Imaging & Physiology Summit FFR Workshop

HYPEREMIA

Seoul, Korea, december 6th, 2013

CATHARINA-ZIEKENHUIS

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catharina ziekenhuis

Disclosures:

- Dr Pijls received institutional research grants from St Jude Medical and Maquet and is consultant for St Jude Medical

- Dr Pijls has equity interest in Philips, General Electric, and Heartflow

Is Hyperemia Mandatory ?

For practical reasons, it is advocated presently by some investigators to skip hyperemia,
as defended by Dr Matsuo

Why Are Resting Indices Insufficient ?

- *Limited Clinical Significance*
- *iFR is at odds with experimental validation*
- *resting gradients poorly predict hyperemic gradients*
- *Resting Conditions Are Very Hard to Obtain*
- *Large gray zone*
- *no independent outcome data*
- *cumbersome pullback recording*

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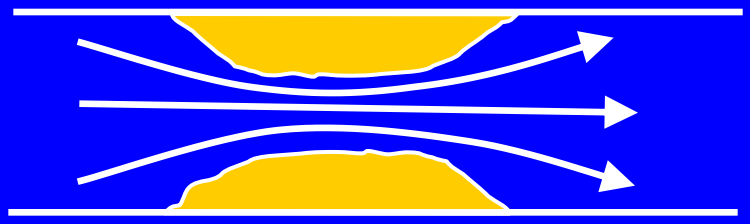
$\Delta P = f.Q + s.Q^2$

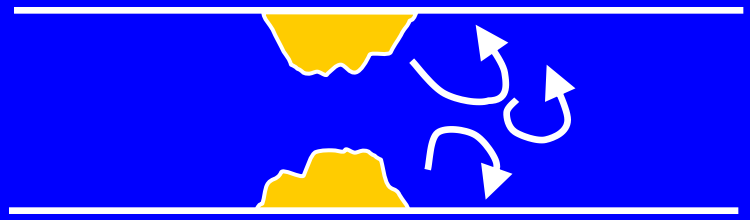
f = friction coefficient



Moderate gradient at rest

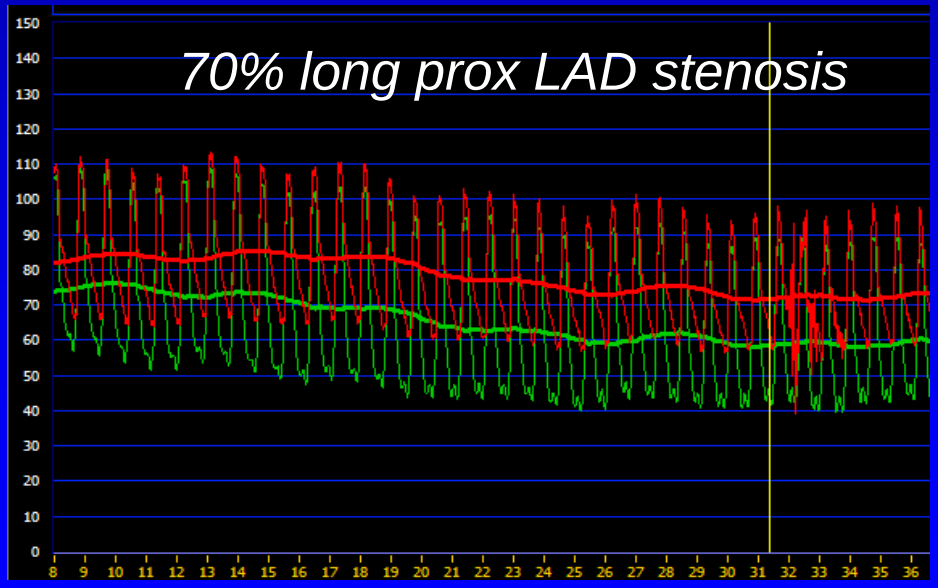
Moderate increment at hyperemia

S = separation coefficient

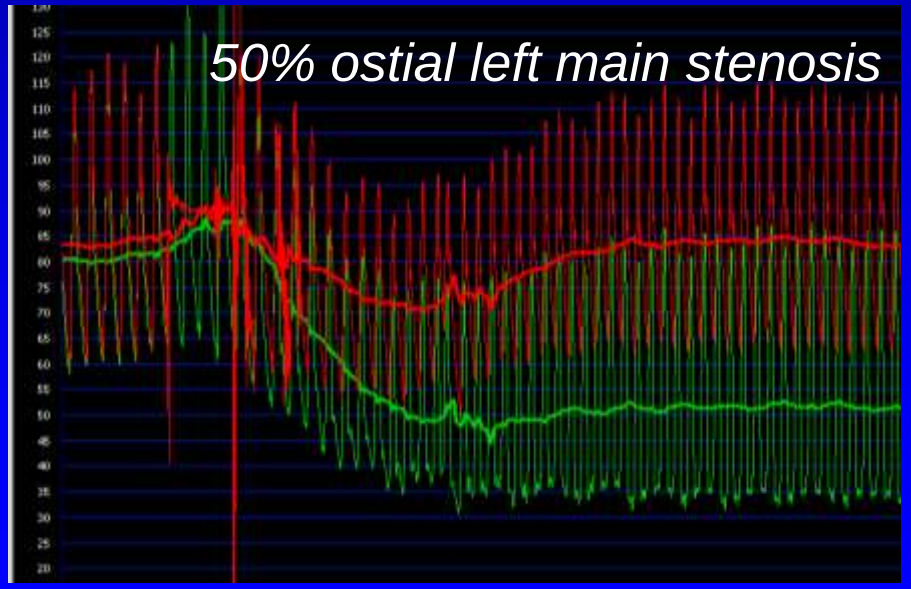


Small gradient at rest

Large gradient at hyperemia



iFR = 0.89 FFR = 0.85



iFR = 0.94 FFR = 0.57

In general:

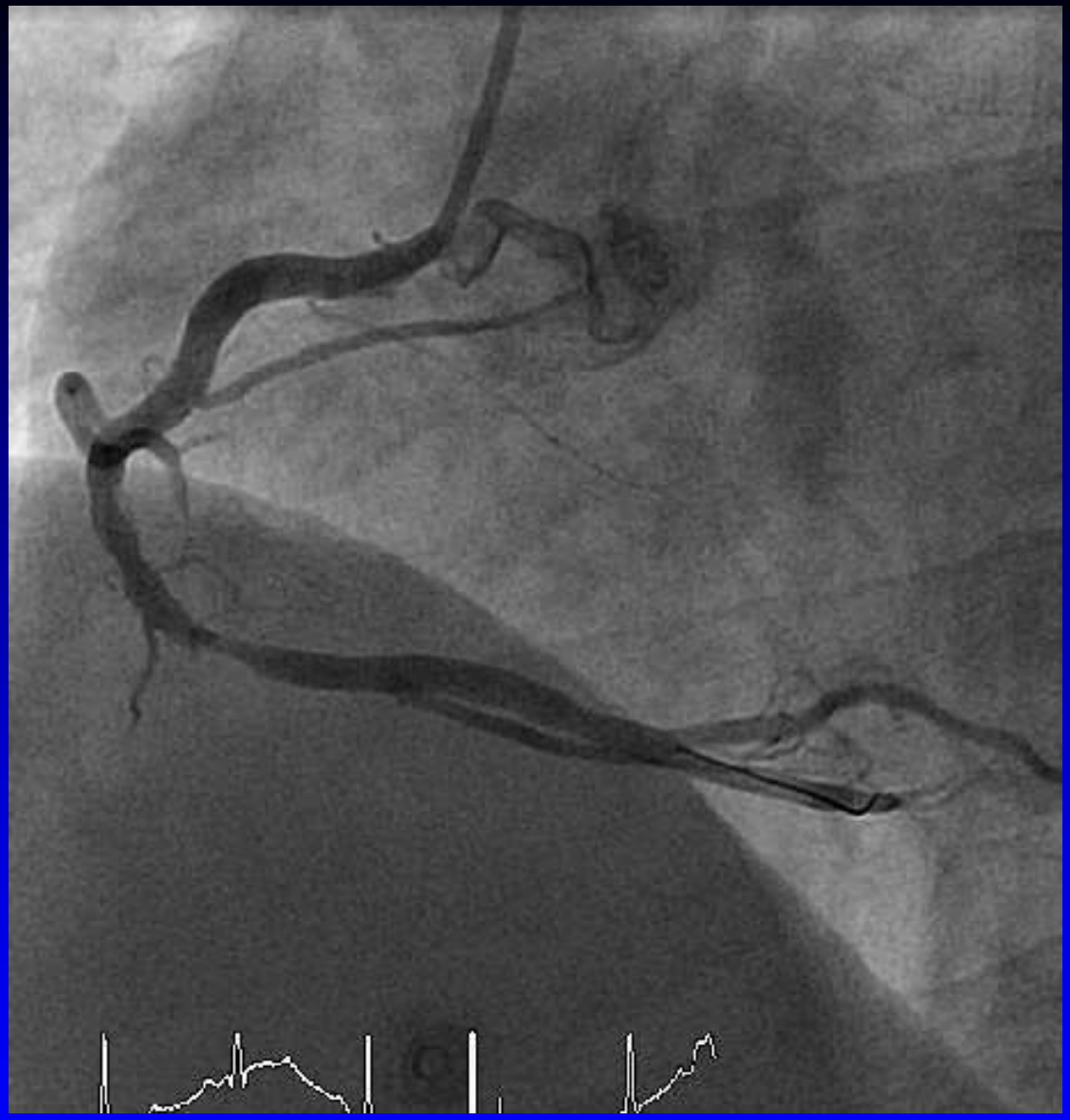
- small perfusion territory, distal stenosis, older patient, moderate long lesion, small artery, microvascular disease:

  → *often moderate gradient at rest with little increase at hyperemia*

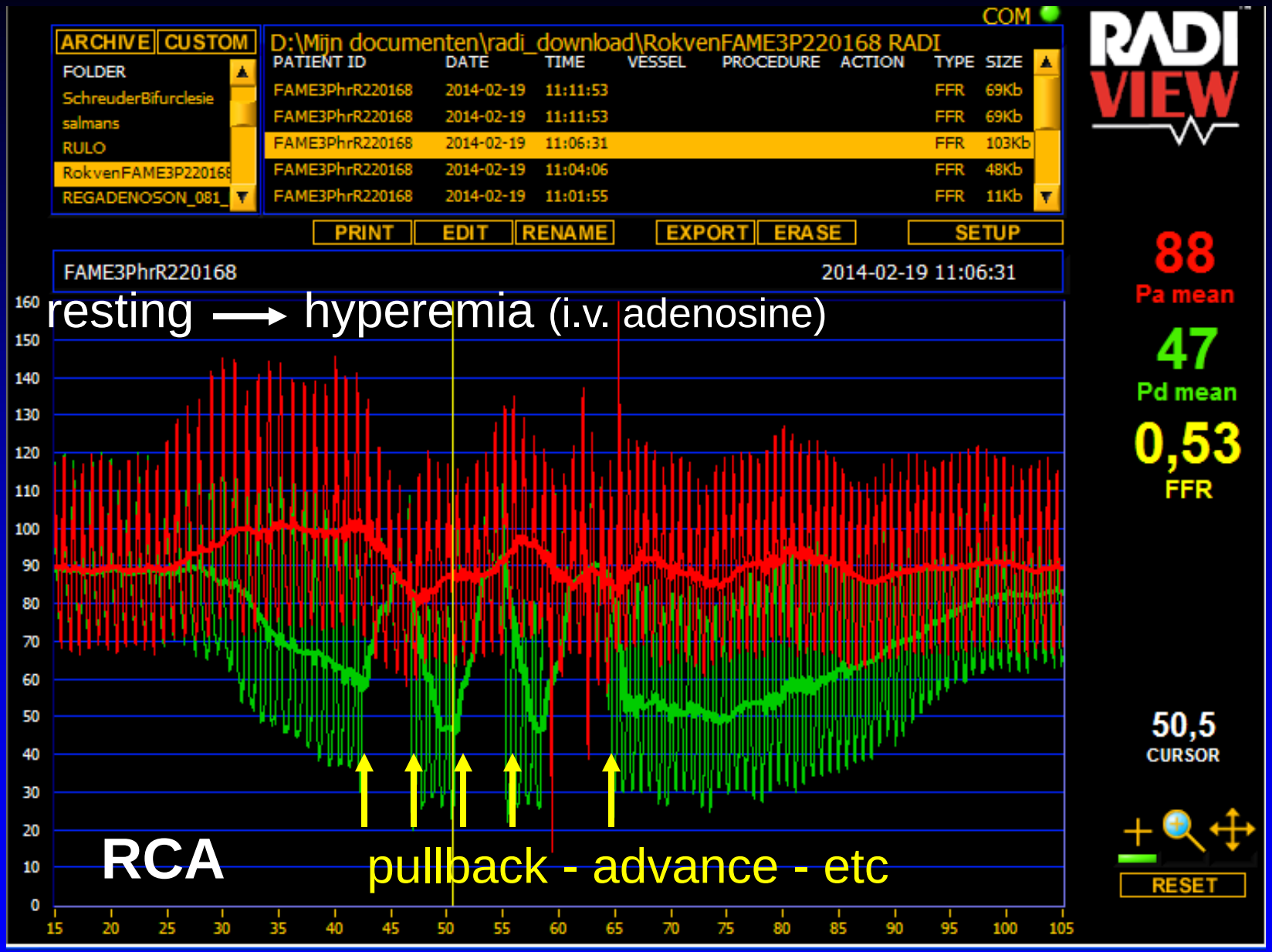
- large perfusion territory, proximal stenosis, young patient, short lesion, large artery, good microvasculature:

  → *often minimal gradient at rest with large increase at hyperemia*

Especially these lesions are missed by resting indexes



Male 46 years old, PressureWire in RCA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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
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RENAME
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ERASE
SETUP
FAME3PhrR220168
2014-02-19 11:06:31
RADI VIEW
88
Pa mean
47
Pd mean
0,53
FFR
50,5
CURSOR
RESET
resting → hyperemia (i.v. adenosine)
RCA
pullback - advance - etc
160
150
140
130
120
110
100
90
80
70
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50
40
30
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10
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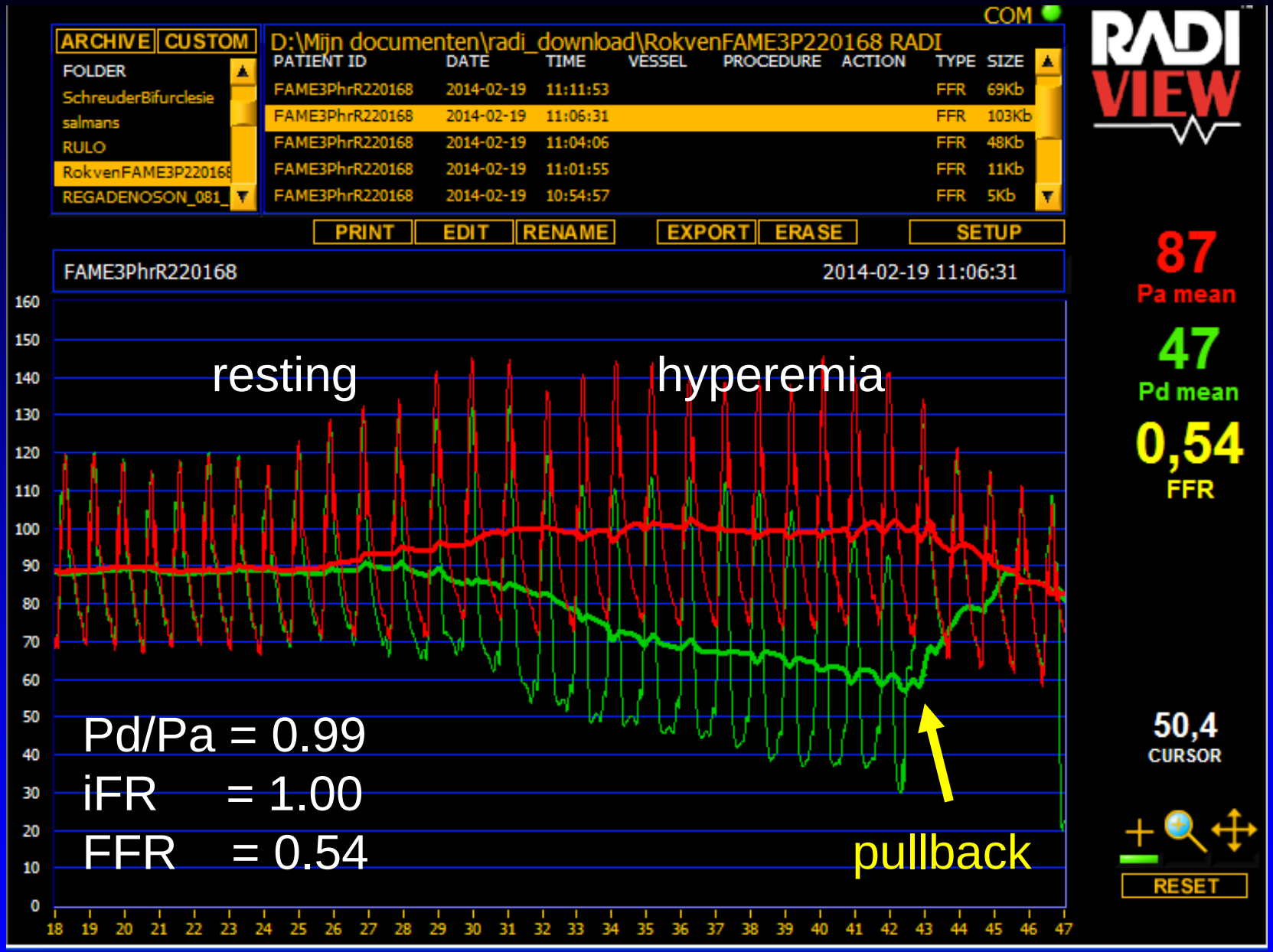
15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105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FAME3PhrR220168 2014-02-19 11:04:06 FFR 48Kb
FAME3PhrR220168 2014-02-19 11:01:55 FFR 11Kb
FAME3PhrR220168 2014-02-19 10:54:57 FFR 5Kb
PRINT
EDIT
RENAME
EXPORT
ERASE
SETUP
RADI VIEW
FAME3PhrR220168
2014-02-19 11:06:31
87
Pa mean
47
Pd mean
0,54
FFR
resting
hyperemia
Pd/Pa = 0.99
iFR = 1.00
FFR = 0.54
pullback
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

Why Are Resting Indices Insufficient ?

- *Limited Clinical Significance*
- *iFR is at odds with experimental validation*
- *resting gradients poorly predict hyperemic gradients*
- *Resting Conditions Are Very Hard to Obtain*
- *Large gray zone*
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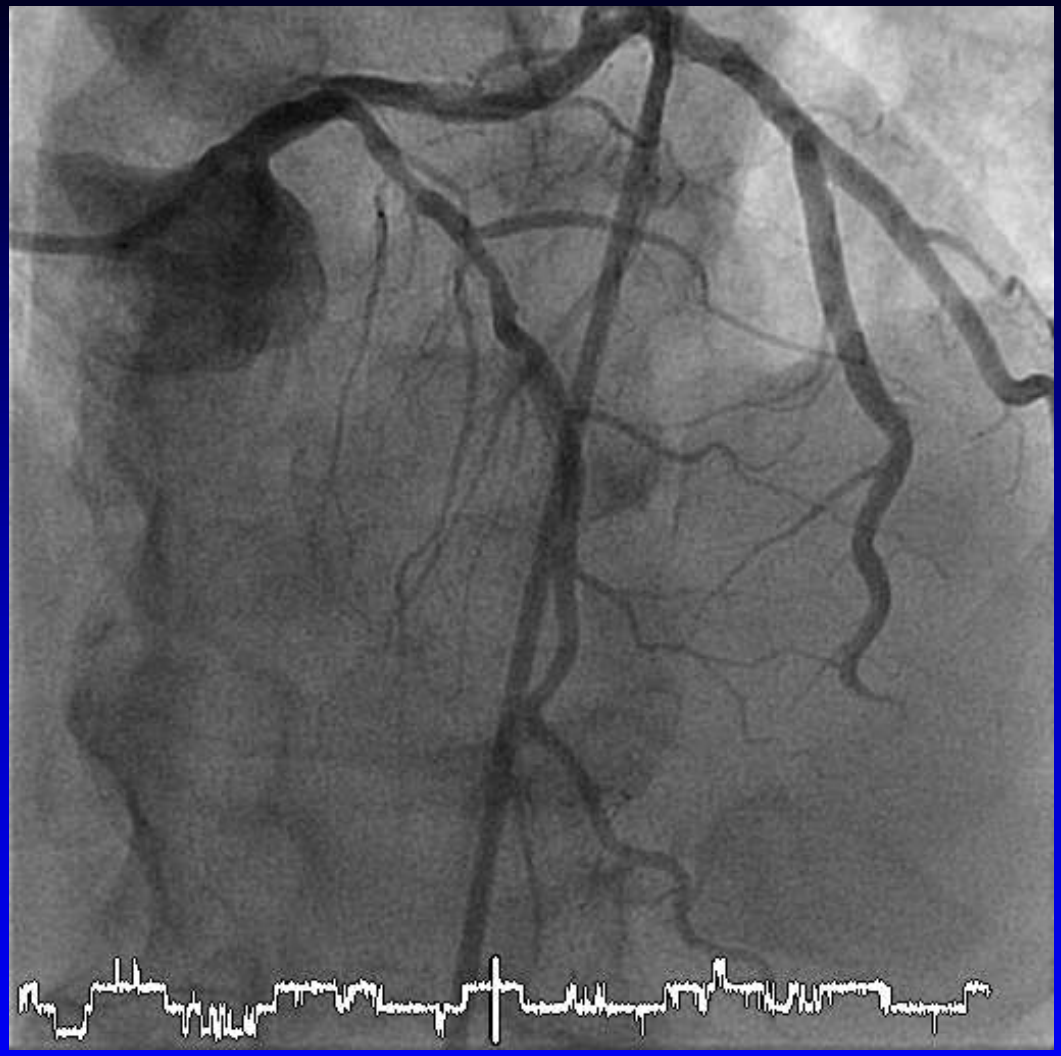
Resting Conditions Are Very Hard to Obtain

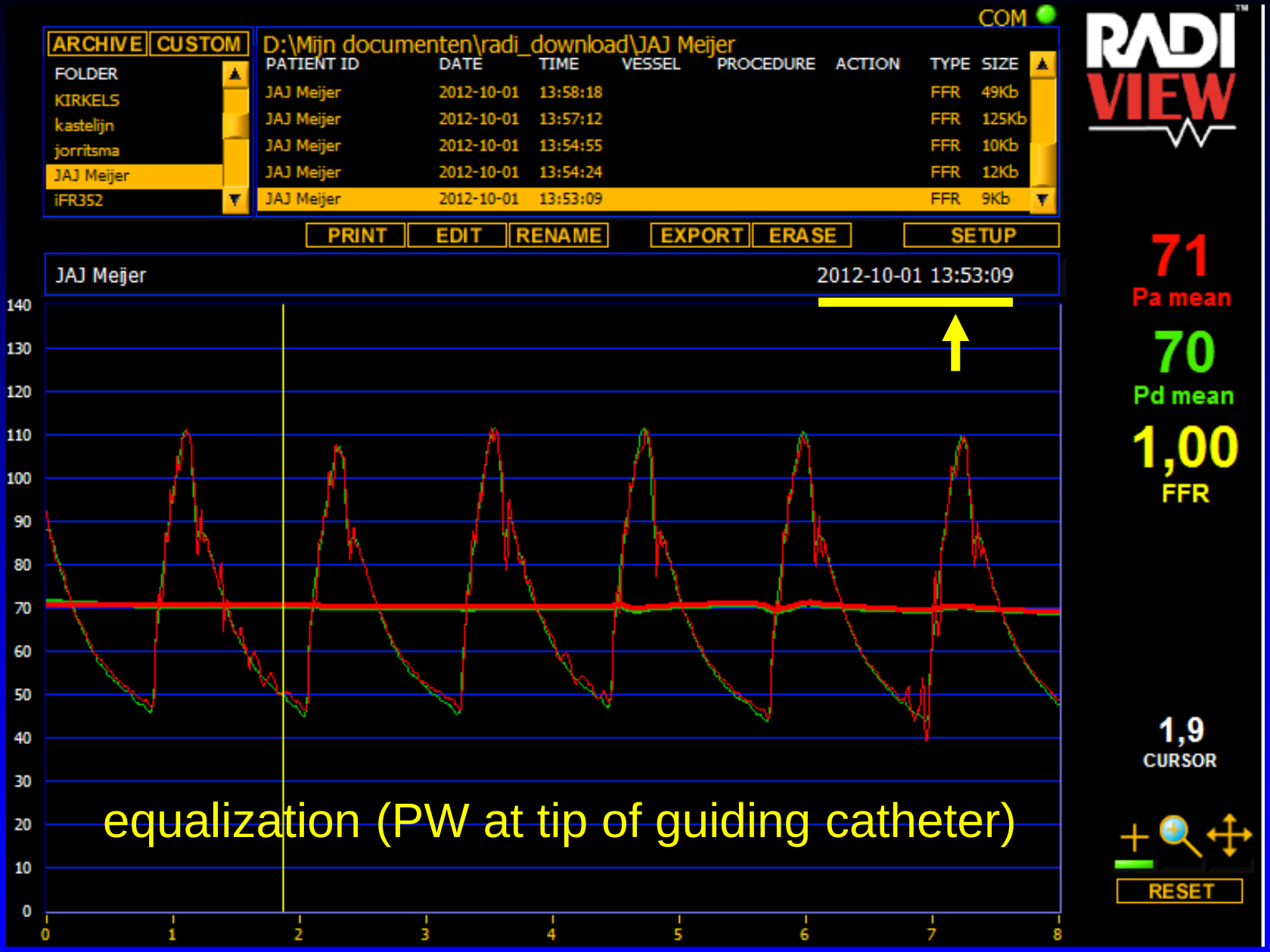
- it is illusionary to believe that truec resting conditions exist in a conscious human in the cath lab

