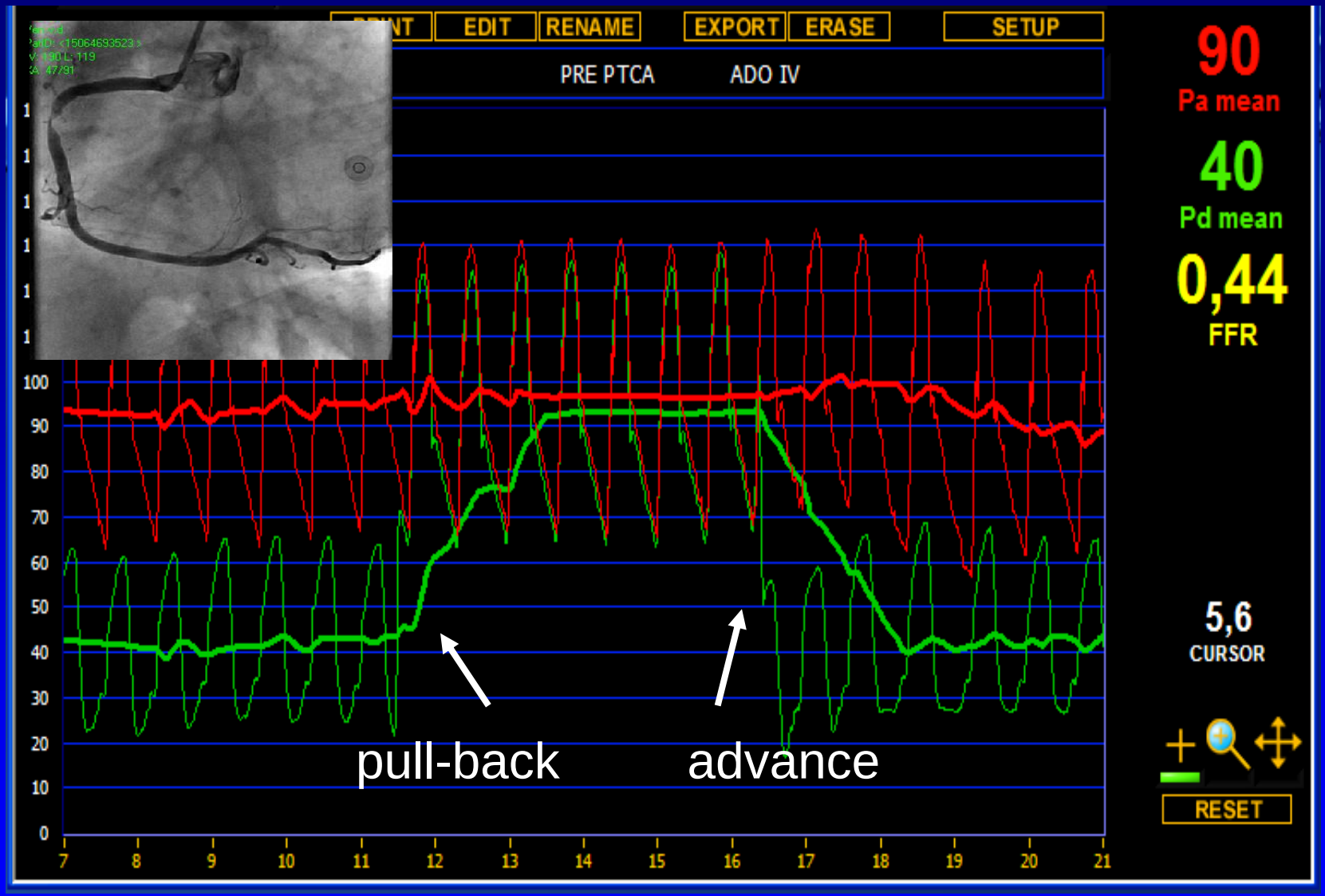
Typical chest pain; positive MIBI-Spect inferior wall

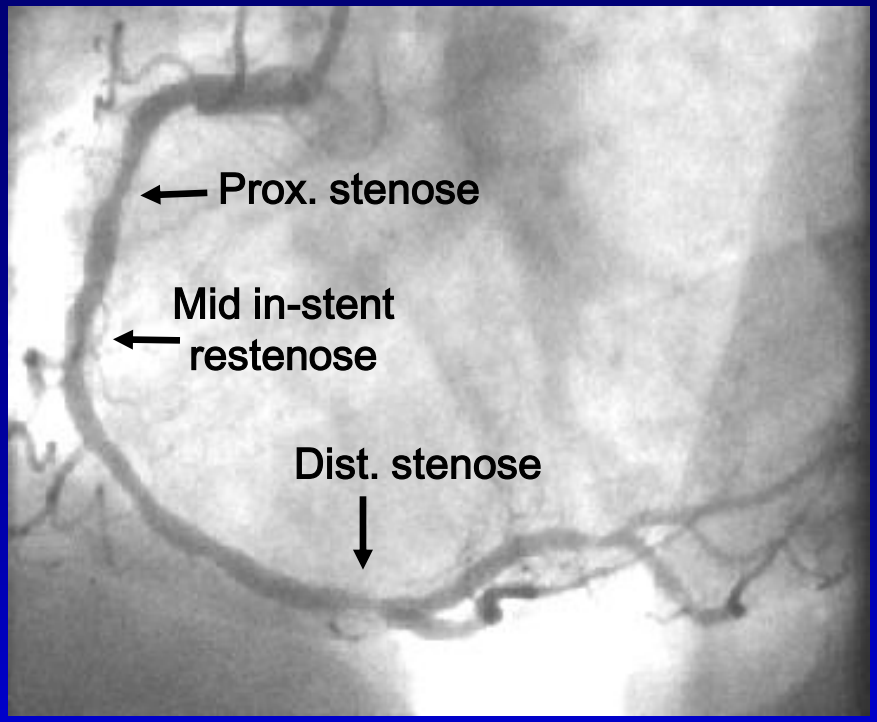


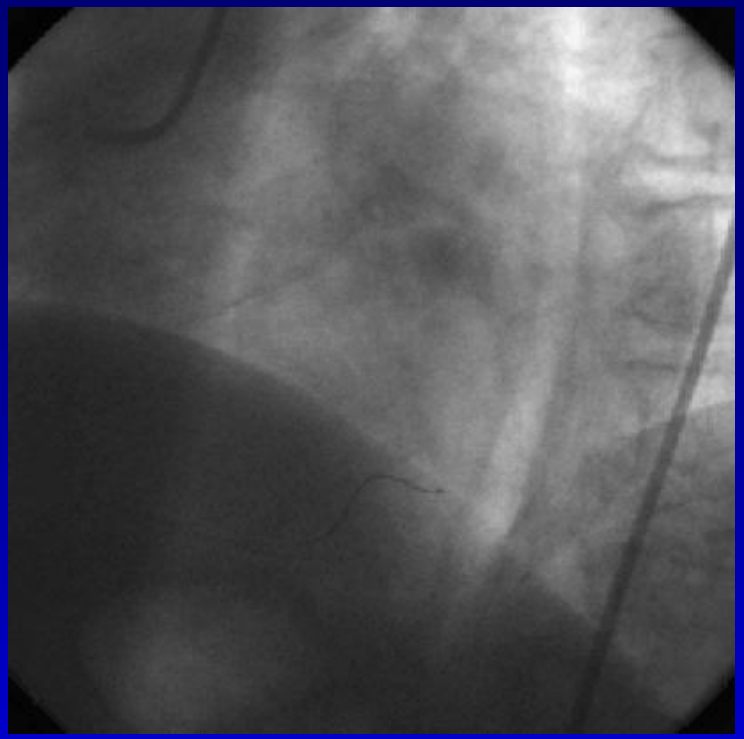
Very obese male, typical chest pain; positive MIBI-Spect inferior wall

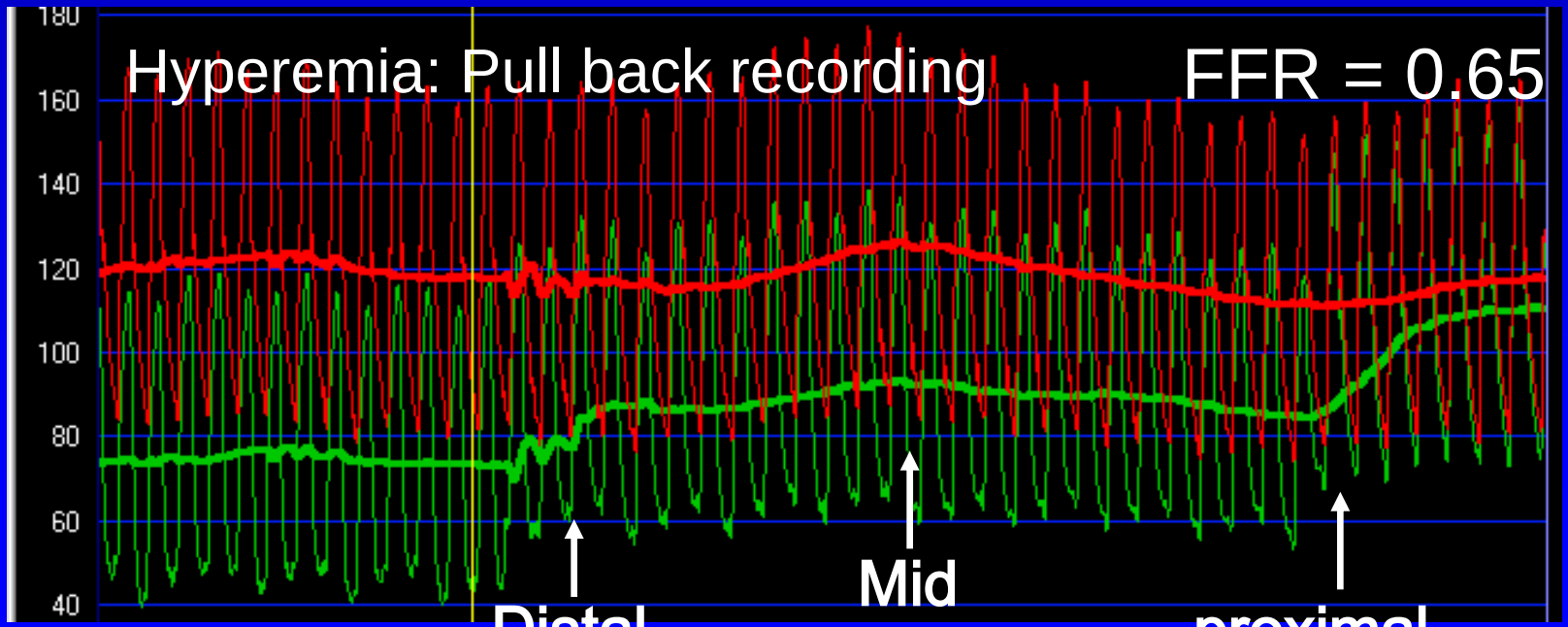
roughly identical MIBI in all 3 patients: reversible defect inferior wall




EDIT
RENAME
EXPORT
ERASE
SETUP
PRE PTCA
ADO IV
90
Pa mean
40
Pd mean
0,44
FFR
5,6
CURSOR
RESET
pull-back
advance
100
90
80
70
60
50
40
30
20
10
0
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21


Prox. stenose
Mid in-stent restenose
Dist. stenose




Hyperemia: Pull back recording
FFR = 0.65
180
160
140
120
100
80
60
40
Distal
Mid
proximal