→

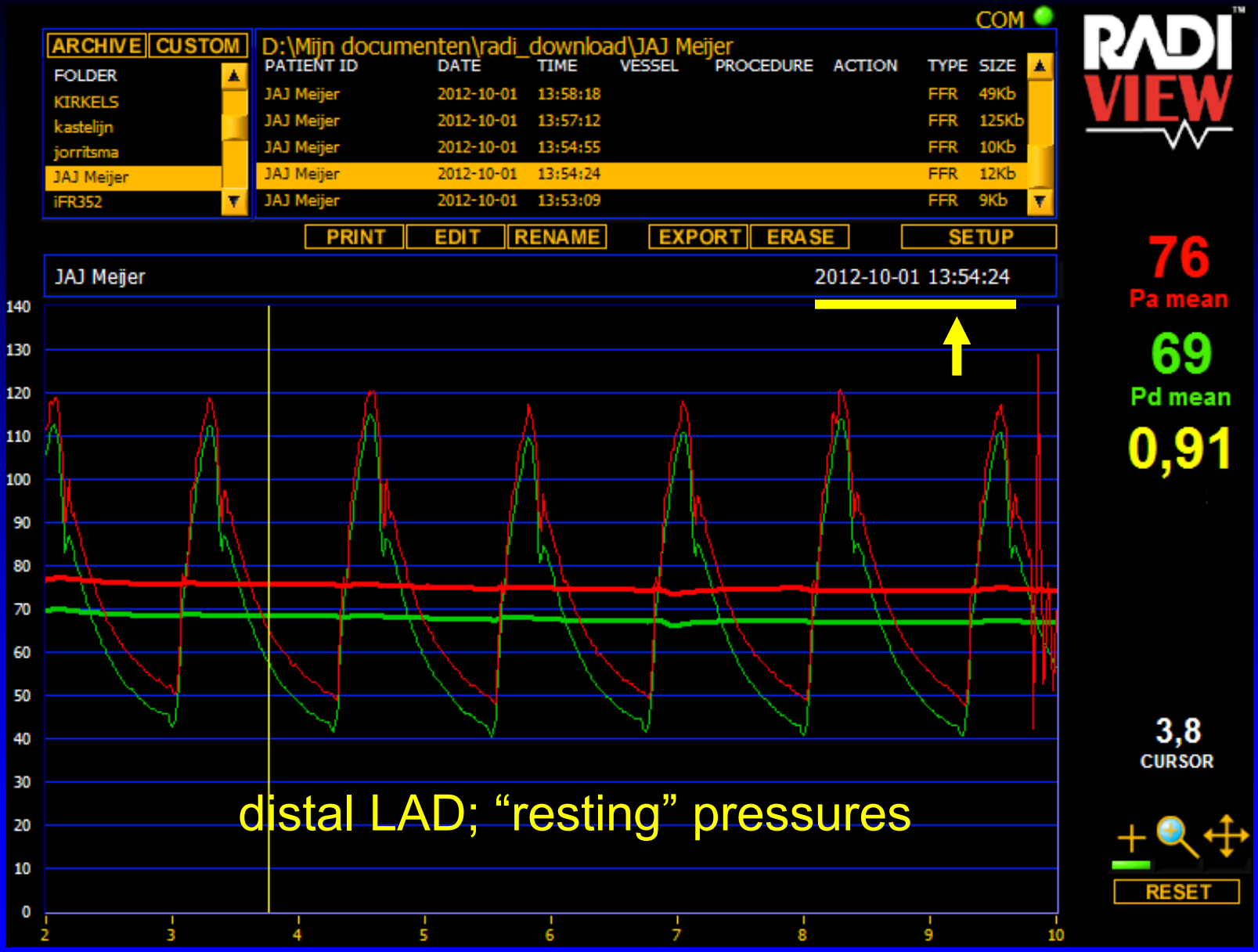
- in fact, the only condition which can be reliably obtained in the cathlab, is ***maximum hyperemia:***
  it is more difficult to create true resting conditions than true hyperemia !!



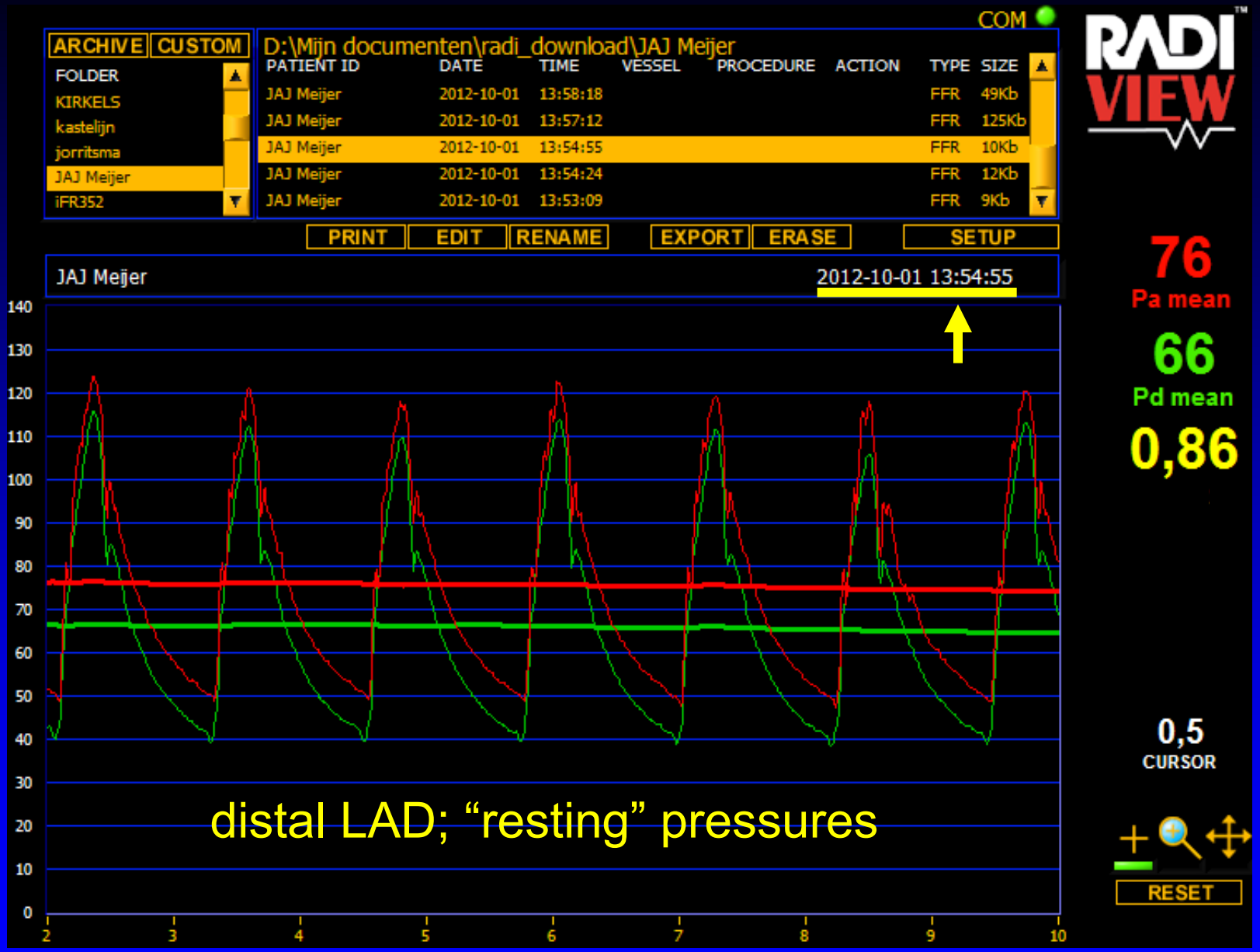
Mr M, born 26-03-1937,
long mild/moderate proximal LAD lesion



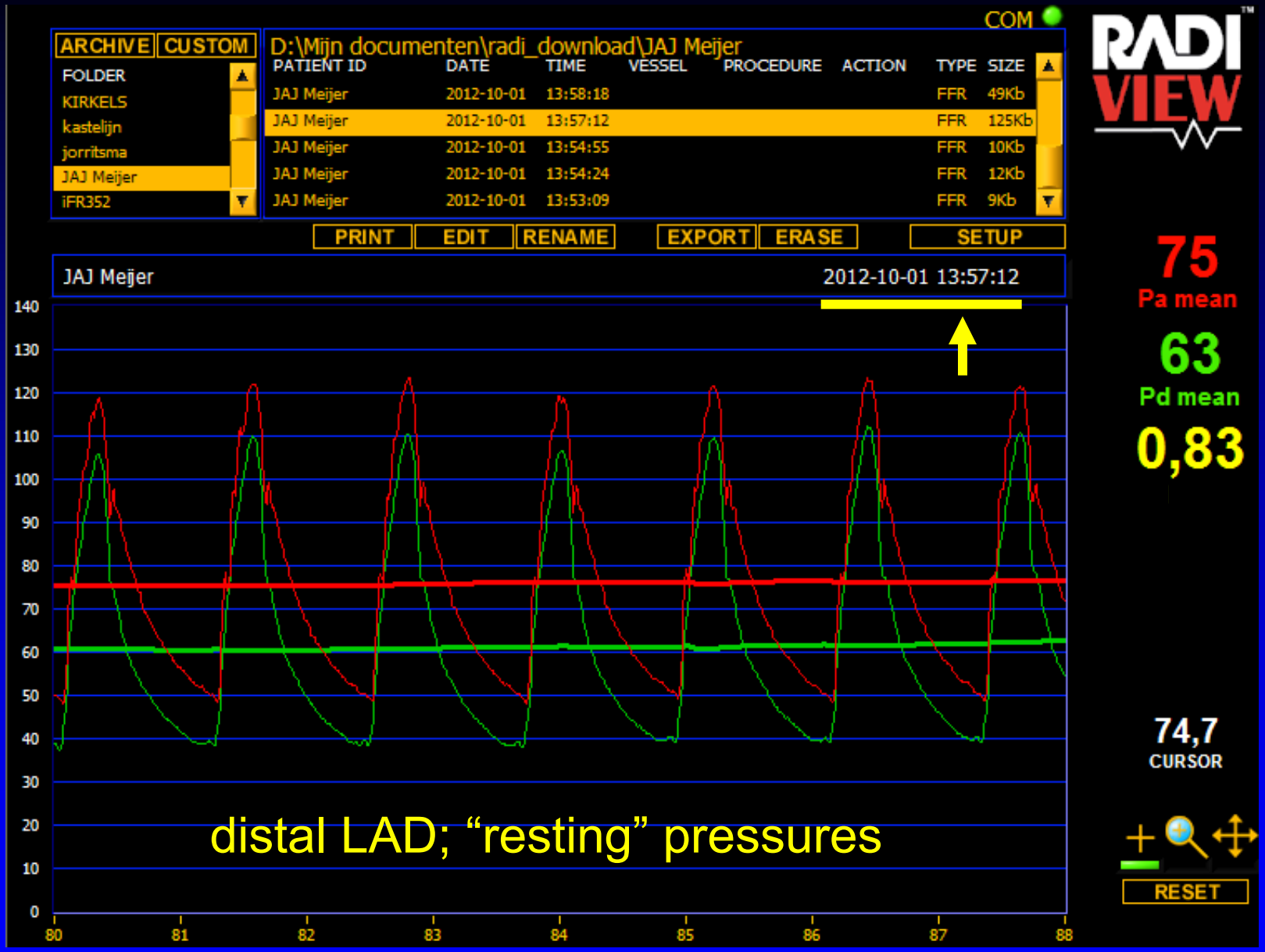
long moderate proximal LAD lesion; equalization



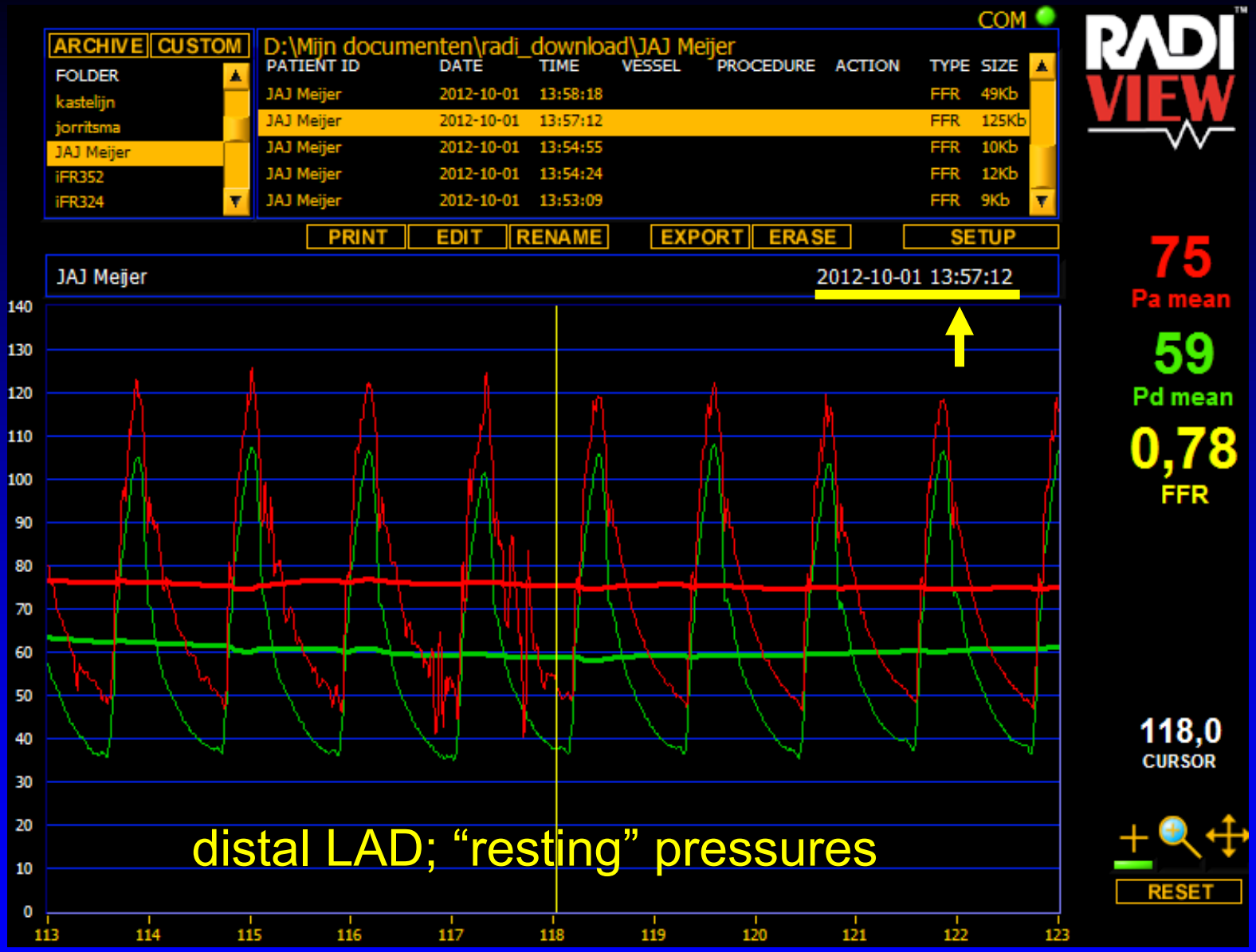
PW in distal LAD; patient “asleep” (relaxed)



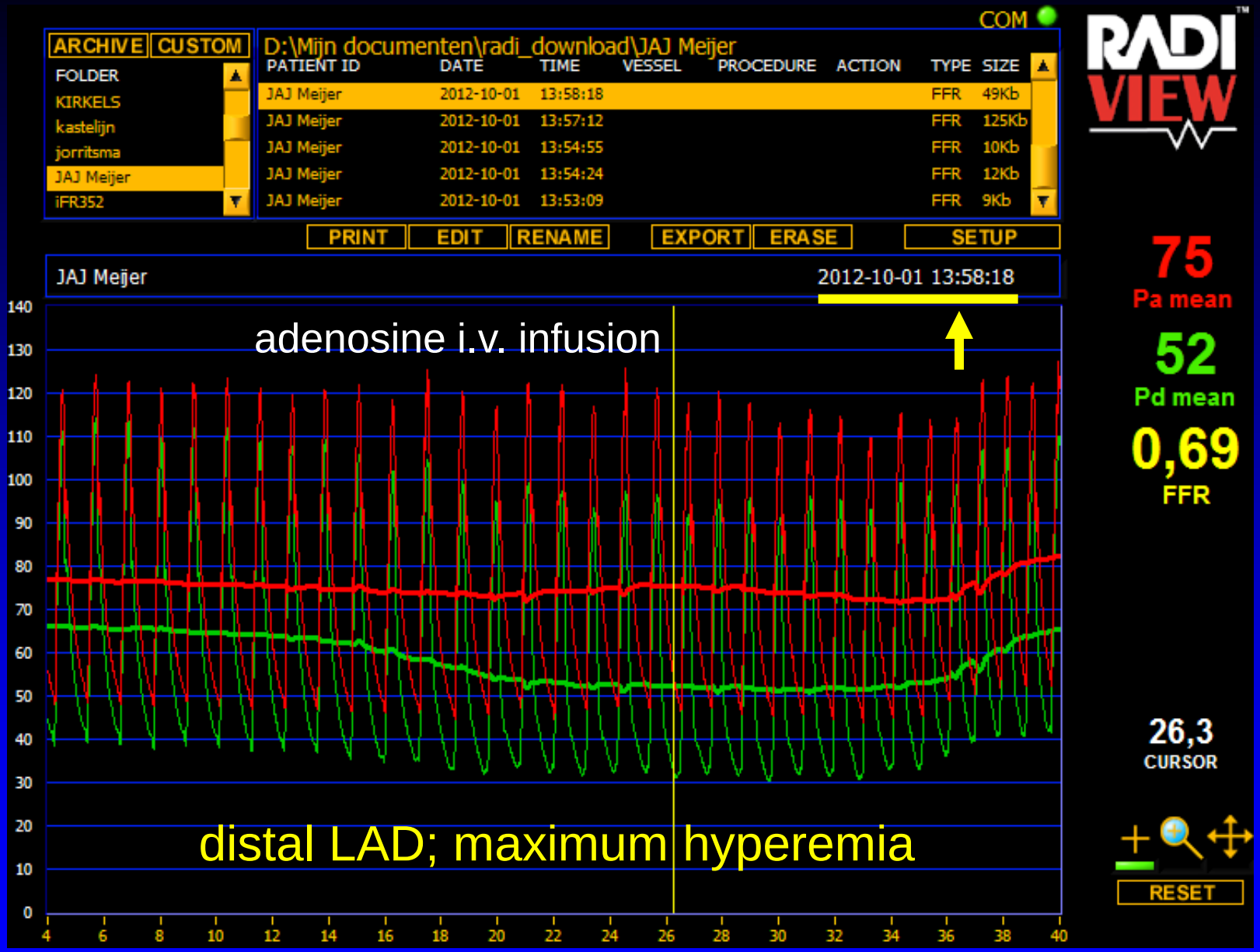
PW in distal LAD; patient “awake”



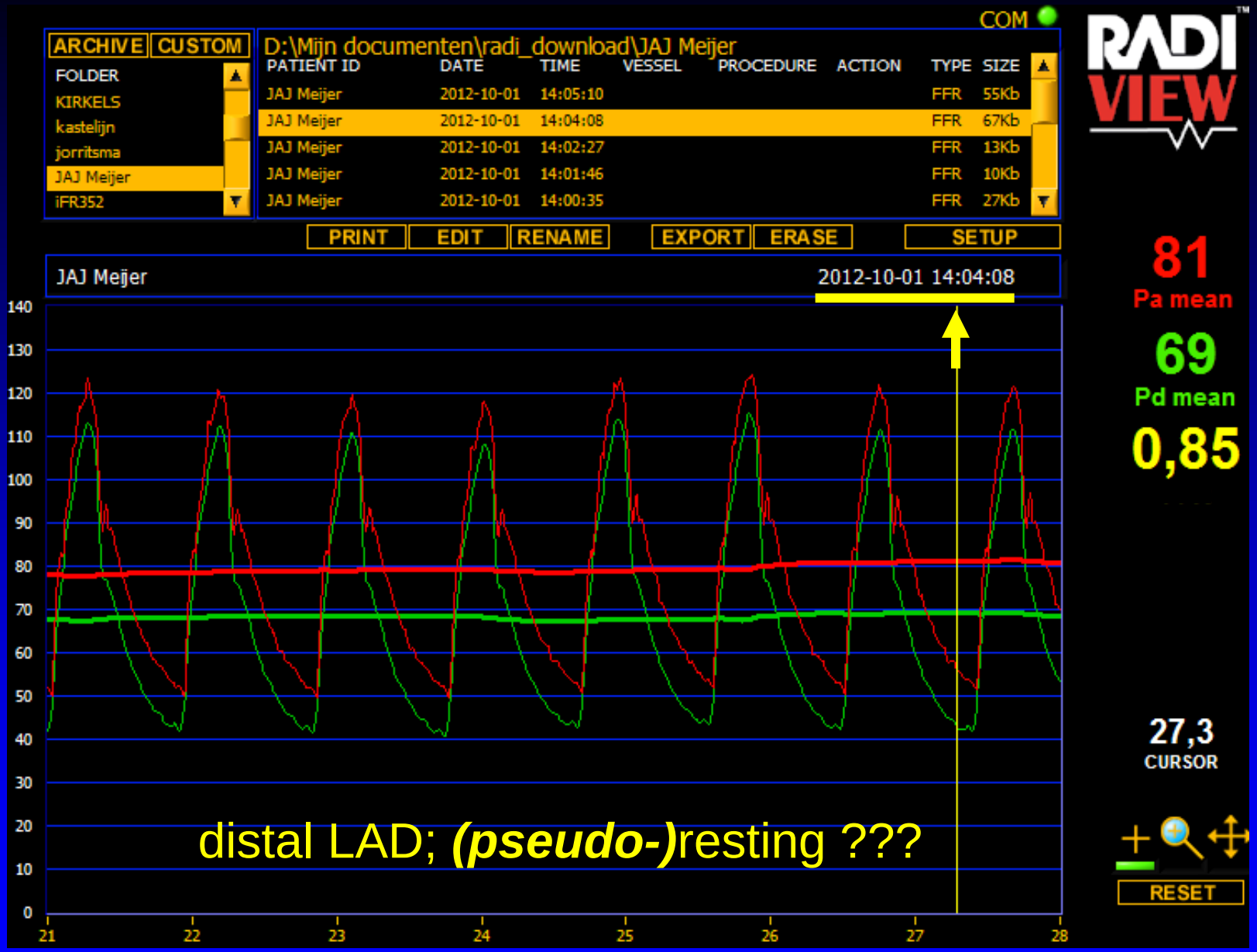
prior to adenosine: explanation to patient what is going to happen



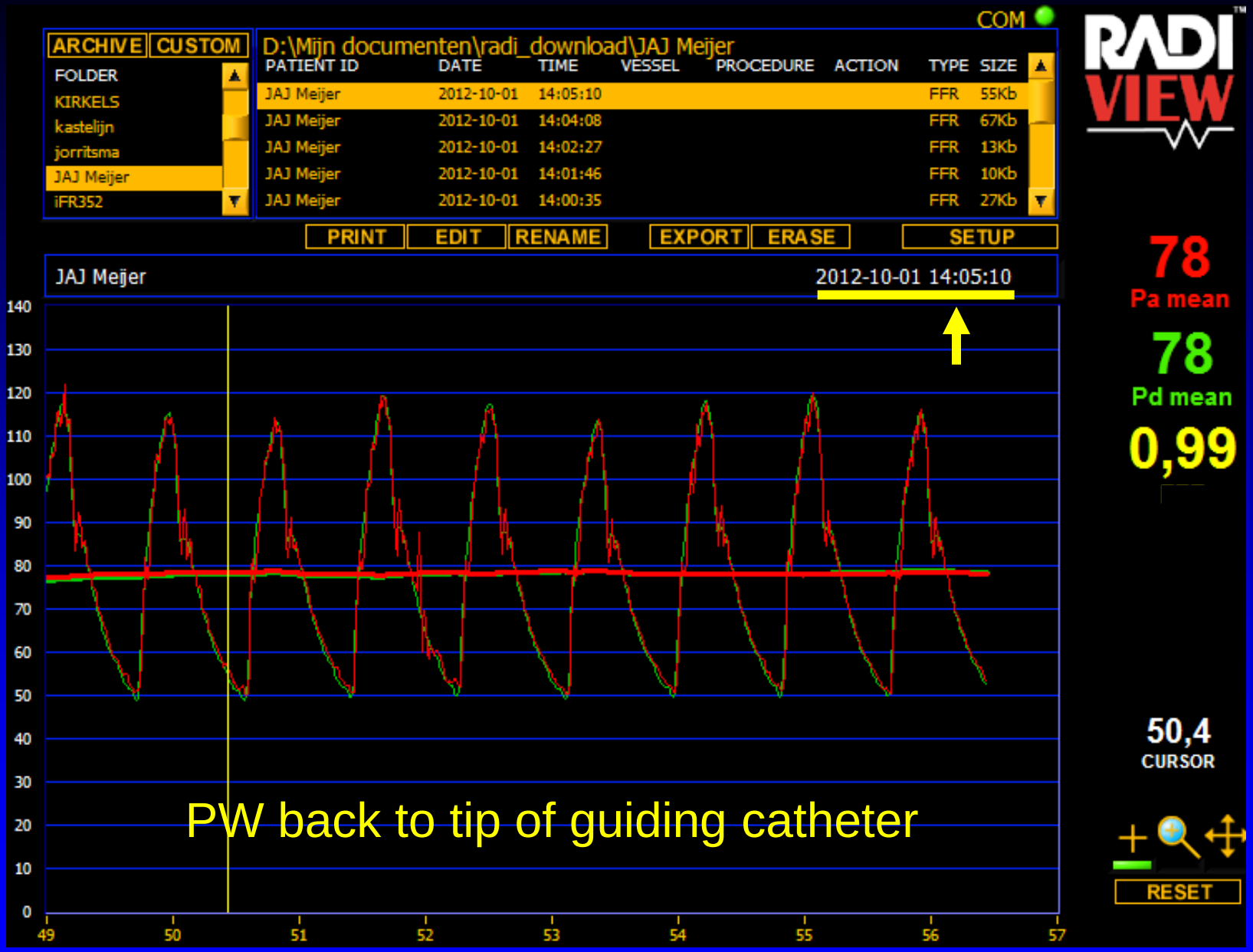
advancing the wire 2 cm and pulling it back again