EDIT RENAME EXPORT ERASE SETUP

2004-06-14 15:55:19

109
Pa mean

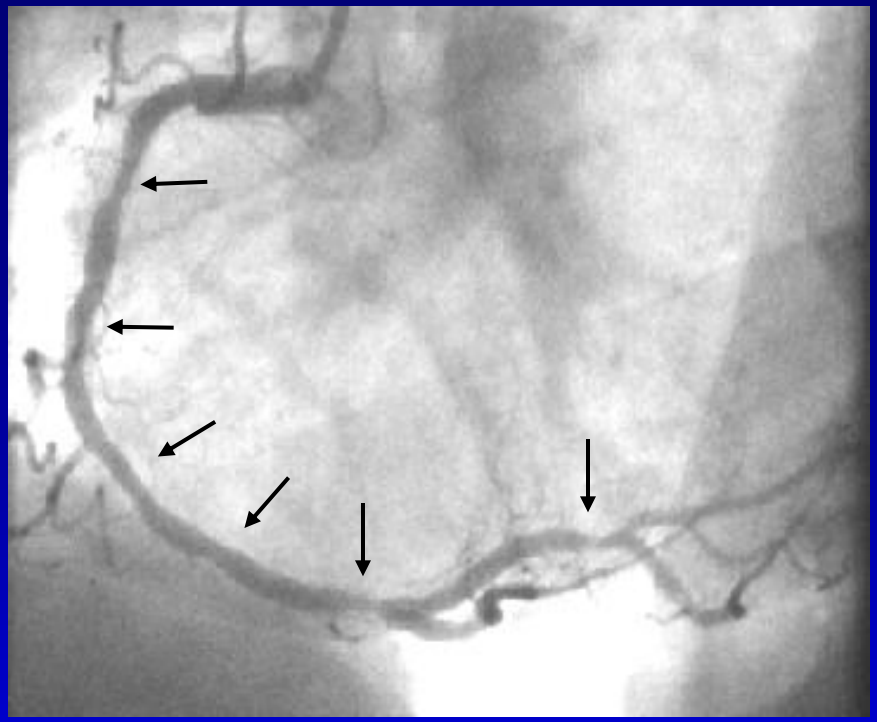
84
Pd mean

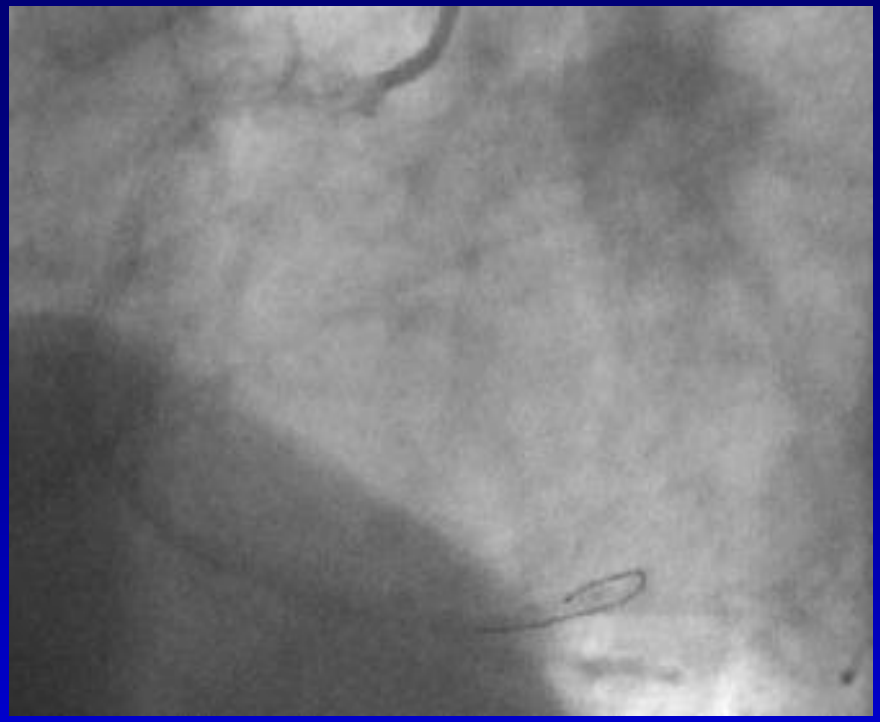
0,77
FFR

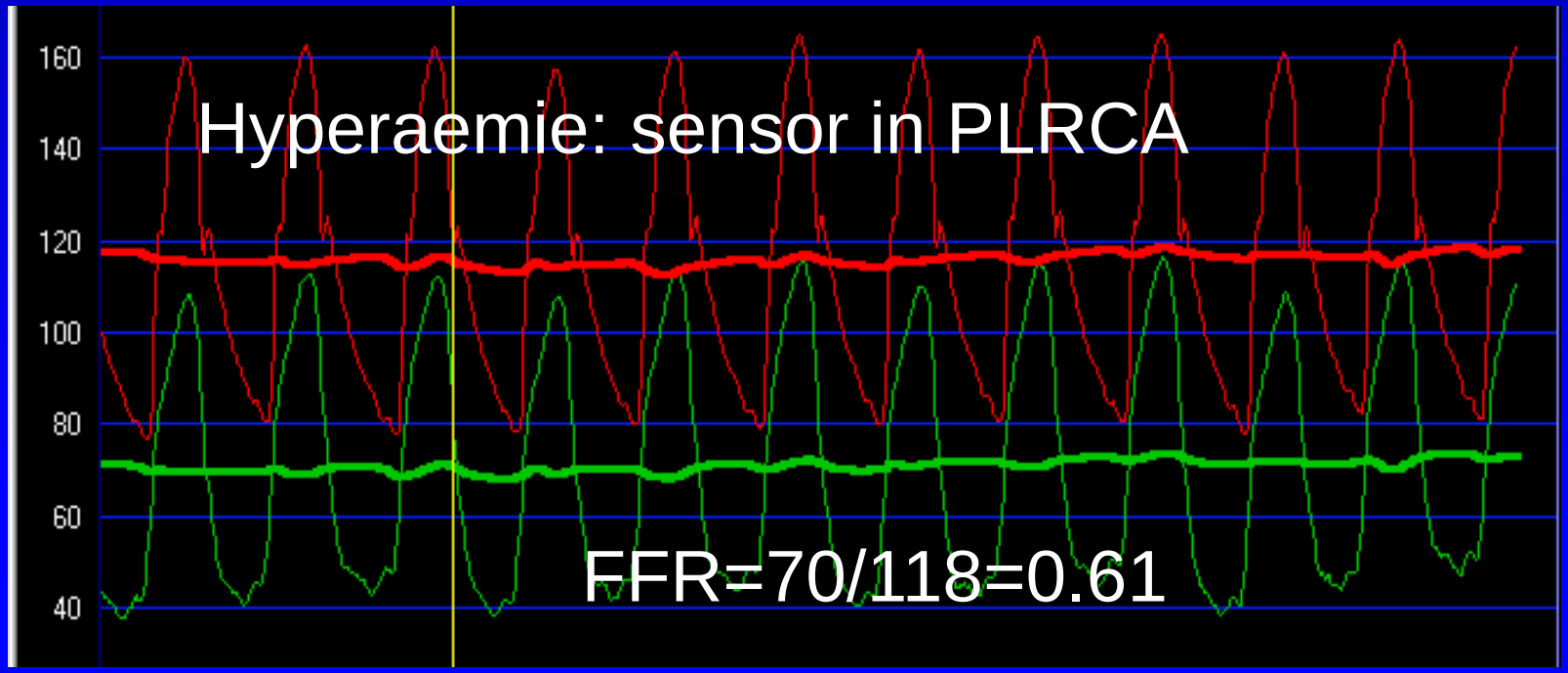
7,9
Cursor

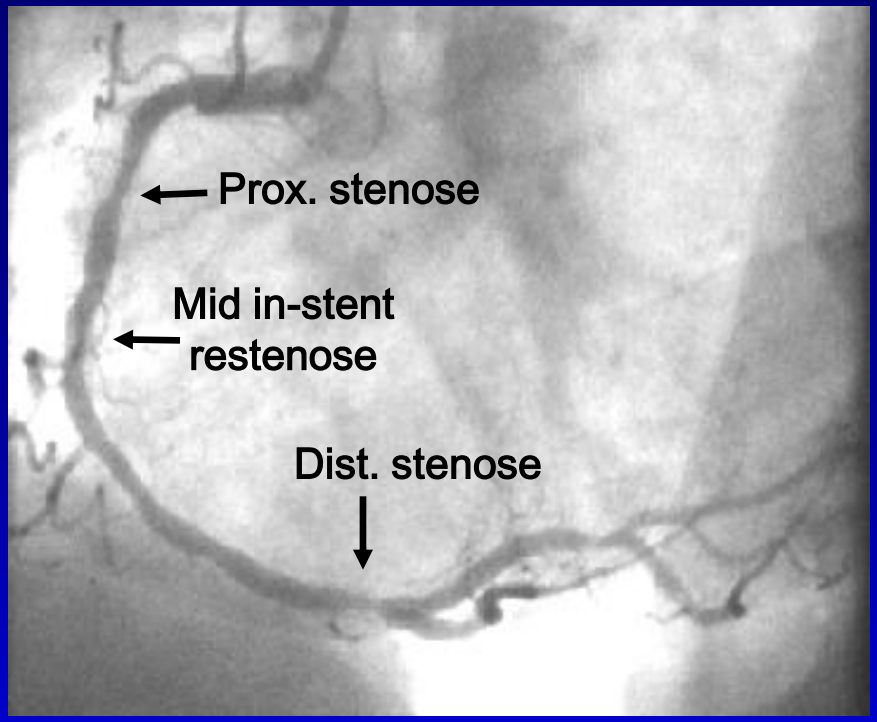
RESET

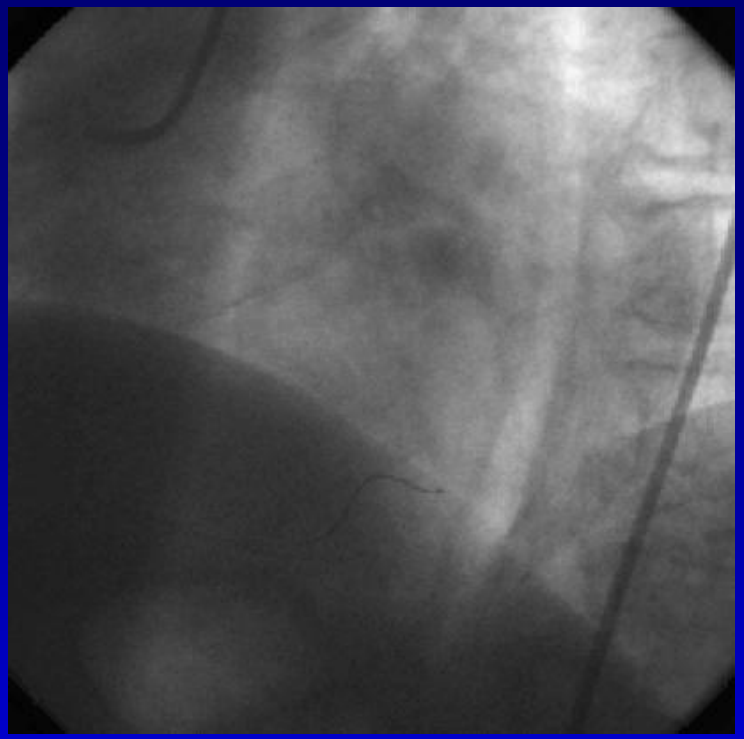
Hyperemic pull-back recordingalong the RCA