Measurement of FFR



After waiting for 5 minutes, not touching anything



verification of equal pressures and absence of drift

iFR = 0.89

P_d/P_a=0.90

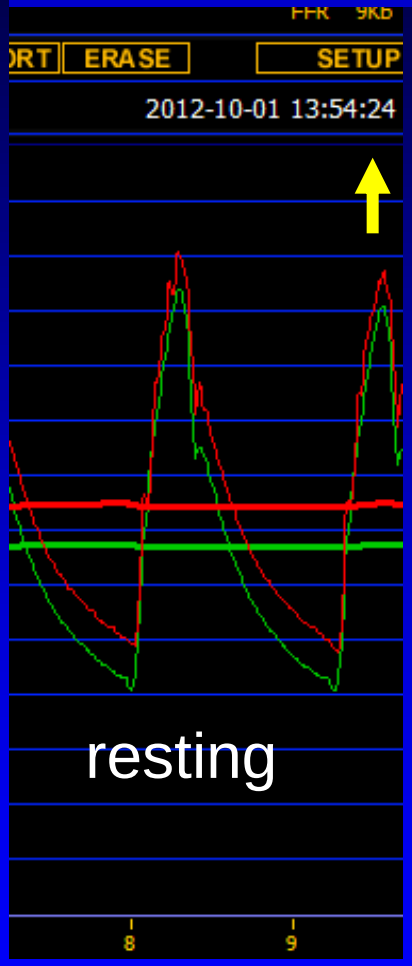
iFR = 0.84

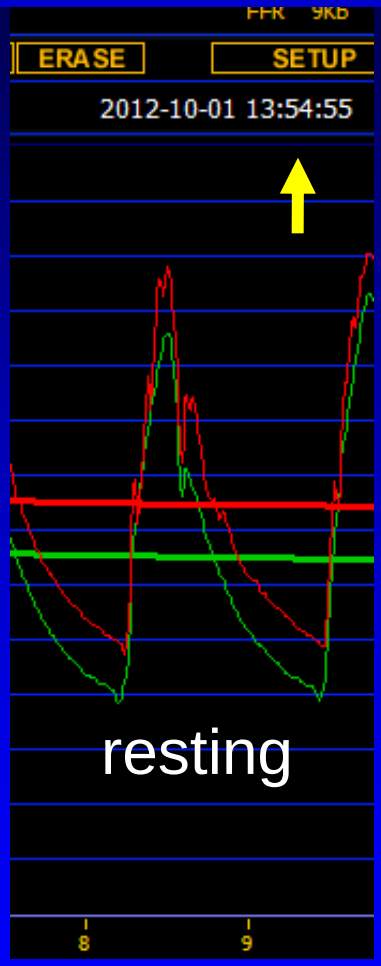
P_d/P_a=0.87

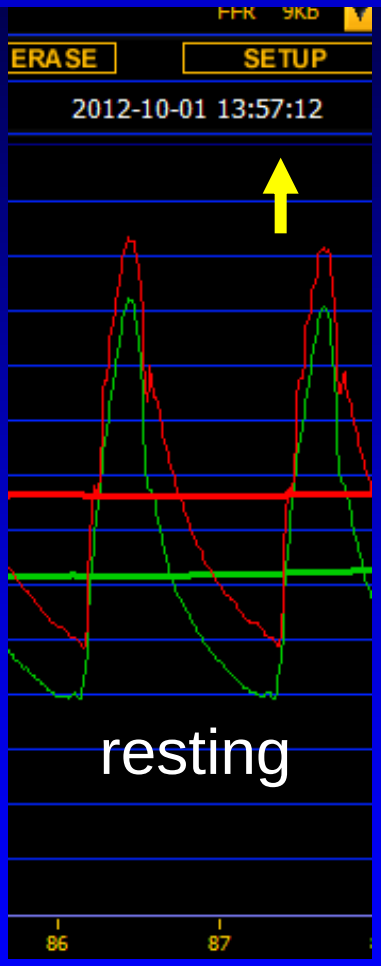
iFR = 0.76

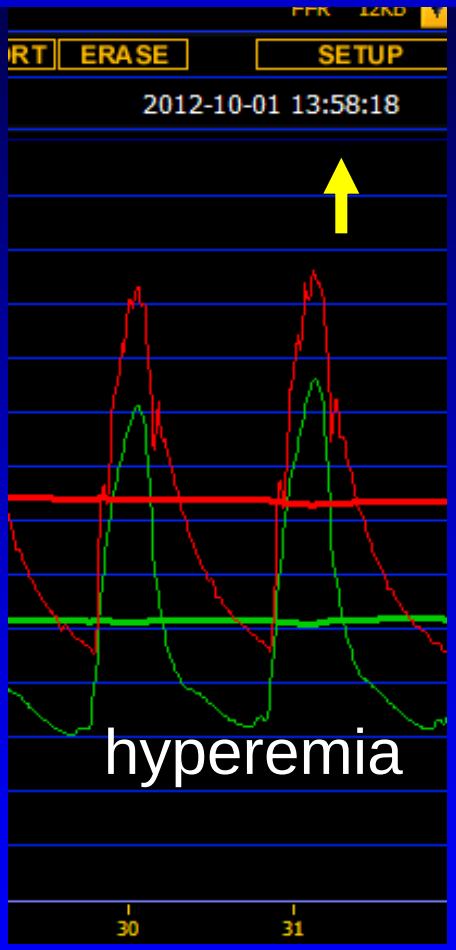
P_d/P_a=0.80

FFR = 0.69









what is "resting"?

nothing is so variable in the cathlab as "resting"

- obtaining true resting conditions in a conscious patient in the catheterization laboratory, is illusionary…….

…..and as a consequence, large variation in cut-off values to detect ischemia are found for resting indices:

Traditional CFR: ischemic threshold varies from 1.6 to 3.5

iFR: 0.83 (Advise study, Sen et al)
0.88 (Koo et al)
0.90 (Jeremias et al)

Similar for all indexes which rely upon resting value of flow

Why Are Resting Indices Insufficient ?

- *Limited Clinical Significance*
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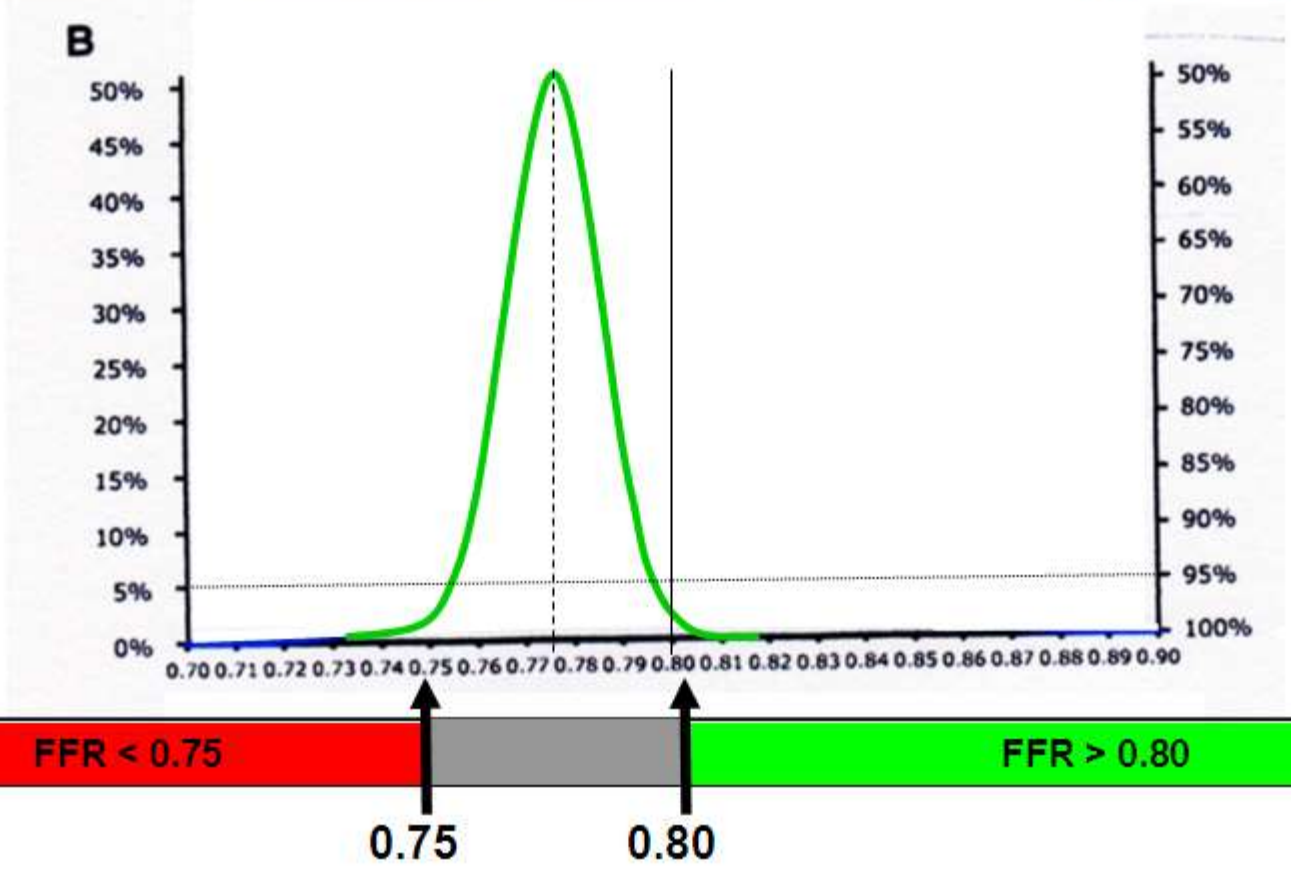
- *resting gradients poorly predict hyperemic gradients*
- *Resting Conditions Are Very Hard to Obtain*
- *Large gray zone between ischemic and non-isch values*
- *no independent outcome data*
- *cumbersome pullback recording*

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

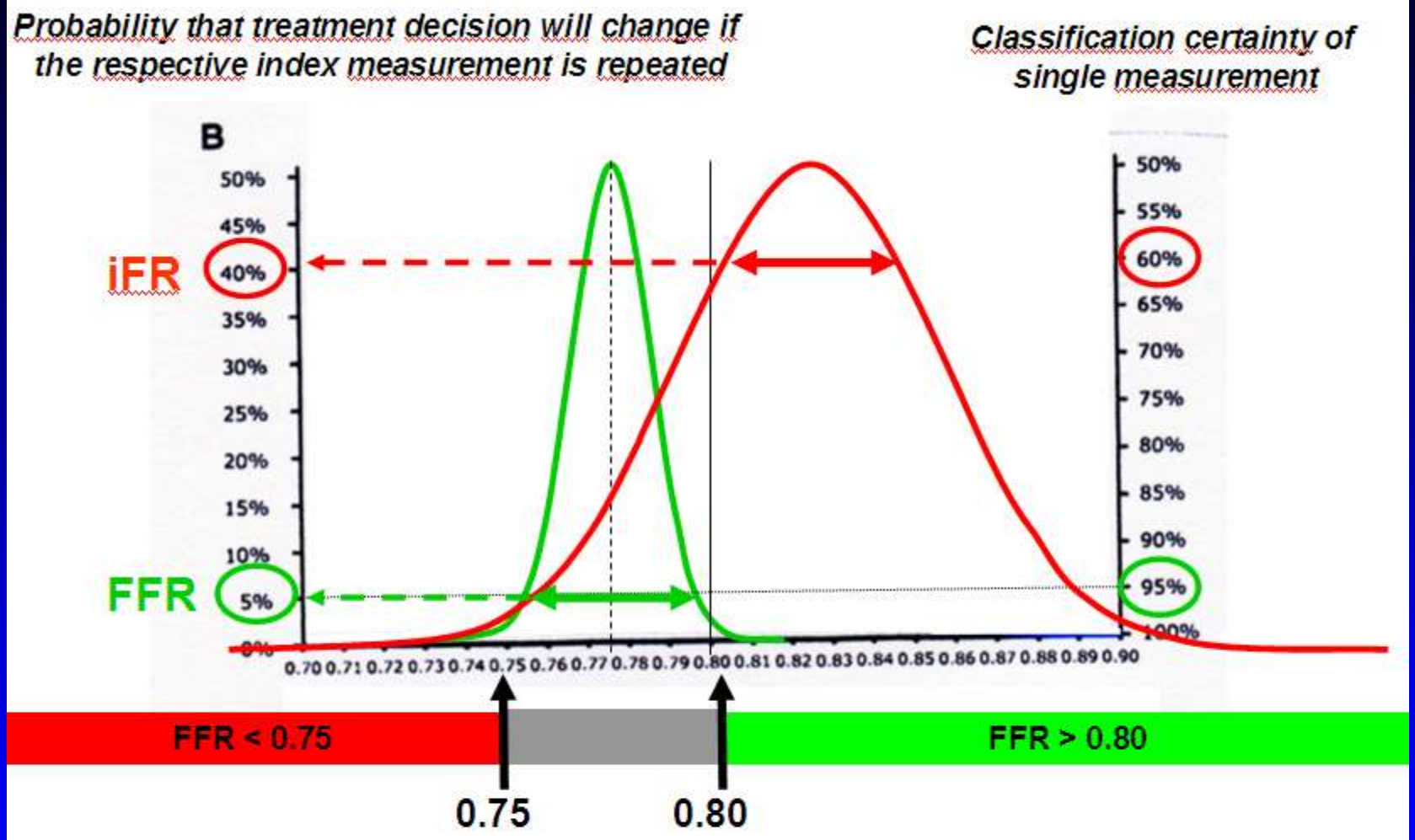
Classification certainty of single measurement

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.

FFR (Fractional Flow Reserve)


Probability that treatment decision will change if the respective index measurement is repeated
Classification certainty of single measurement
B
iFR
FFR
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
50%
55%
60%
65%
70%
75%
80%
85%
90%
95%
100%
0.70 0.71 0.72 0.73 0.74 0.75 0.76 0.77 0.78 0.79 0.80 0.81 0.82 0.83 0.84 0.85 0.86 0.87 0.88 0.89 0.90
FFR < 0.75
FFR > 0.80
0.75
0.80
FFR, VERIFY study (coefficient of variation 2.4 %)
iFR, ADVISE study (coefficient of variation 6.1 %)

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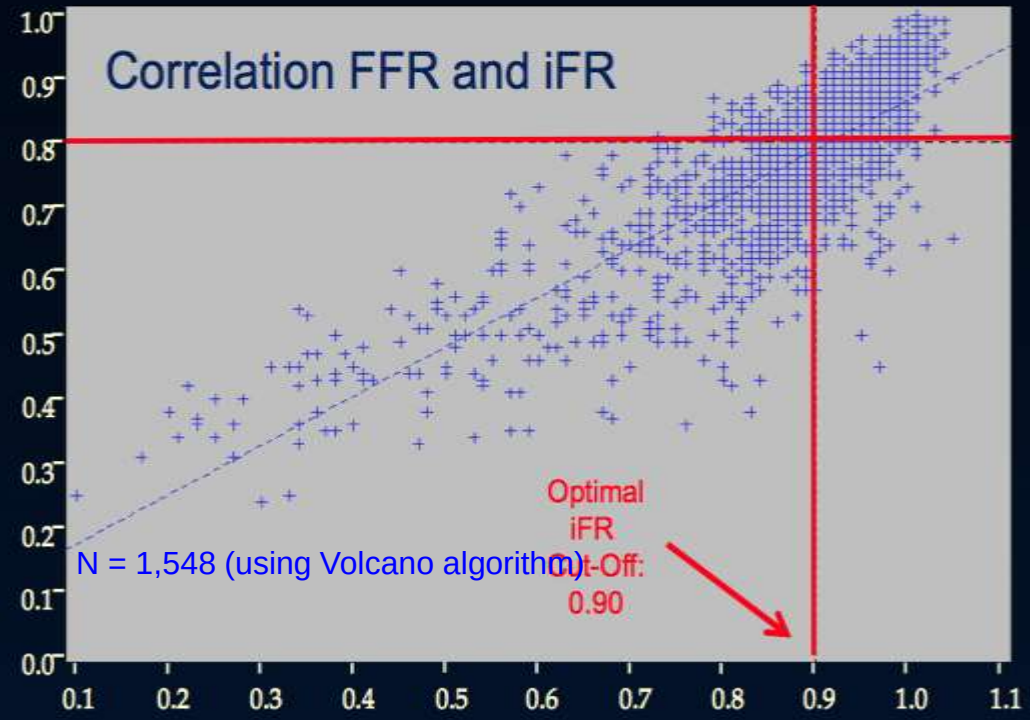
- *iFR is at odds with experimental validation*
- *resting gradients poorly predict hyperemic gradients*
- *Resting Conditions Are Very Hard to Obtain*
- *Large gray zone*
- *no independent outcome data*
  (only retrospective data or non-inferiority studies)
- *cumbersome pullback recording*

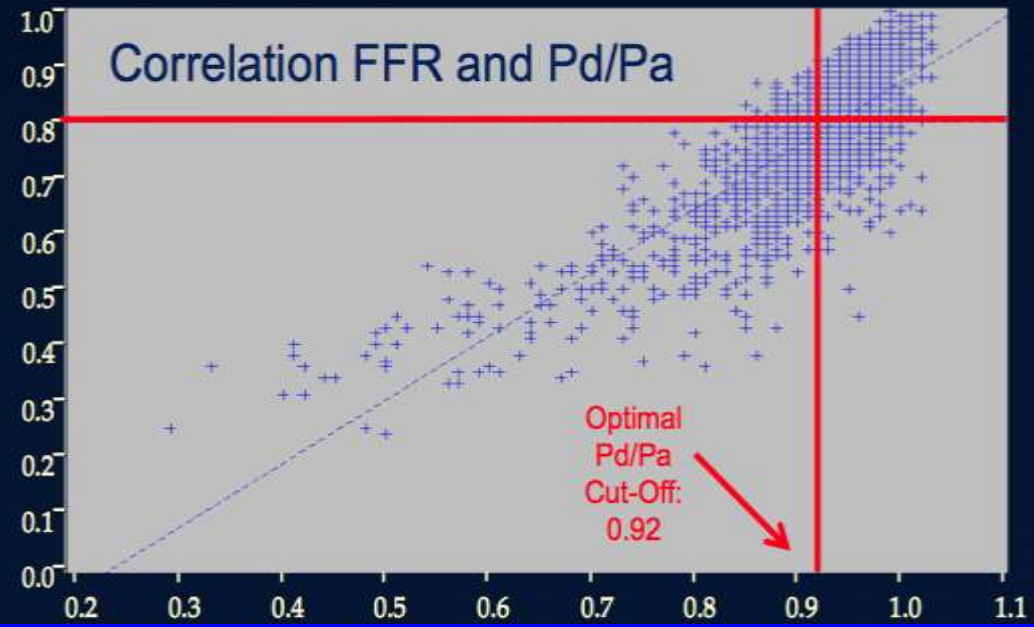
RESOLVE STUDY:

- Largest registry comparing the different resting indexes to FFR as a gold standard
- 1768 patients
- independent analysis by core-lab of CRF
- *no difference between different resting indexes*
- *agreement rate with FFR ~ 80 %*

Jeremias et al, JACC 2013

RESOLVE study (N=1768)





iFR

C-Statistic	0.80
Sensitivity	78.5%
Specificity	82.3%
PPV	86.0%
NPV	73.5%
Accuracy	80.1%

Pd/Pa

C-Statistic	0.82
Sensitivity	75.9%
Specificity	87.4%
PPV	89.3%
NPV	72.6%
Accuracy	80.7%

Jeremias, CRF, 2013

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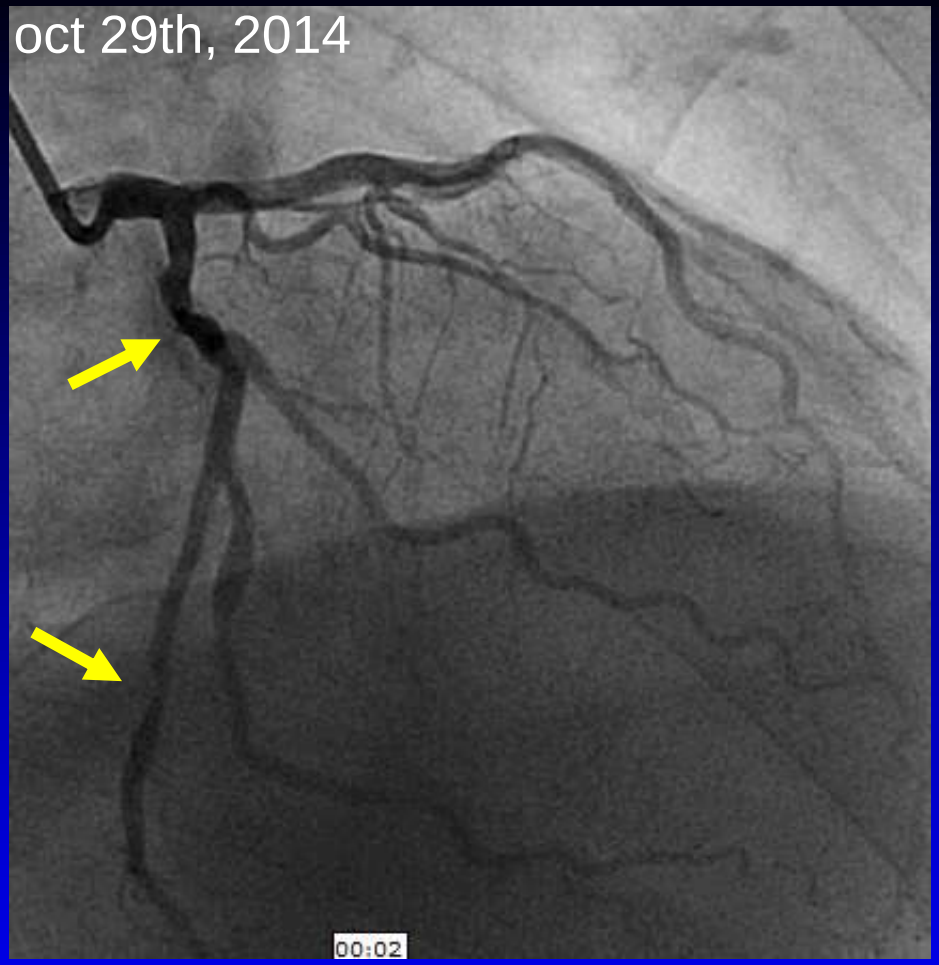
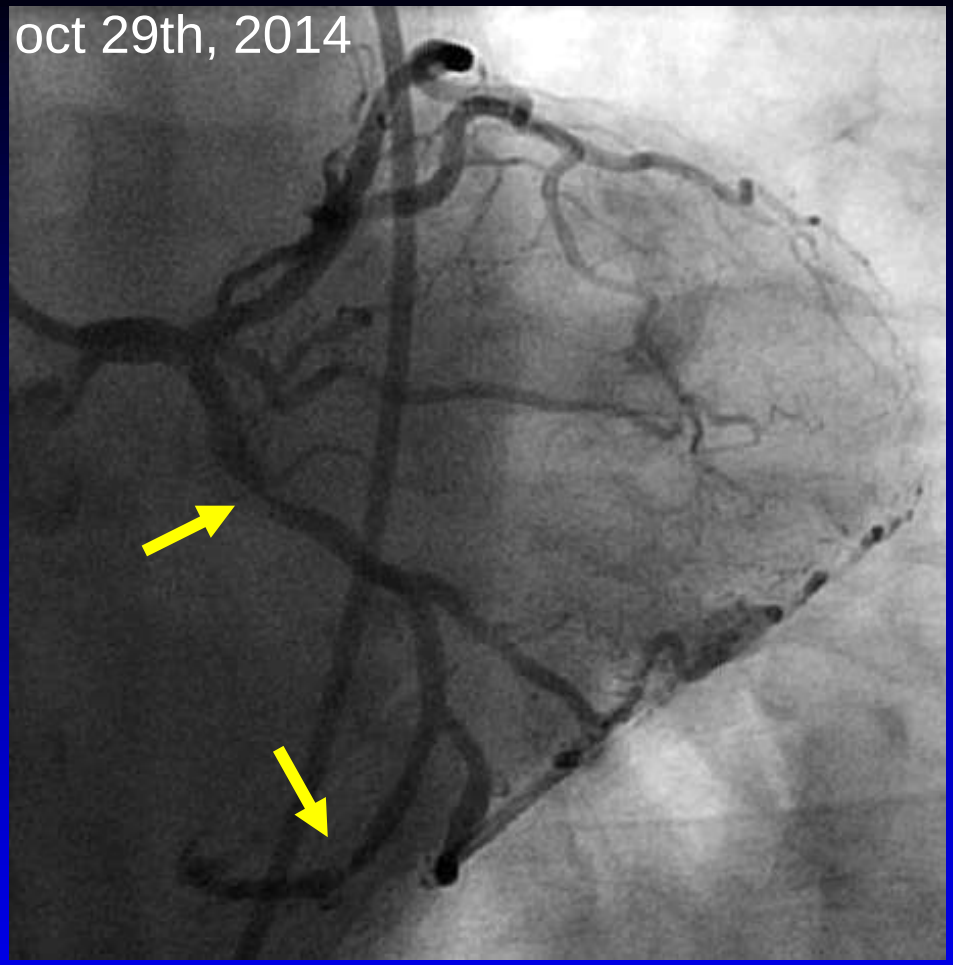
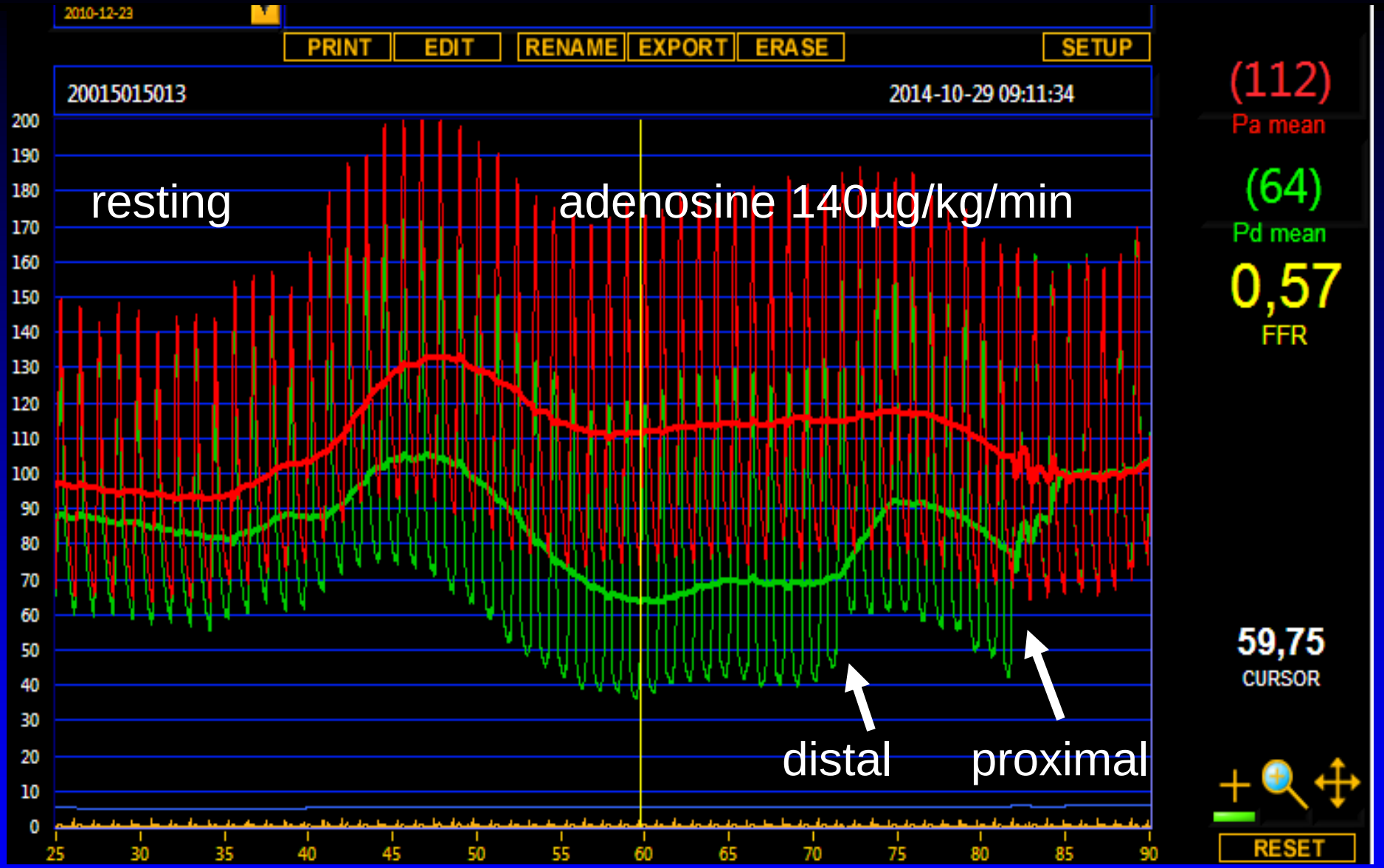