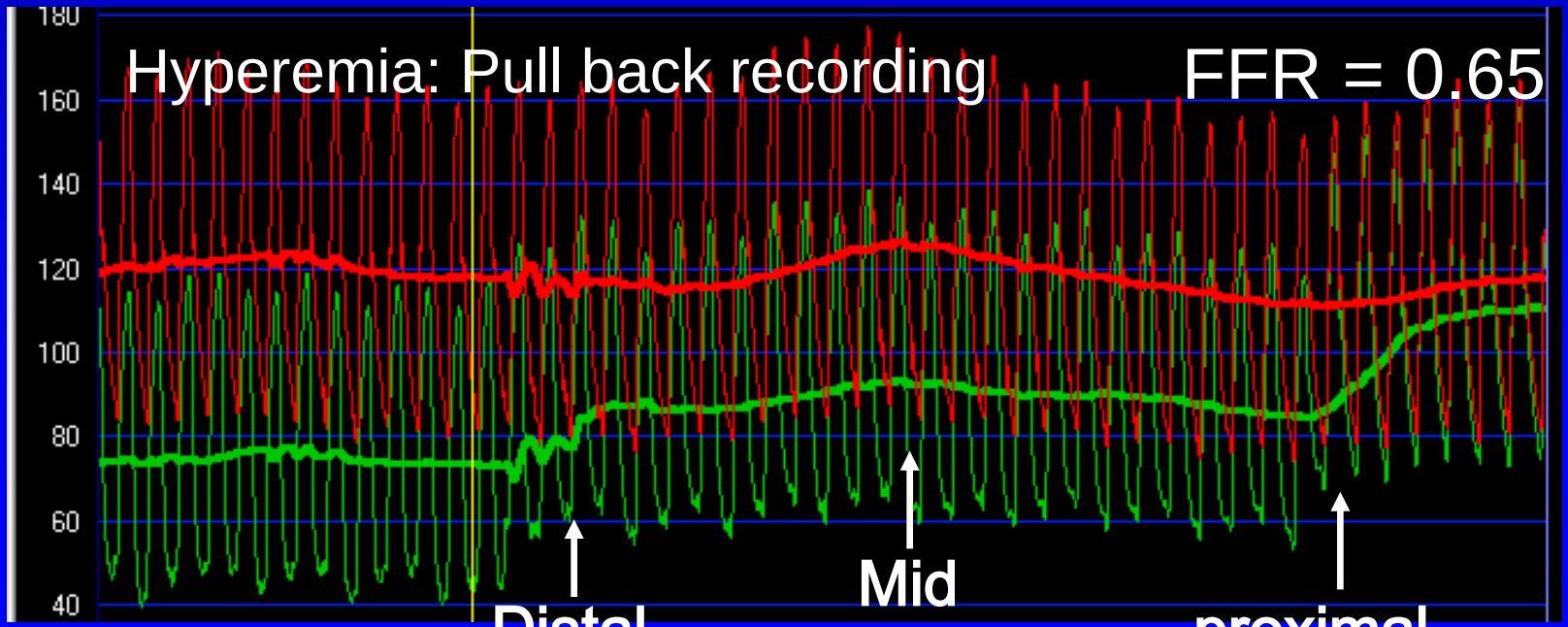


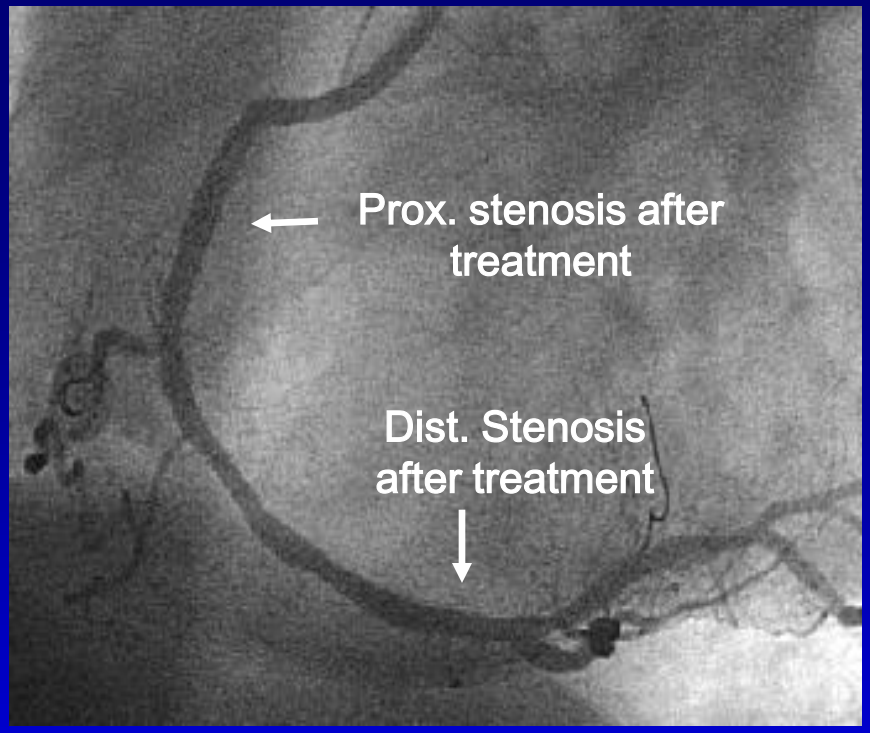


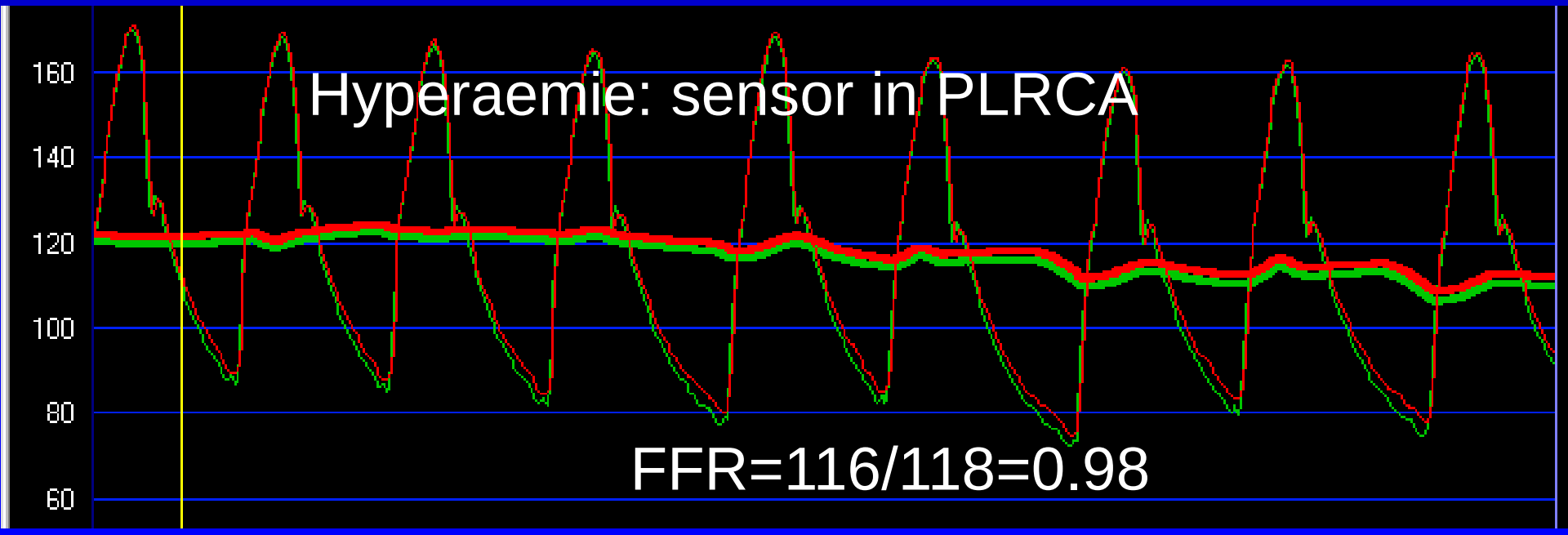

160
140
120
100
80
60
40
Hyperaemie: sensor in PLRCA
FFR=70/118=0.61


Prox. stenose
Mid in-stent restenose
Dist. stenose




Hyperemia: Pull back recording
FFR = 0.65
180
160
140
120
100
80
60
40
Distal
Mid
proximal


Prox. stenosis after treatment
Dist. Stenosis after treatment


160
140
120
100
80
60
Hyperaemie: sensor in PLRCA
FFR=116/118=0.98

A few final issues:

- **pressure pullback recording**
- ***always necessary to induce hyperemia ?***
- **regadenoson**

FFR - light

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

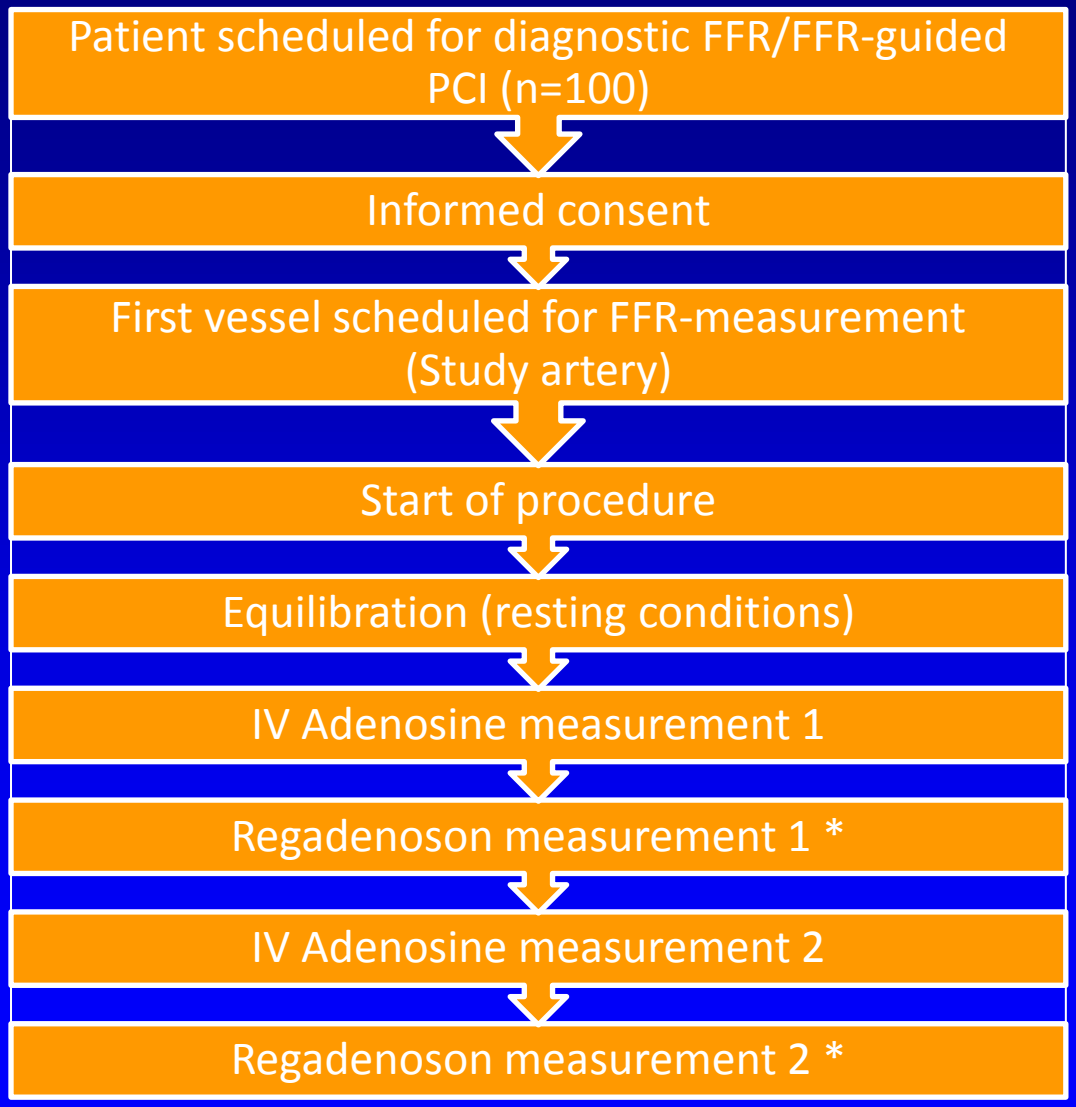
necessity of hyperemia

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

- but without hyperemia, you cannot make a meaningful *pull-back recording* and you are loosing a lot of valuable information

- and without hyperemia and FFR , you cannot judge how much a patient improved by stenting:
  you don't know where you came from
  (*"did FFR go from 0.78 to 0.91 or from 0.65 to 0.91 ?"*)
  and no resting conditions exist after PCI
  (paradoxical deterioration of resting indexes)