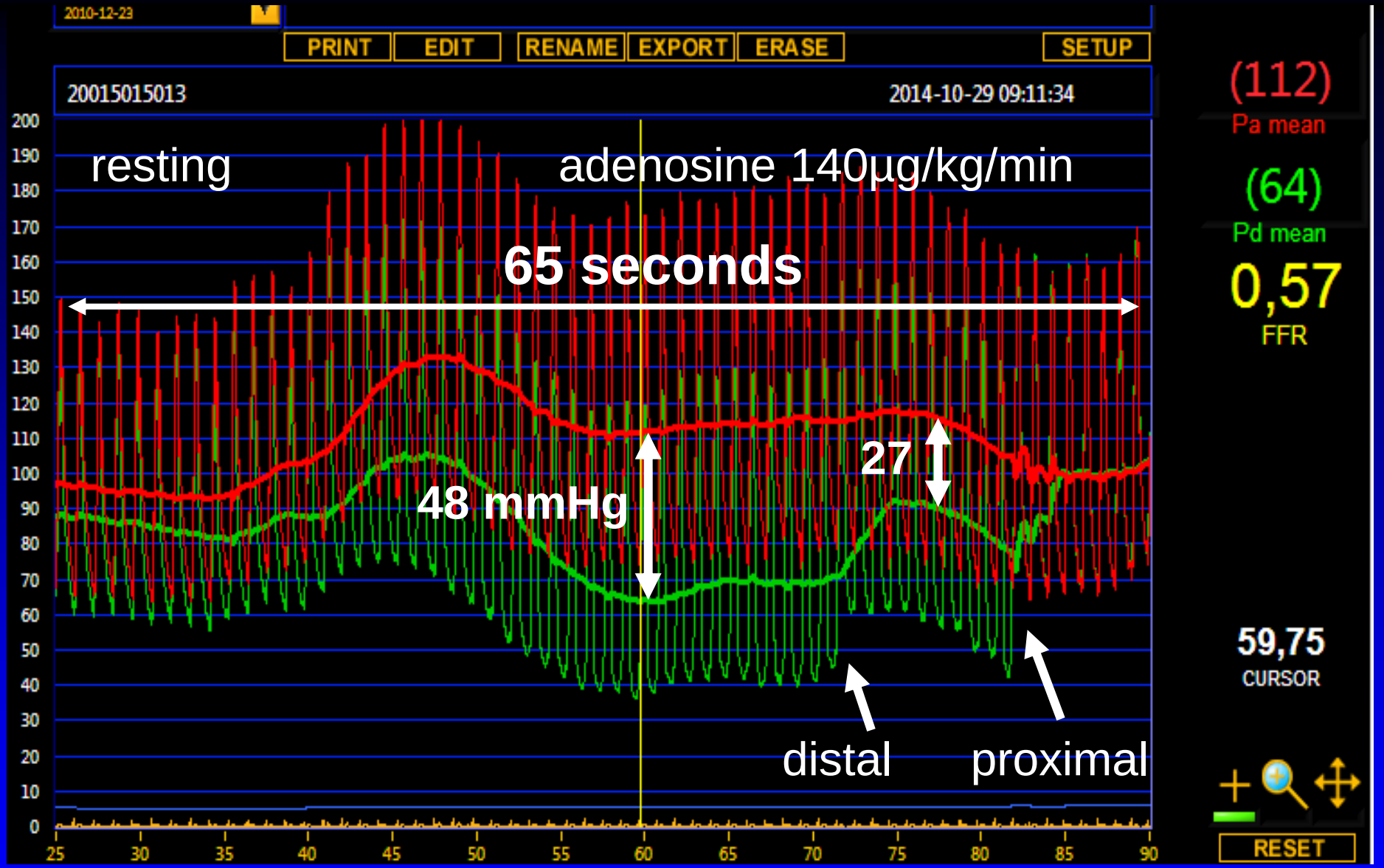


Male, 65-year-old, typical angina,
inferolateral reversible defect at MIBI-SPECT
70% lesions in proximal & distal dominant LCX



hyperemic pullback recording:

rapid, reliable, detailed information within seconds



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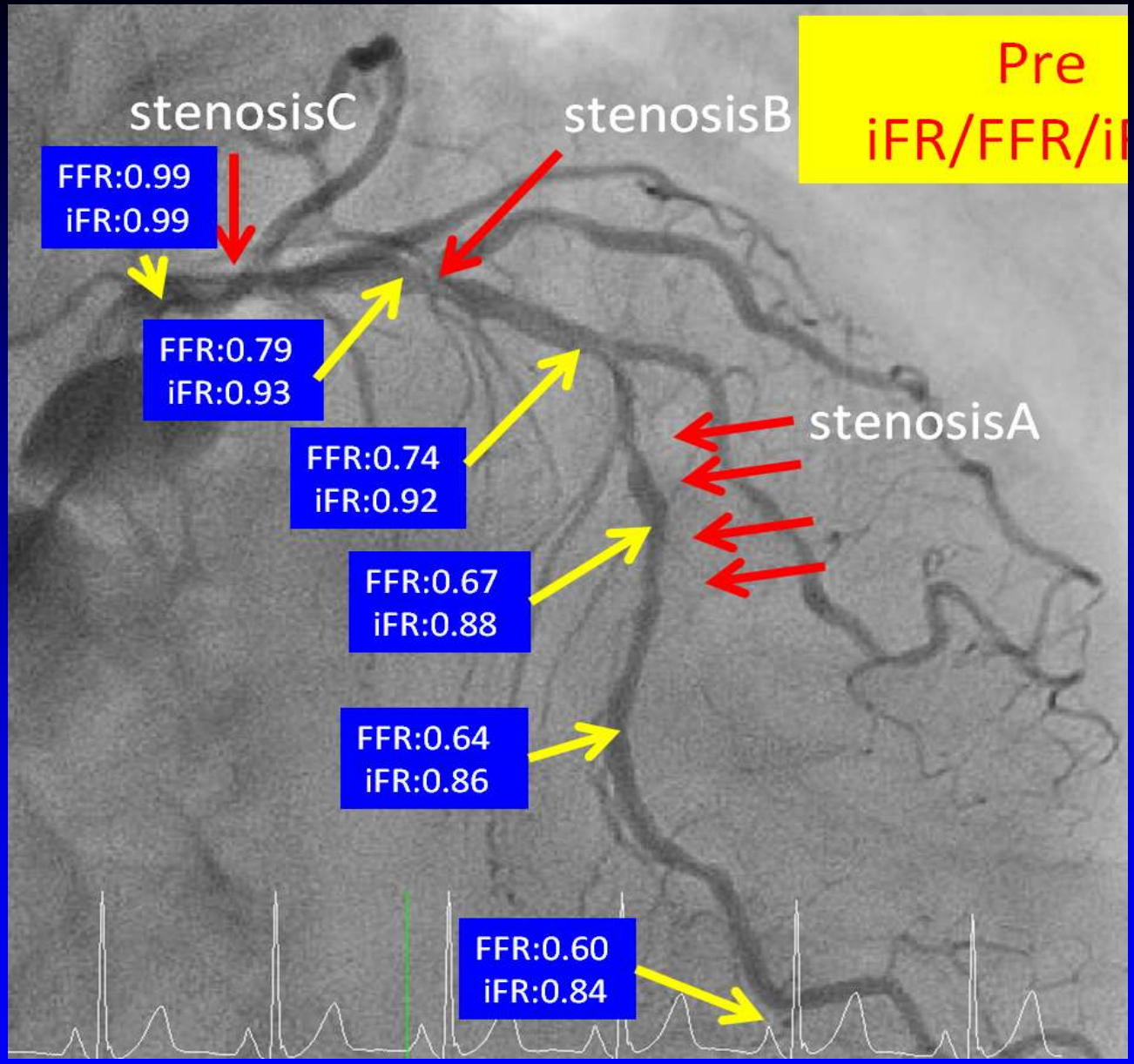
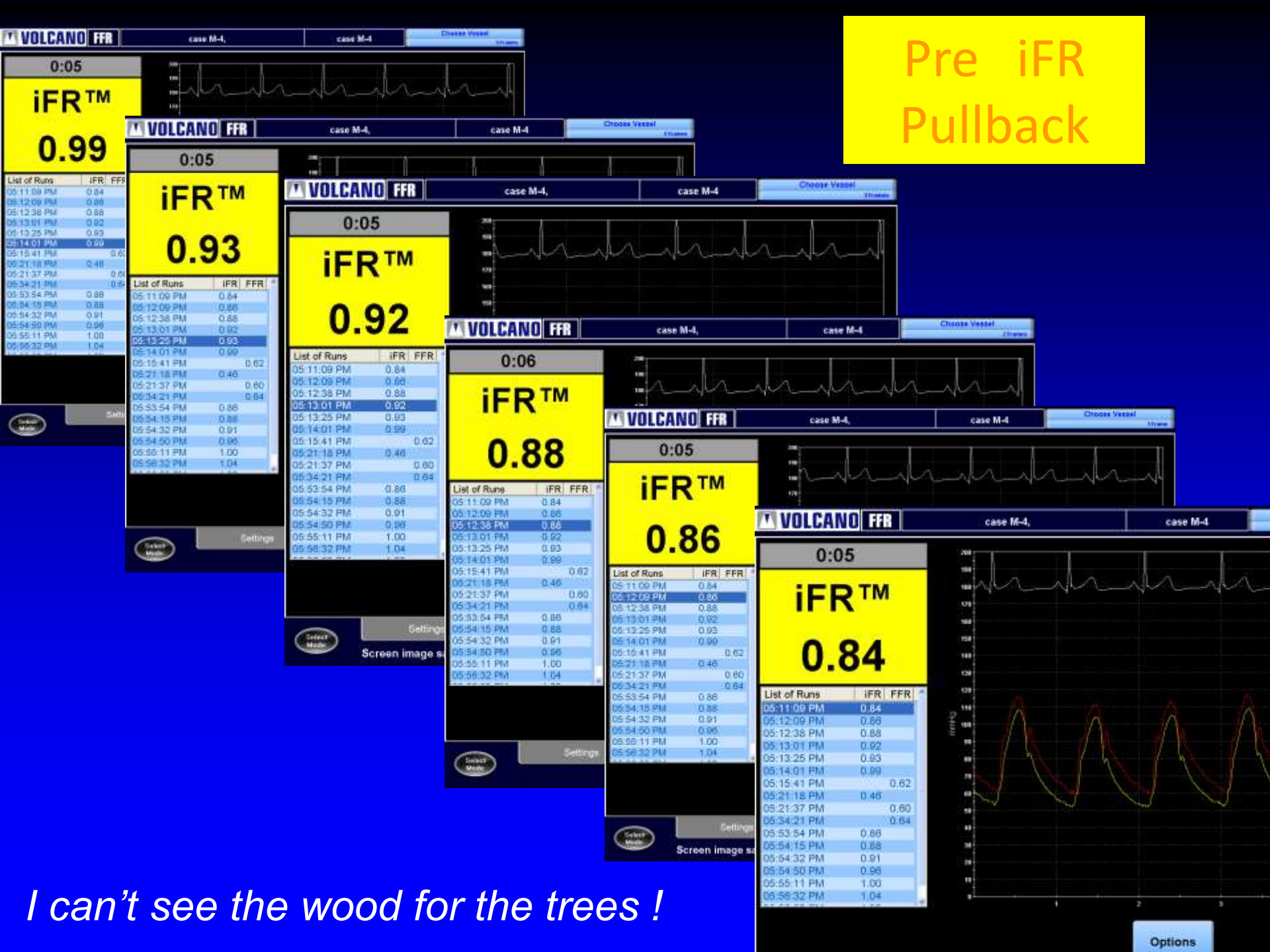


"resting" pullback recording with multiple iFR:
time-consuming, less reliable, poorly detailed information


Pre iFR Pullback
VOLCANO FFR
0:05
iFR™
0.99
0:05
iFR™
0.93
0:05
iFR™
0.92
0:06
iFR™
0.88
0:05
iFR™
0.86
0:05
iFR™
0.84
List of Runs
iFR
FFR
Settings
Options
I can't see the wood for the trees !

Pullback recording is cumbersome without hyperemia

- *poor signal to noise ratio*
- *time consuming because no fluent pullback but multiple interruptions*
- *multiple numbers,small diifferences, difficult interpretation*

In conclusion:

Is Hyperemia Essential ??

Is Hyperemia Essential ??