Adenosine (central venous infusion) vs Regadenoson

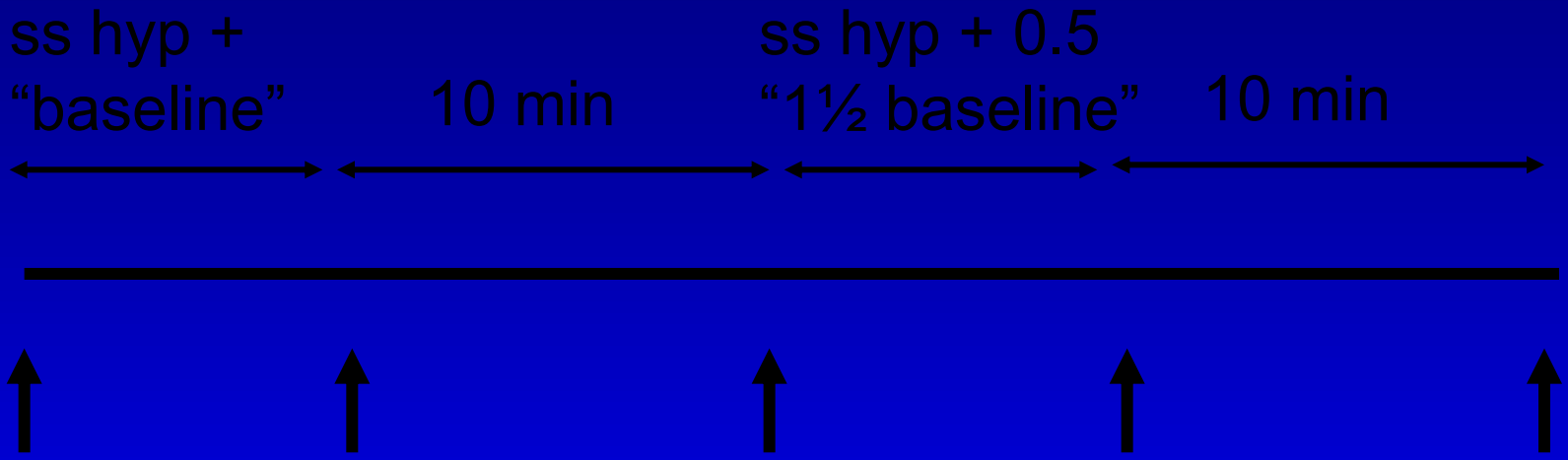


Adenosine (central venous infusion) vs Regadenoson for maximum hyperemia

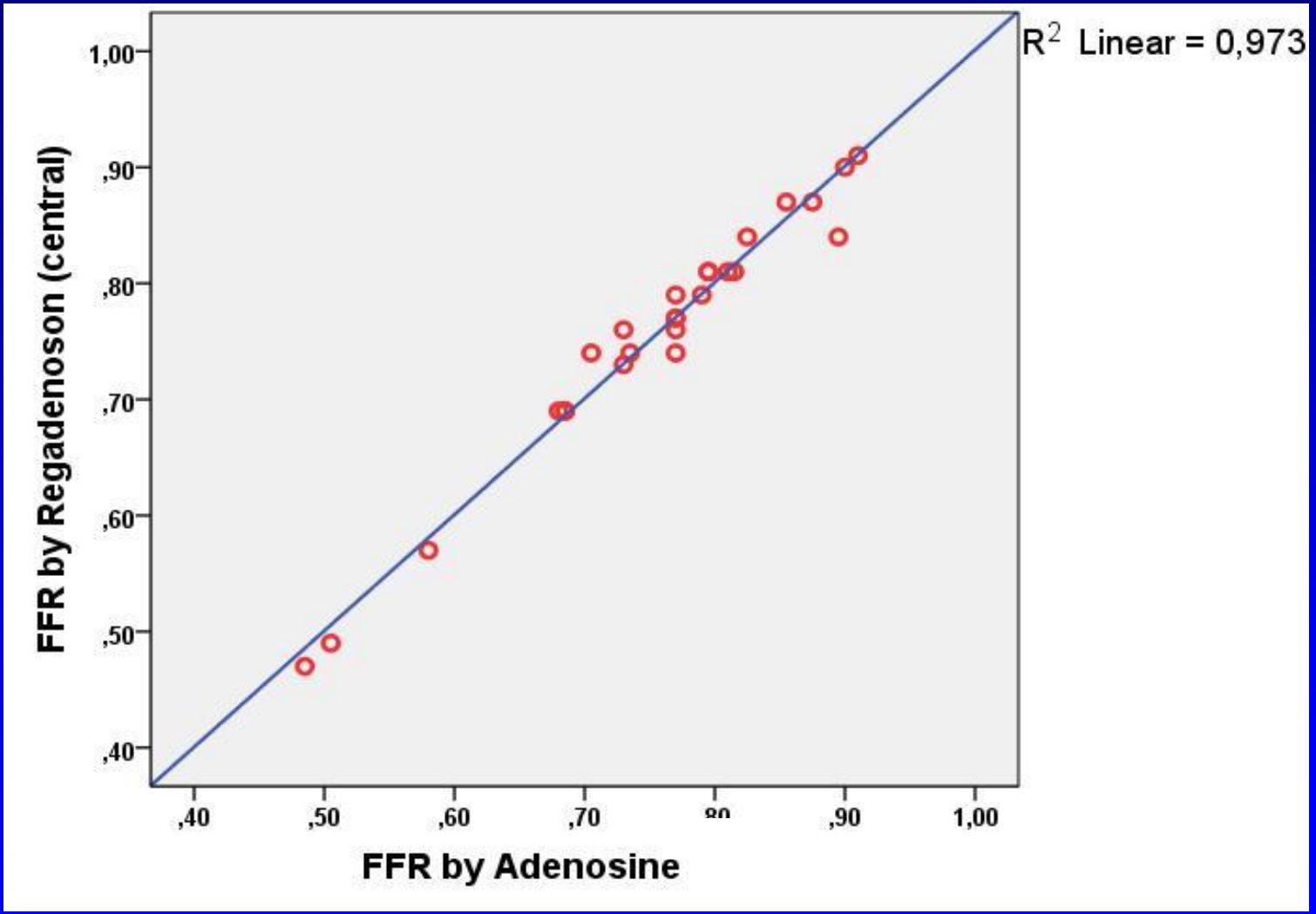
- 100 arbitrary patients admitted for FFR measurement
- central venous line (femoral sheath) and peripheral line
- adenosine 140 µg/kg/min as central venous infusion vs single bolus of 400 µg regadenoson in central or peripheral vein
- adenosine #1, regadenoson #1, adenosine#2, regadenoson #2
- randomization with respect to regadenoson:

central/central (N=25)
peripheral/central (N=25)
central/peripheral (N=25)
peripheral/peripheral (N=25)

Adenosine (central venous infusion) vs Regadenoson for maximum hyperemia



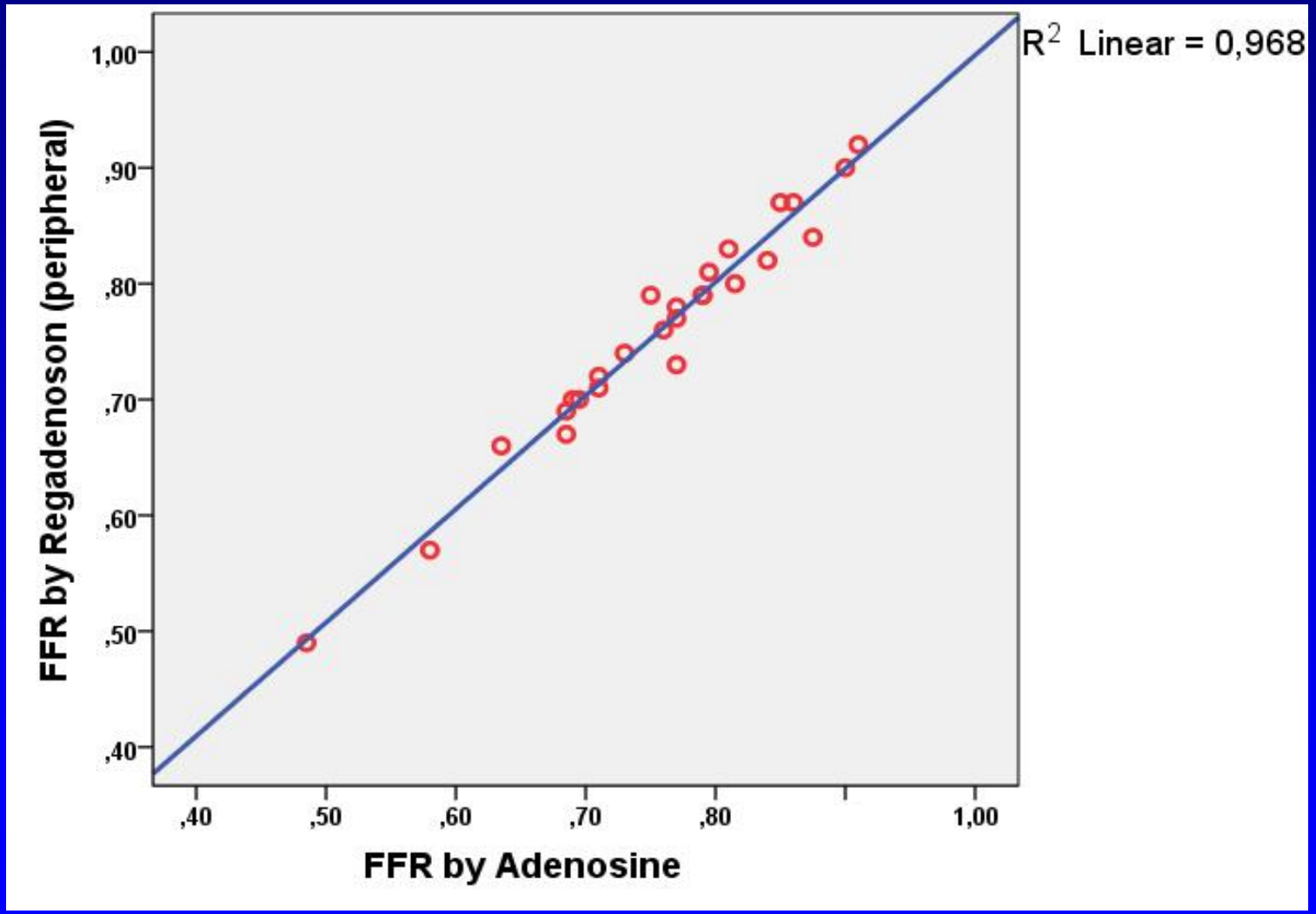
Adenosine (central venous infusion) vs Regadenoson (central venous single bolus injection 400 µg)



N=30

courtesy of Dr Lokien van Nunen

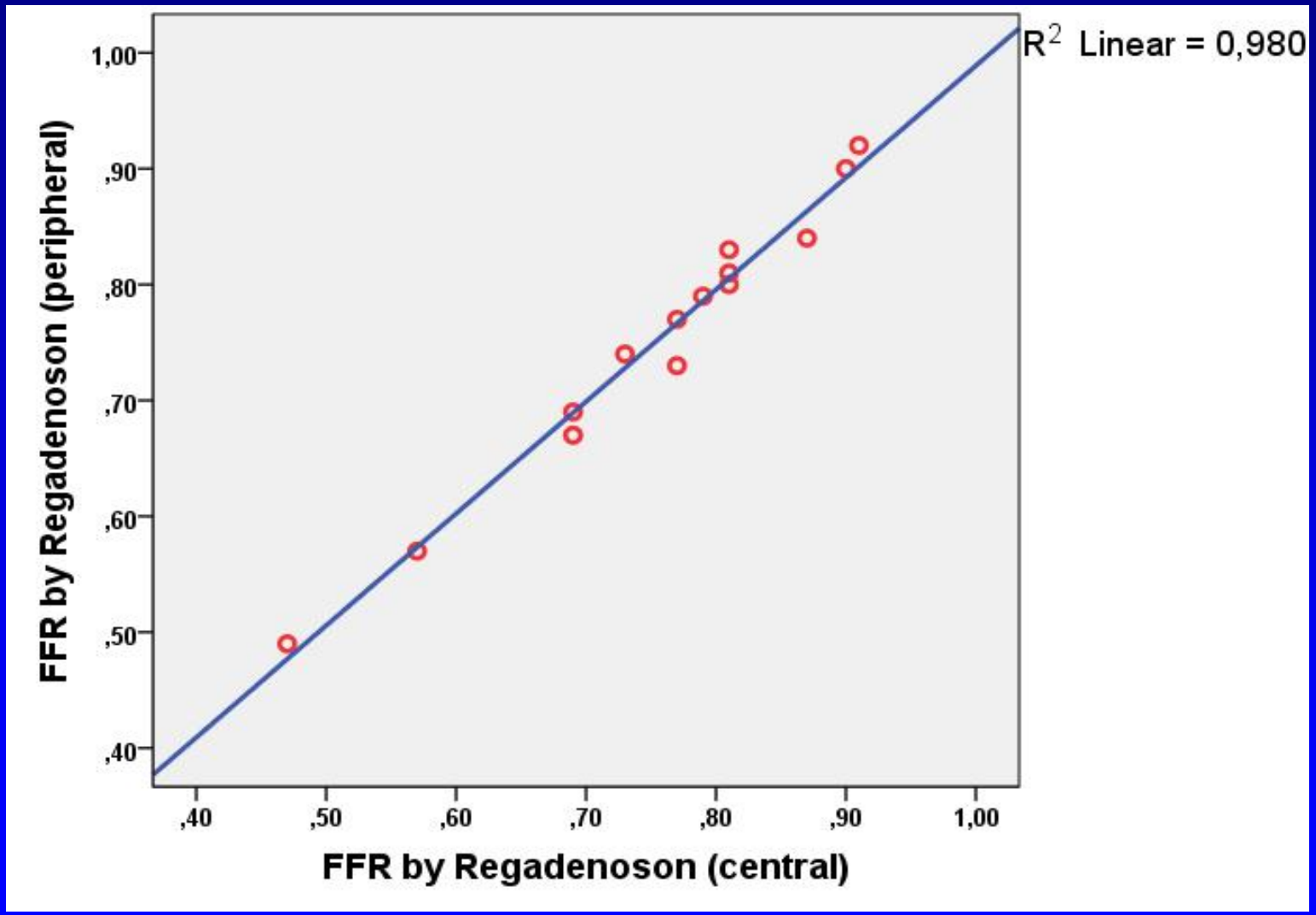
Adenosine (central venous infusion) vs Regadenoson (peripheral venous single bolus injection 400 µg)



N=30

courtesy of Dr Lokien van Nunen

Regadenoson
(central venous single bolus injection 400 µg vs peripheral single bolus 400 µg)



N=20

courtesy of Dr Lokien van Nunen

Results of first 47 Patients

- Maximum hyperemia achieved by regadenoson in ALL patients (difference compared to central venous adenosine 0.00 +/- 0.02)
- No difference between central and peripheral regadenoson
- Hyperemic plateau reached ≤ 40 sec in all patients both for central and peripheral regadenoson
- Duration of hyperemic plateau varied from 75 sec to 9 minutes (sufficient for pull-back recording in all patients)
- Zero complications or side-effects both for adenosine *(94 runs*) or (repeated) regadenoson (94 injections), except the well-known and innocent chest discomfort (graded 6/10 vs 5/10, respectively) and a few skipped beats in 2 patients (adeno) without necessity to interrupt administration

Adenosine (Central Venous Infusion)
versus
Single Bolus Injection ofRegadenoson For Maximum Hyperemia

Logo
CAZI

Lokien X Van Nunen, MD
Catharina Hospital, Eindhoven
The Netherlands

Aims of this study:

- To investigate if the hyperemic effect of single bolus regadenoson injection is equal to the present gold standard i.e. central venous adenosine infusion
- To determine time intervals to onset of maximum hyperemia and the duration of steady state hyperemia if present
- To compare central venous vs peripheral venous administration of regadenoson
- To investigate side-effects as well as safety of repeated regadenoson injections, if desired

Conclusions (halfway this study)

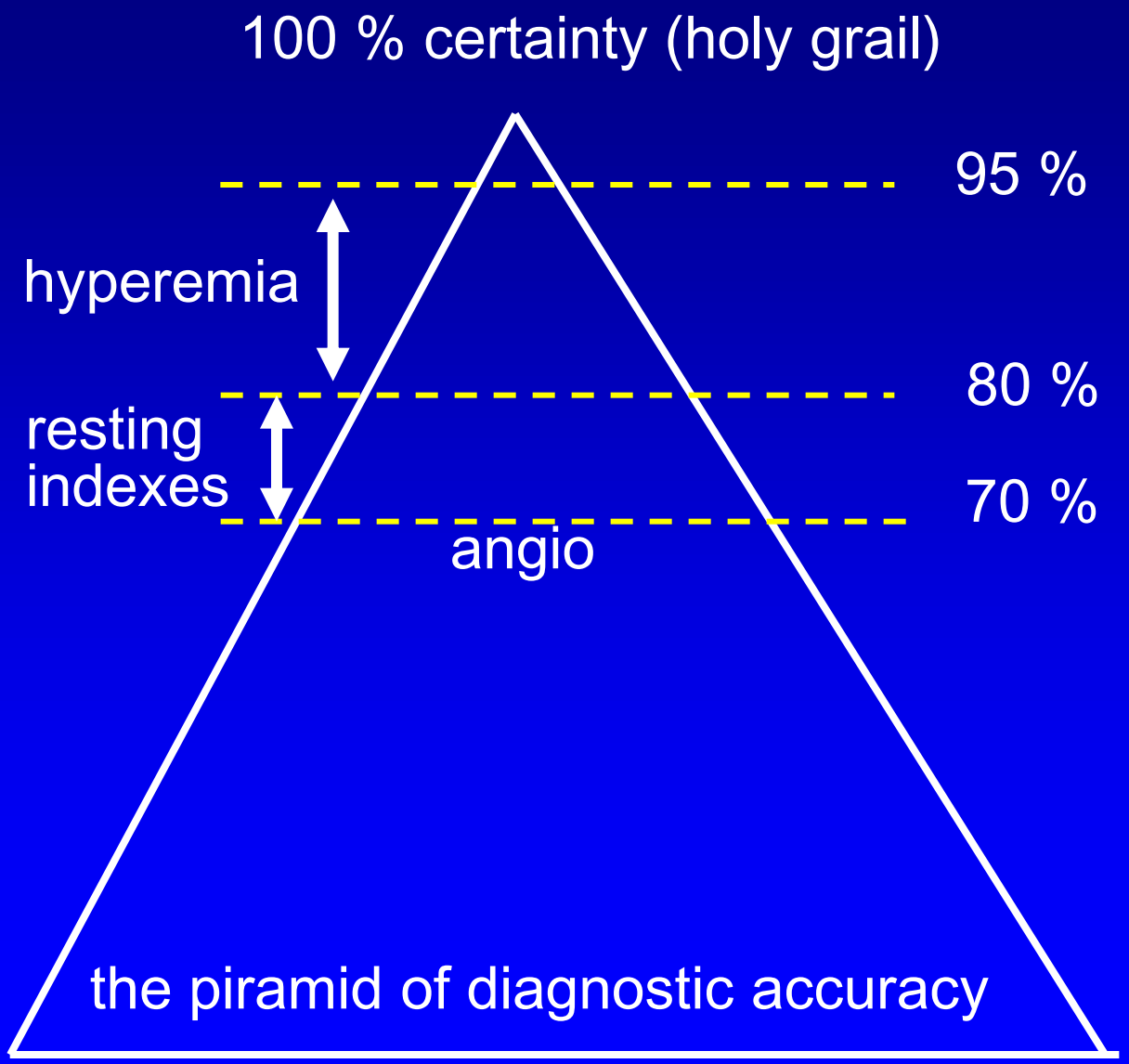
- Regadenoson as a single bolus injection of400 µg, is an excellent alternative for central venous adenosine infusion to induce maximum hyperemia
- Rapid onset (~ 30 sec) and steady state long enough (at least 75 sec) to perform pressure pullback recording,
- In case multiple arteries need to be investigated, repeated injection can be performed and is safe
- No noticeable side effects of regadenoson or adenosine, except the harmless chest discomfort

Correct Classification of Ischemic Stenosis

FFR

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

angiography



FRACTIONAL FLOW RESERVE:

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

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

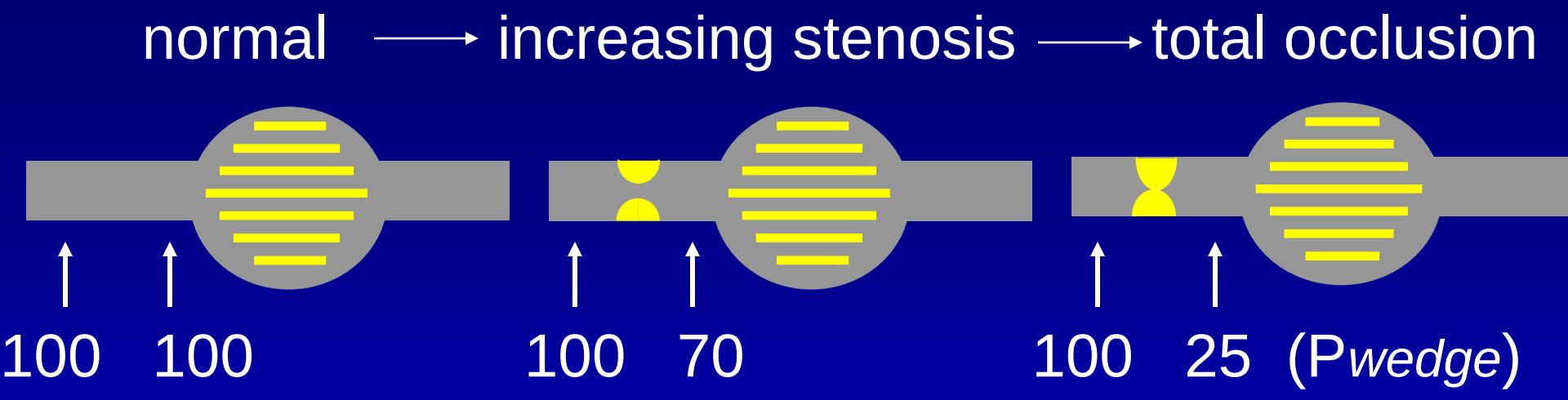
- *At maximum vasodilation (corresponding with maximum hyperemia or with maximum exercise), blood flow to the myocardium is proportional to **myocardial perfusion pressure***
  *(**~hyperemic distal coronary pressure**)*

FRACTIONAL FLOW RESERVE =

MAXIMUM FLOW IN THE PRESENCE OF A STENOSIS

NORMAL MAXIMUM FLOW

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



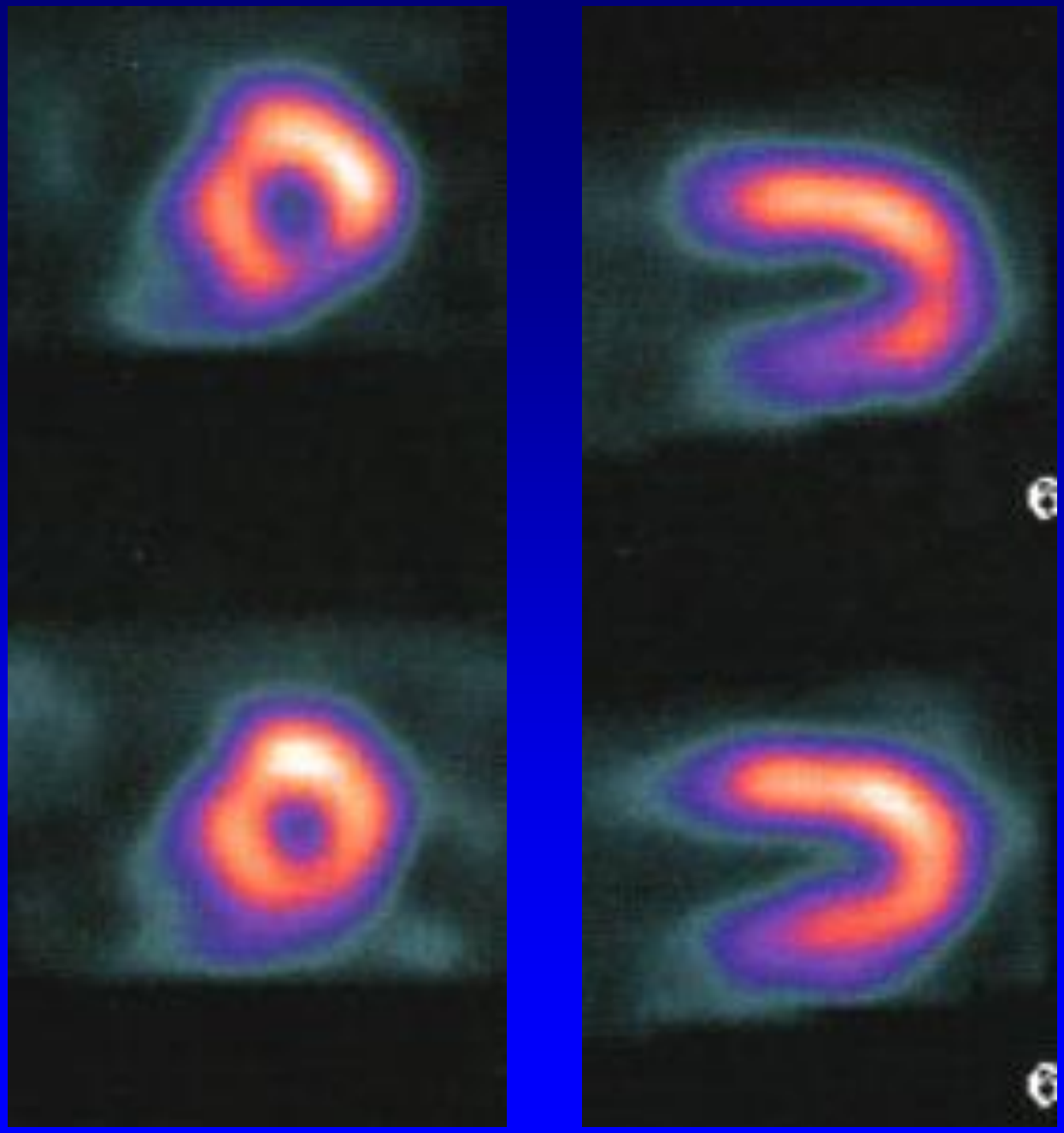
Maximum myocardial perfusion:

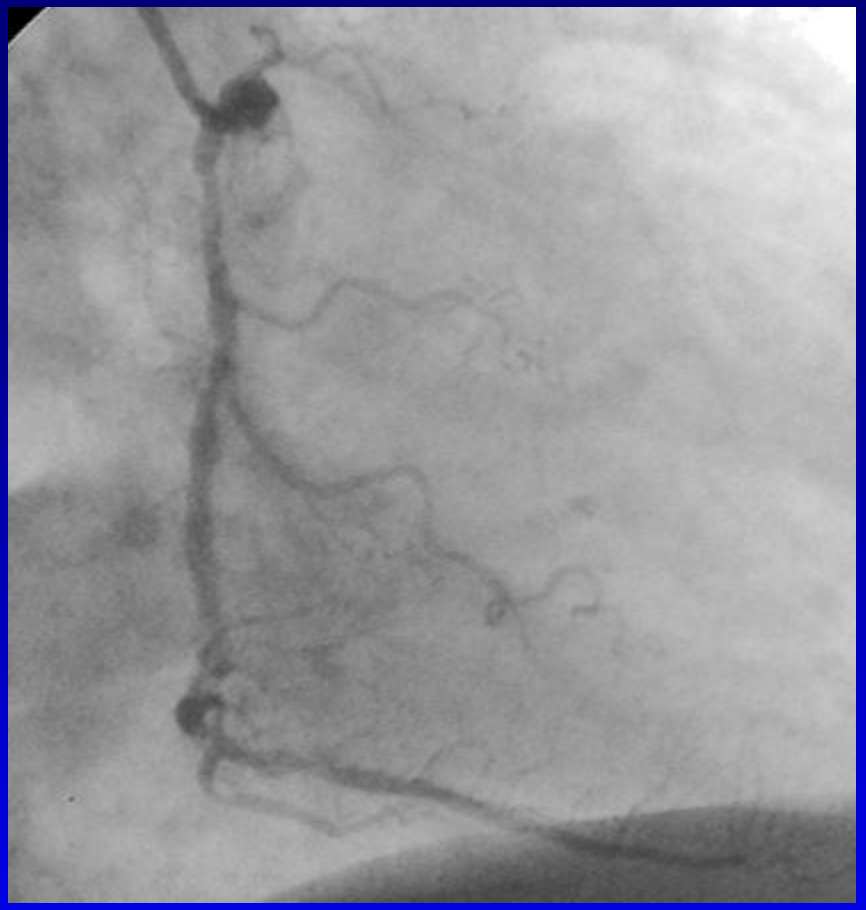
100% ⟶ ***70%*** ⟶ ***25%***

FFR: **1.0** ⟶ **0.7** ⟶ **0.25**

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

Angina
Pectoris
&
Pos MIBI:





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109
Pa mean

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Pd mean

0,77
FFR

7,9
Cursor

RESET

Hyperemic pull-back recordingalong the RCA

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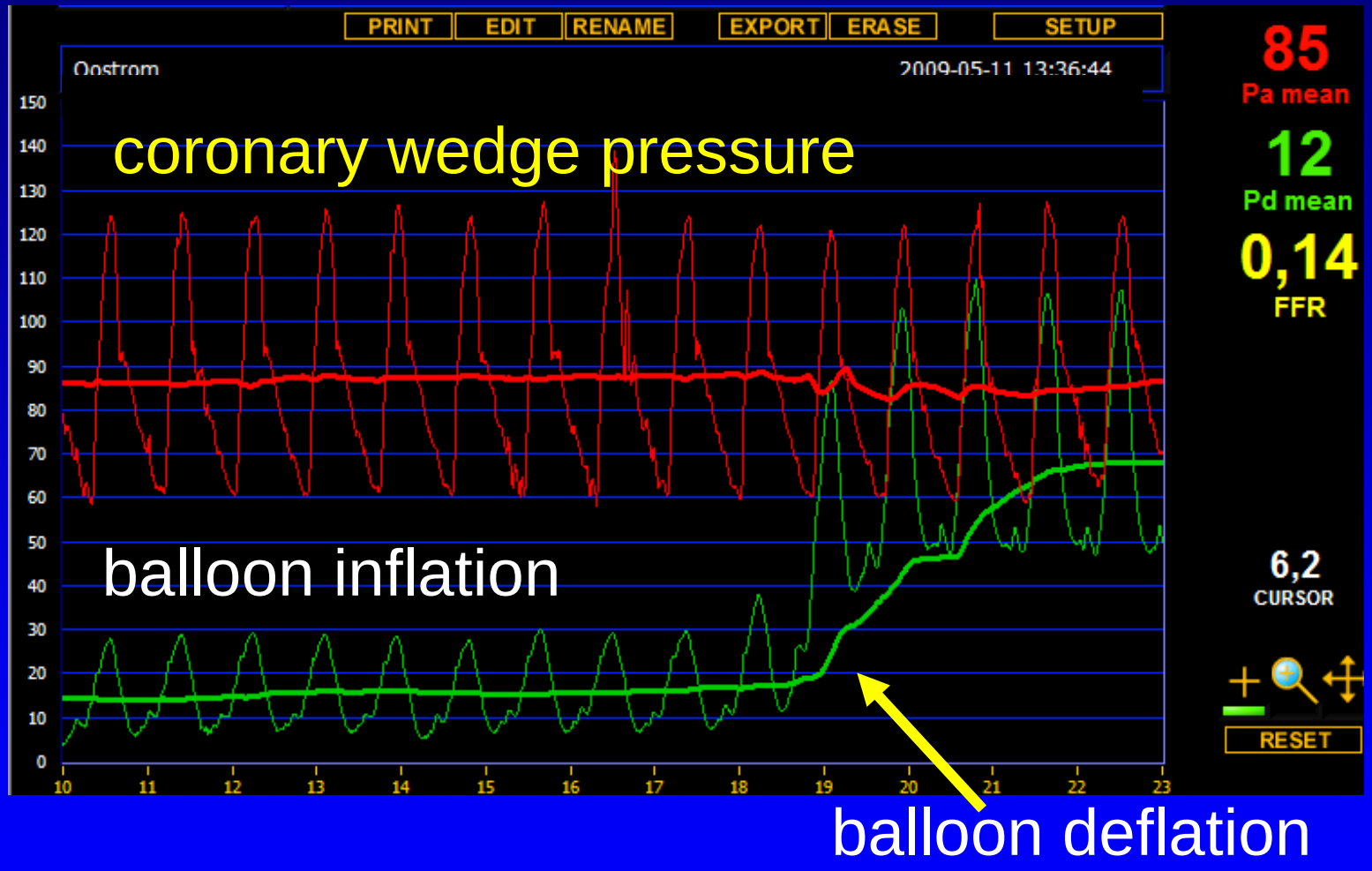
Pressure pull-back curve at maximum hyperemia:

- place sensor in distal coronary artery
- induce sustained maximum hyperemia by i.v. adenosine, or i.c. papaverine
- pull back the sensor slowly under fluoroscopy
- the individual contribution of every segment and spot to the extent of disease can be studied in this way

Coronary pressure is unique in this respect and such detailed spatial information cannot be obtained by any other invasive or non-invasive method

to assess ***collateral flow***: measurement of coronary wedge pressure during balloon inflation can be done



Fractional collateral flow = (Pd-Pw) / (Pa-Pw)

CONCLUSIONS (1):

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

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

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

- Therefore, it is justified to use FFR as gold standard

CONCLUSIONS (2):

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

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

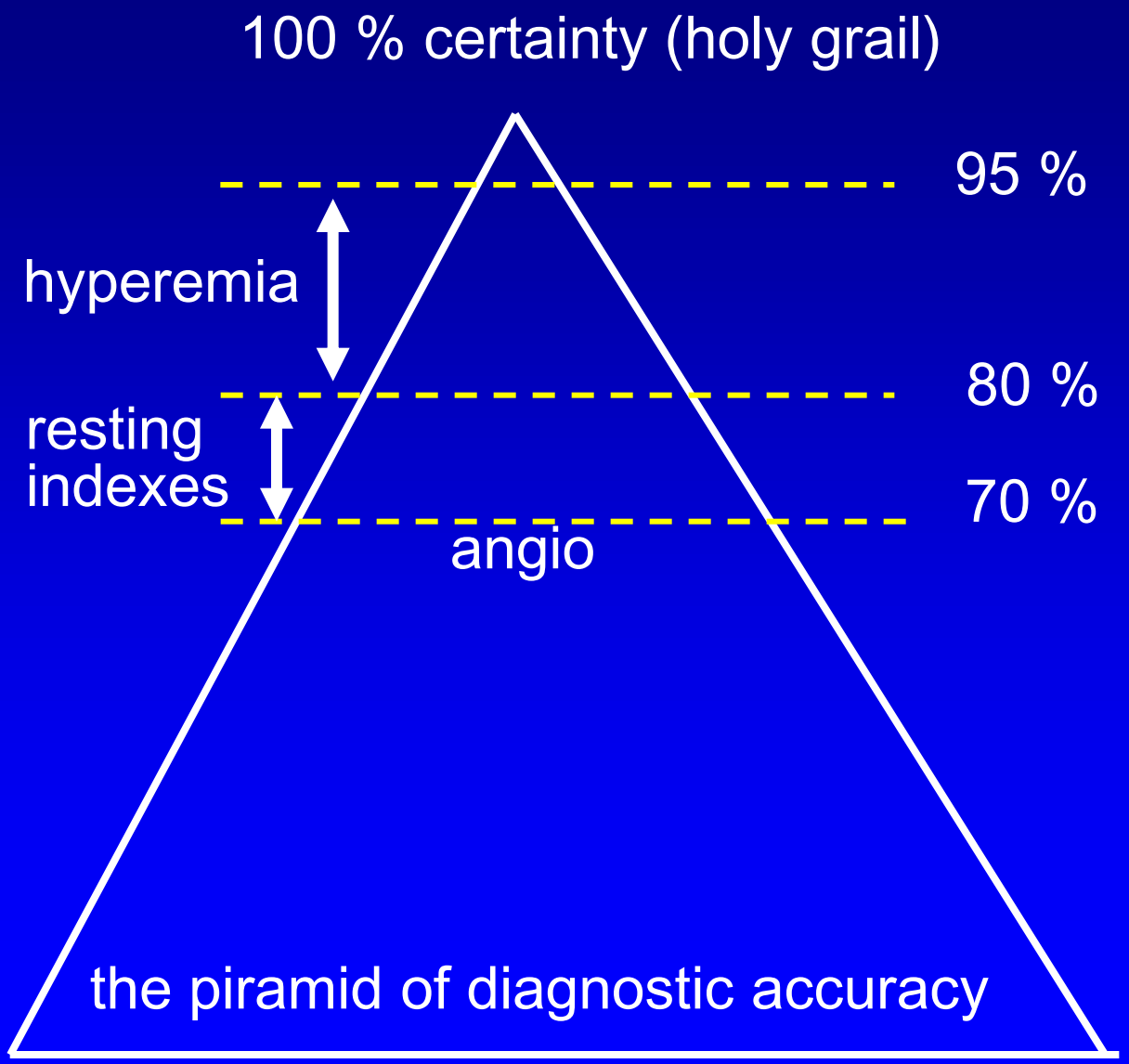
- In complex disease, ostial lesions, tandem stenosis, etc, the full hyperemic pull-back recording remains mandatory

Correct Classification of Ischemic Stenosis

FFR

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

angiography



MAXIMUM VASODILATORY STIMULI

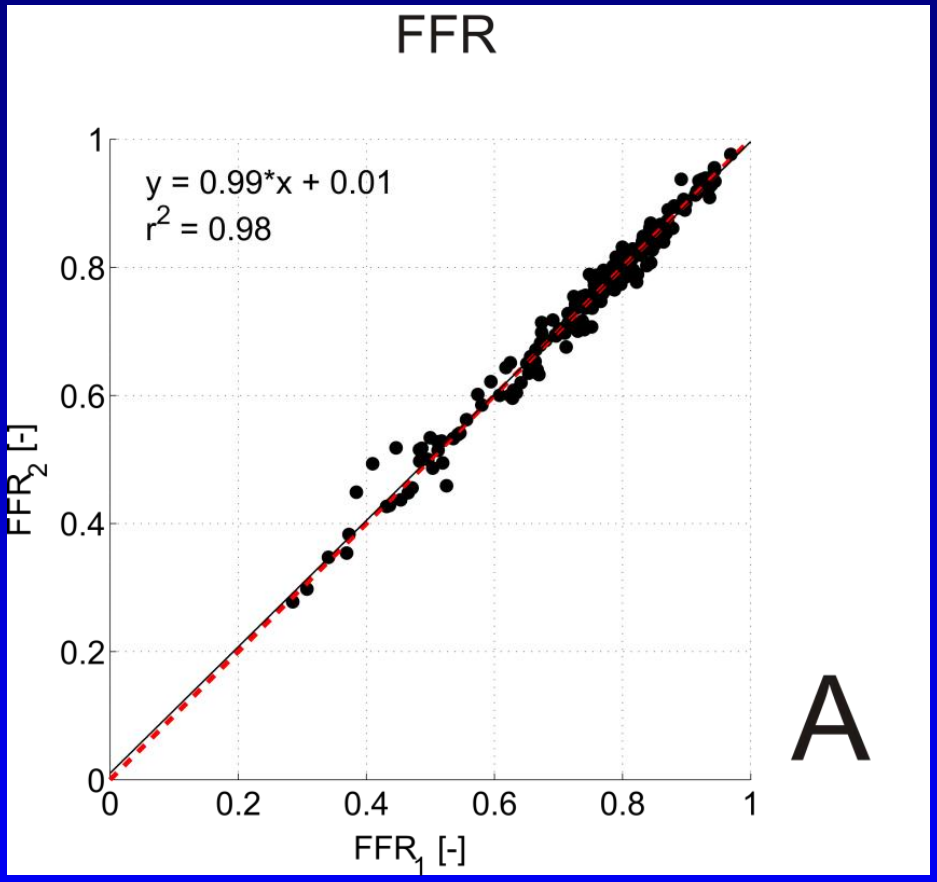
!! Maximum hyperemia is paramount to achieve optimum accuracy
(95% with hyperemia; 80% without hyperemia)

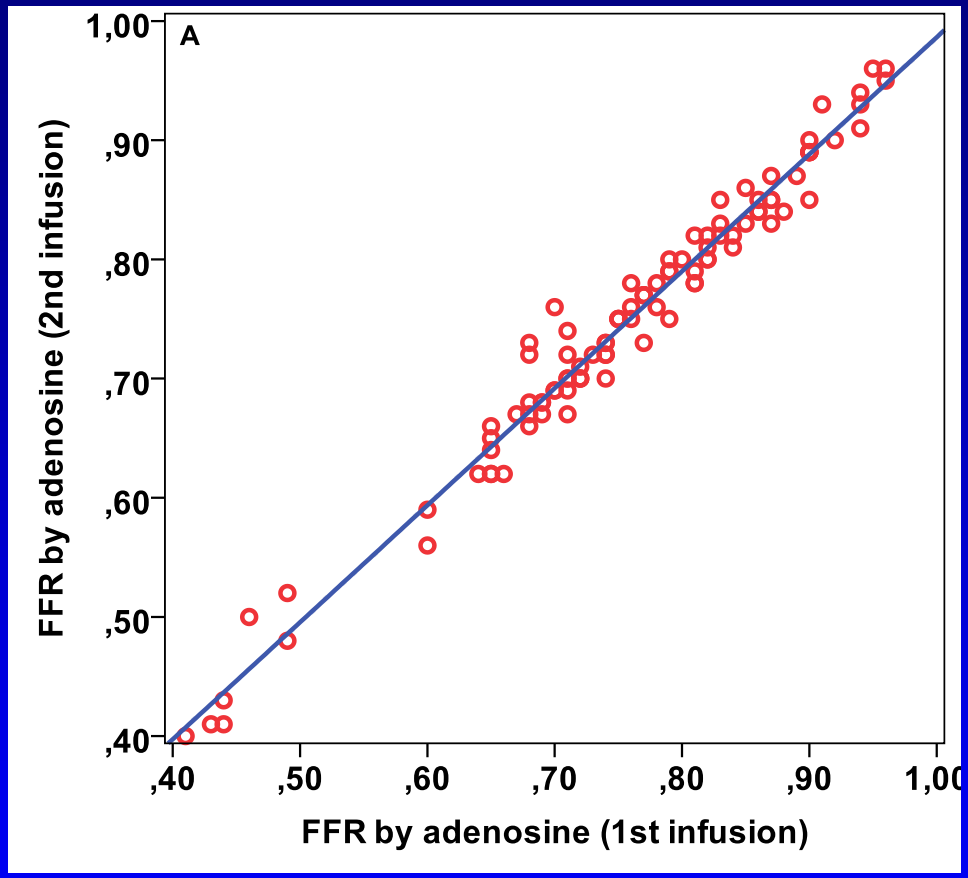
- **PAPAVERINE i.c.**
- **ADENOSINE i.c.**
- **ADENOSINE i.v.**
- **ATP i.c**
- **ATP i.v.**

Well-established

- ***regadenoson ?*** → *new*

Hyperemia with i.v. adenosine is extremely reproducible:





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

Regadenoson study (N=100)
Van Nunen et al, 2014 (in press)
(2x adenosine and 2x regadenoson)

Mr R, born 22-01-1968 (46-year-old

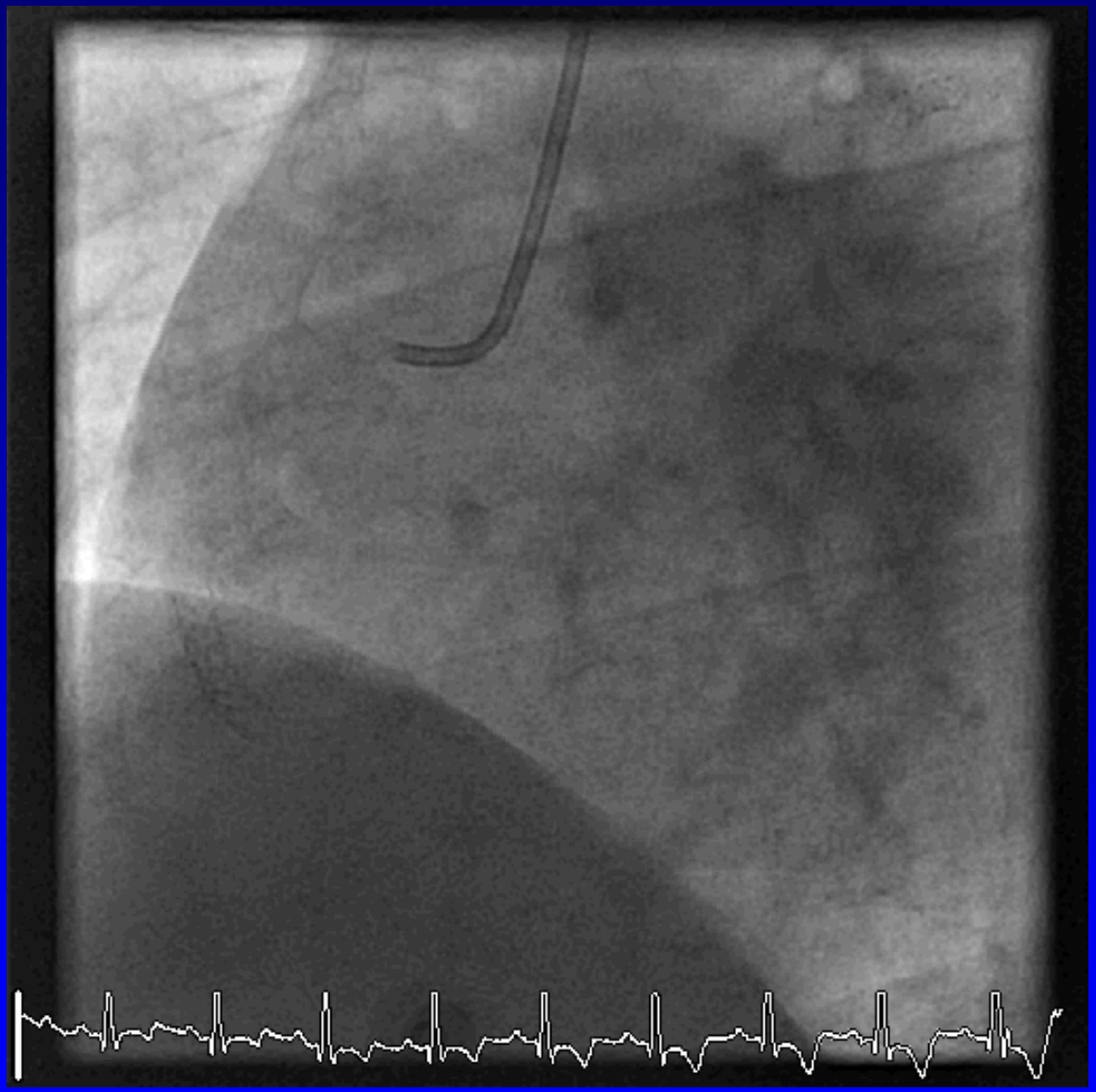
- admission on jan 25th with acute lateral wall MI
- PPCI of occluded diagonal branch

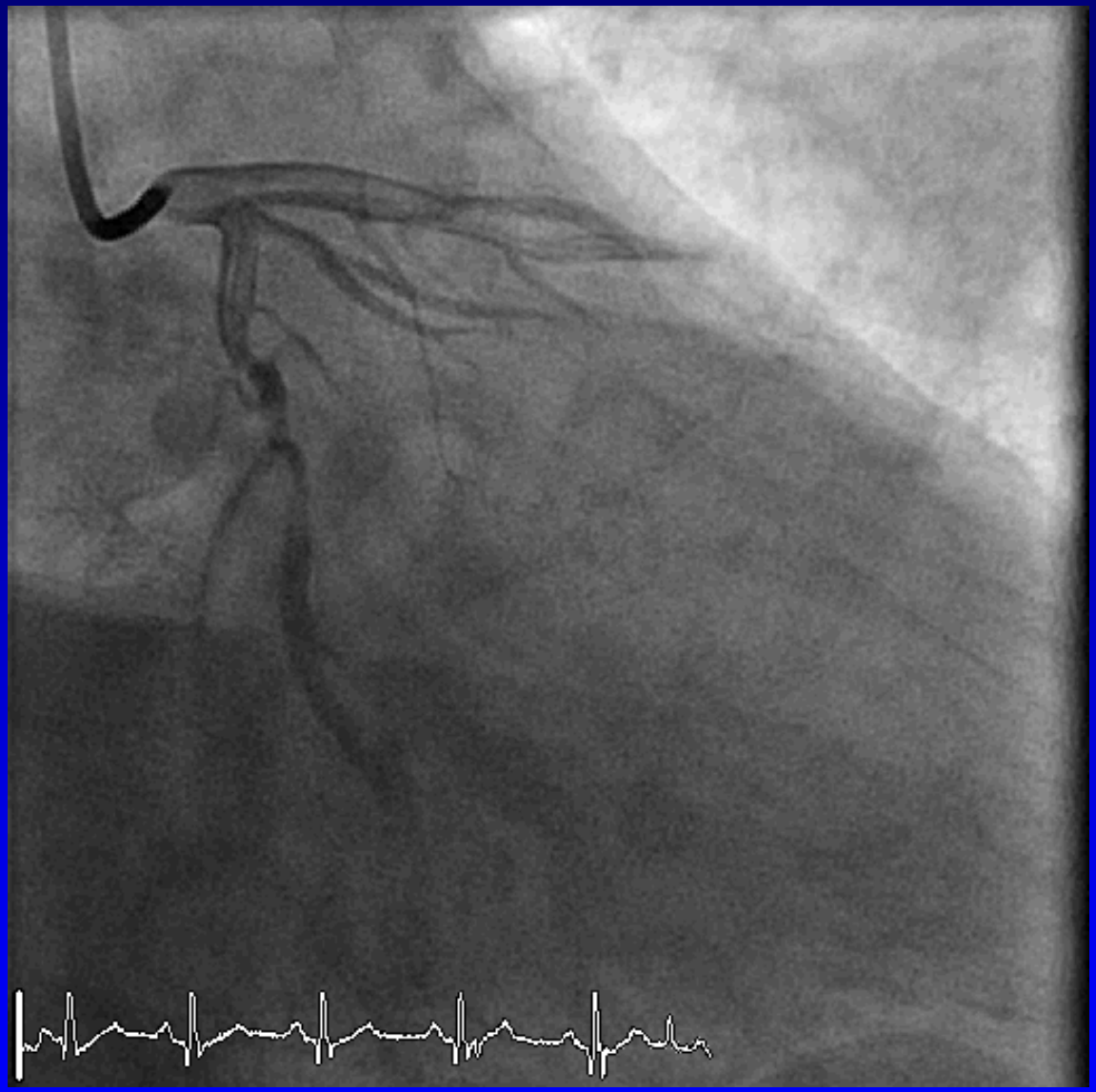
- Concomittant 3-vessel disease:
  - LAD : 50%
  - LCX : long tandem lesion 50-70% + 70-90%
  - RCA : 50-70%

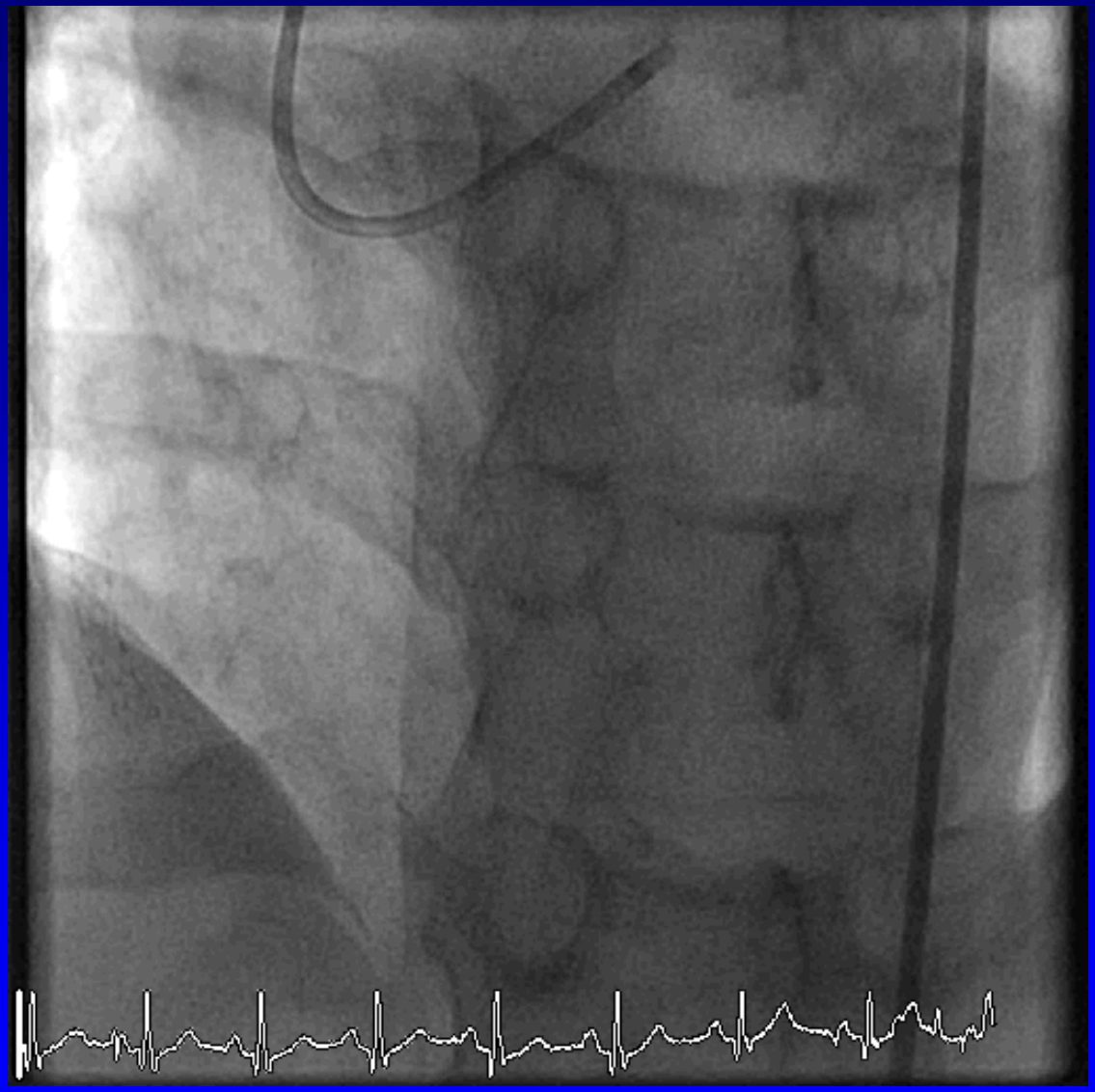
- Syntax score: 22

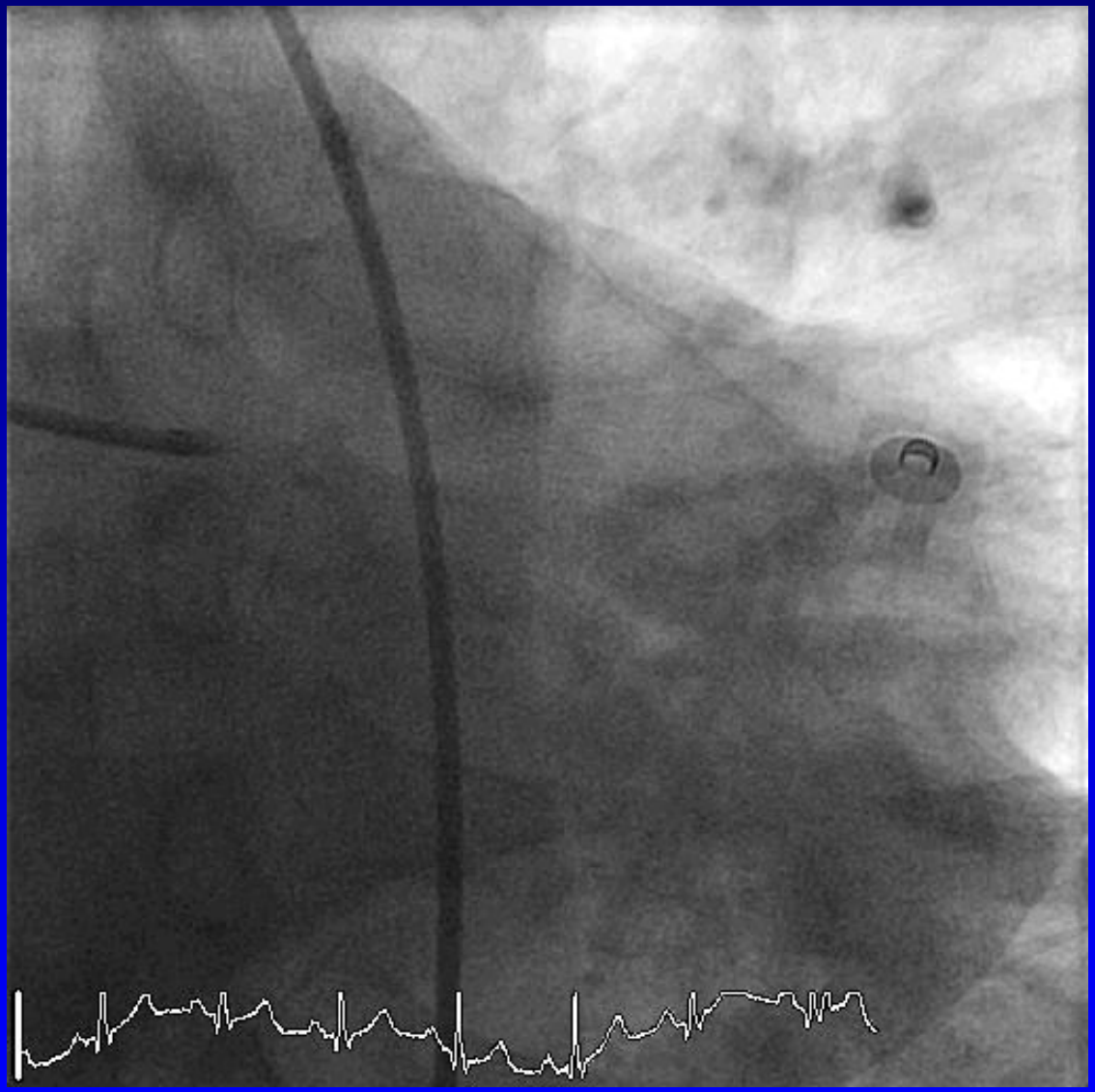
- Heartteam: CABG or FFR-guided MVD PCI

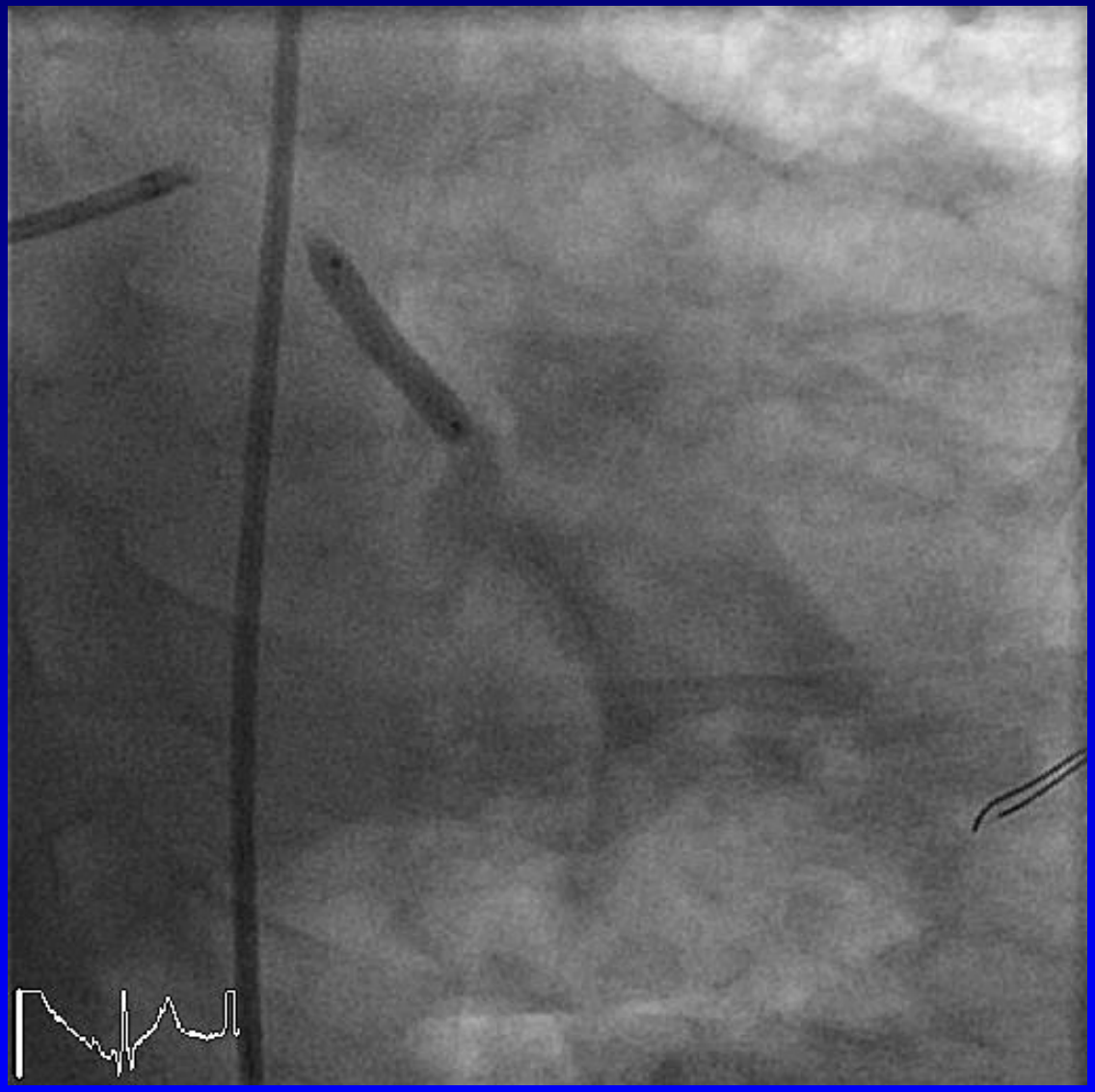
→ ***choice for FFR guided PCI, as pilot for FAME-3***



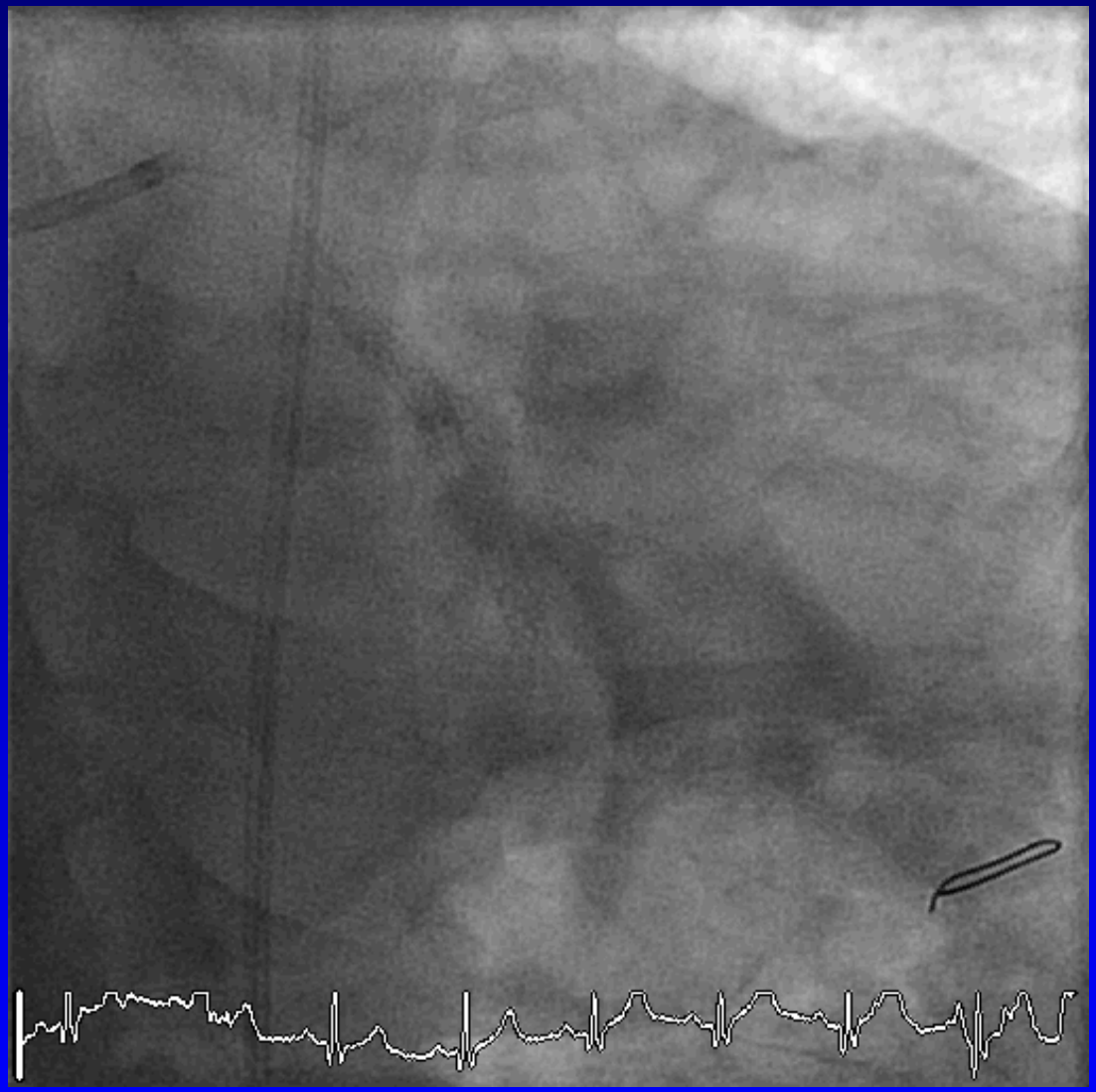








Second stent in CX (3,5x18)



LCX after second stent

Prerequisites for a reliable index for decision making

- sound scientific basis and experimental validation