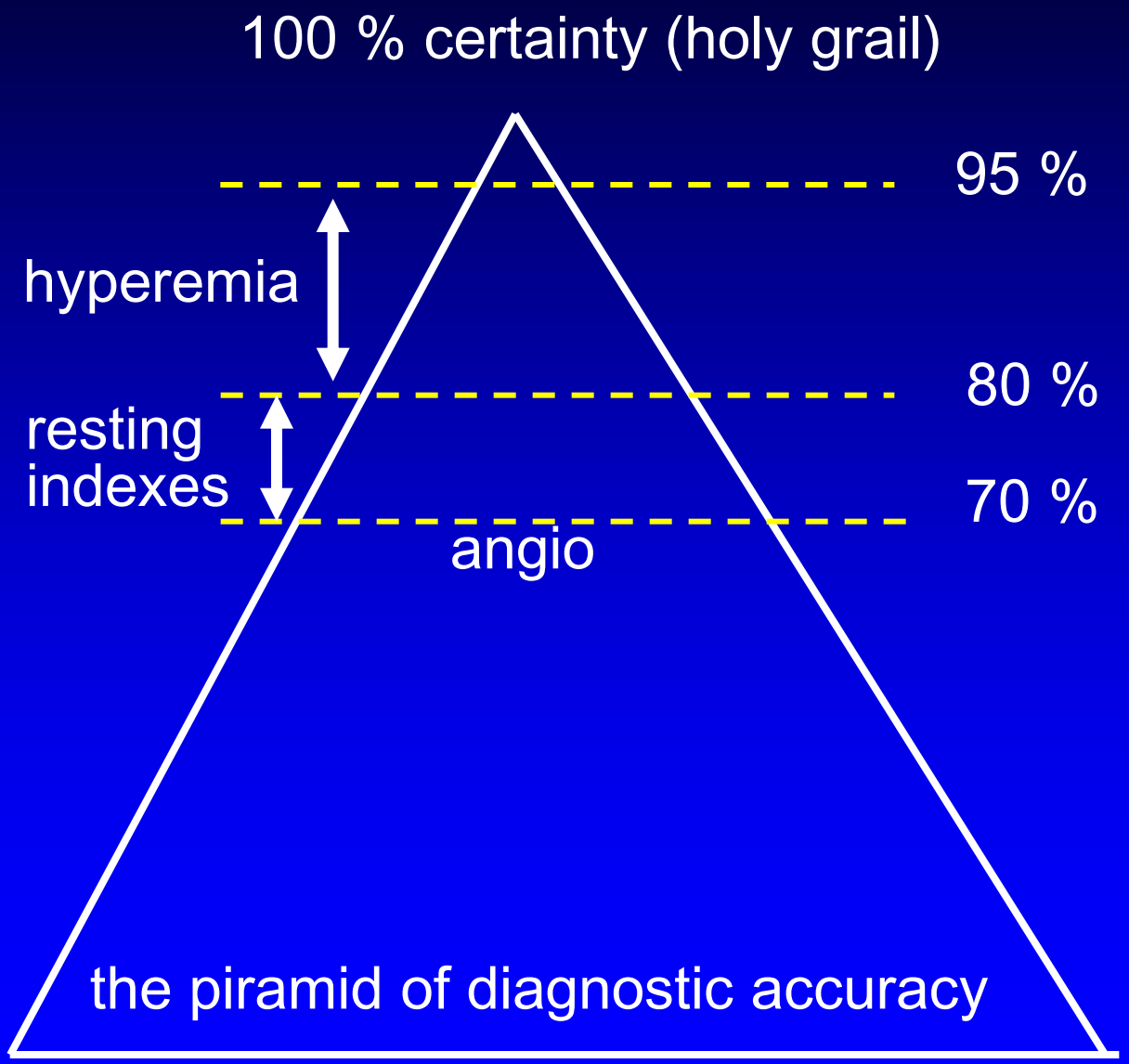
Yes, it is !!

Correct Classification of Ischemic Stenosis

FFR

resting Pd/Pa, iFR, bSVr **("FFR-light")**

angiography



HYPEREMIA MANDATORY ? ⟶ YES !

- Leaving away (full) hyperemia, means decrease of accuracy and false decision making in 20% of patients. With so-called “hybrid” approaches (i.e. hyperemia in part of the patients) 10% false decisions

- *Does a few minutes of extra work and a very moderate saving of money for a hyperemic drug justify a wrong decision in 1 out of every 5-10 patients?*

For us, PCI might be routine….

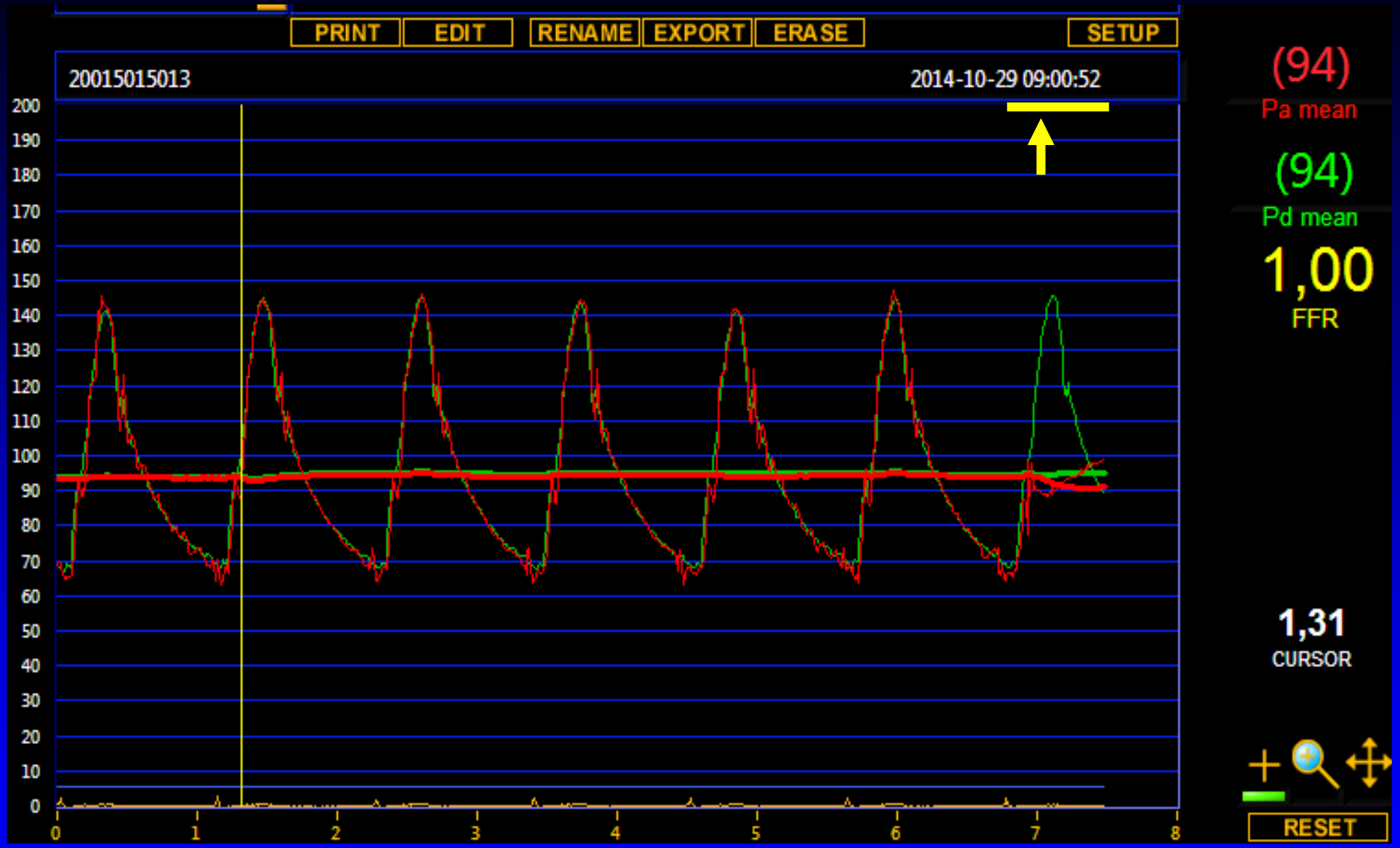
…..for the patient, it is a big deal!

Therefore, we should do it in the best possible way !

EINDE

Why Are Resting Indices Insufficient ?

- ***large gray zone and limited accuracy of P_d / P_a at rest and iFR compared to FFR***



Equalization before entering LCA

“Non-hyperemic indexes”

A collection of older and newer resting indexes derived from pressure measurement at rest:
Pd/Pa at rest, diastolic Pd/Pa, iFR, i-FFR
which have in common that they

- all try to avoid hyperemia
- are not independently validated
- and only have a moderate accuracy (70% -80%) compared to FFR
- questionable underlying scientific assumptions

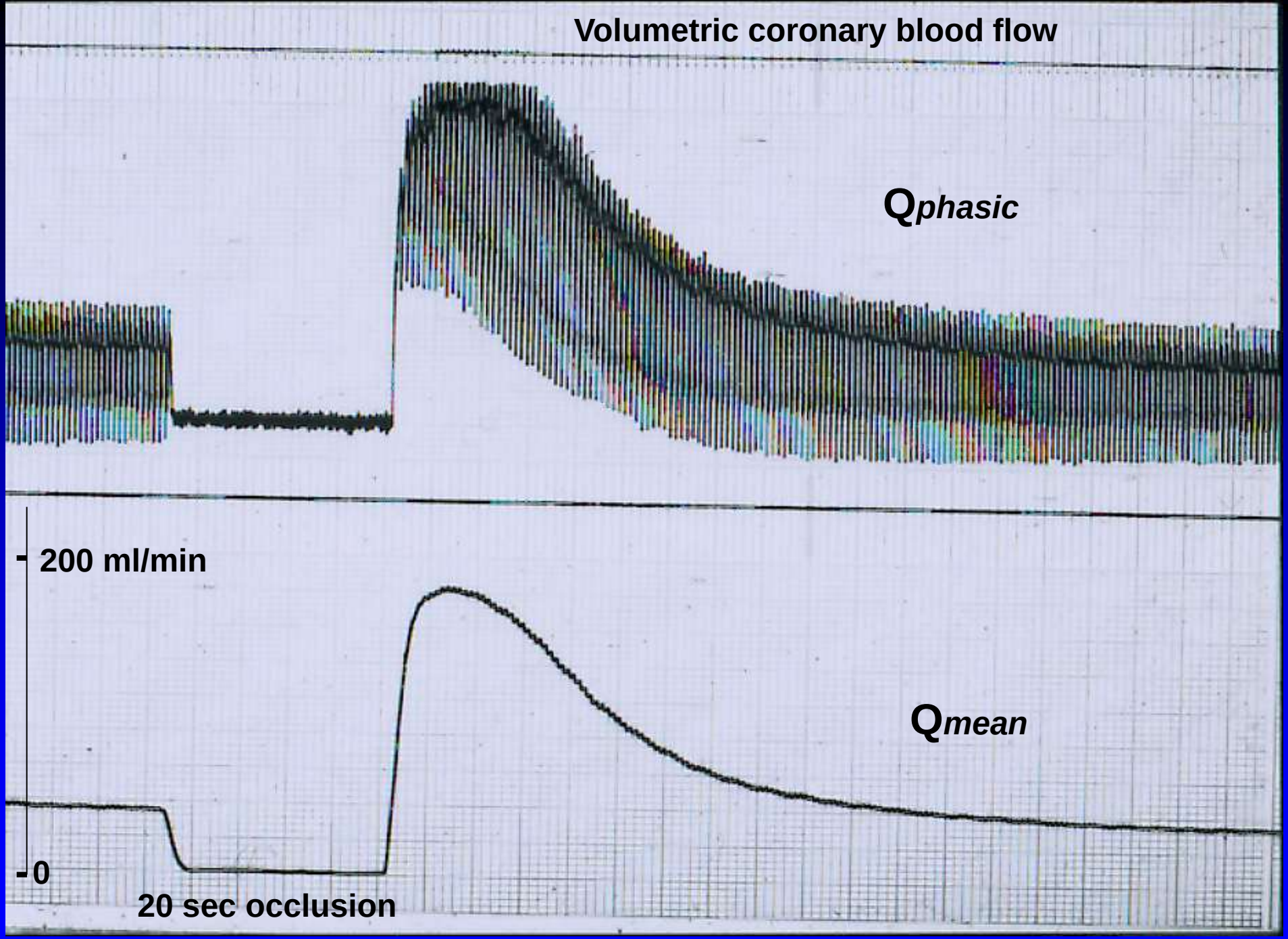
Why Are Resting Indices Insufficient ?

- **Limited Clinical Significance**

- ***Limited Physiological Meaning***
  - poor scientific background
  - no experimental validation
  - deny the fluid-dynamic equation

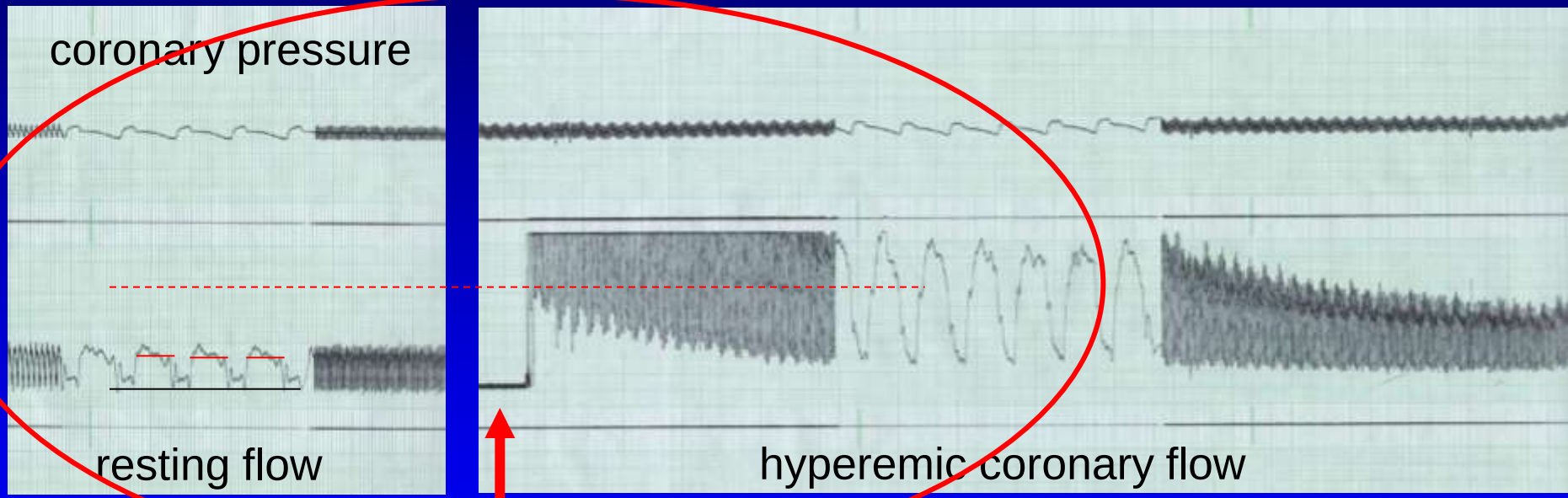
LET OP:

Vanwege de tijd kun je wrschl beter de volgende 5 dia’s weglaten!!!!!!!!


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

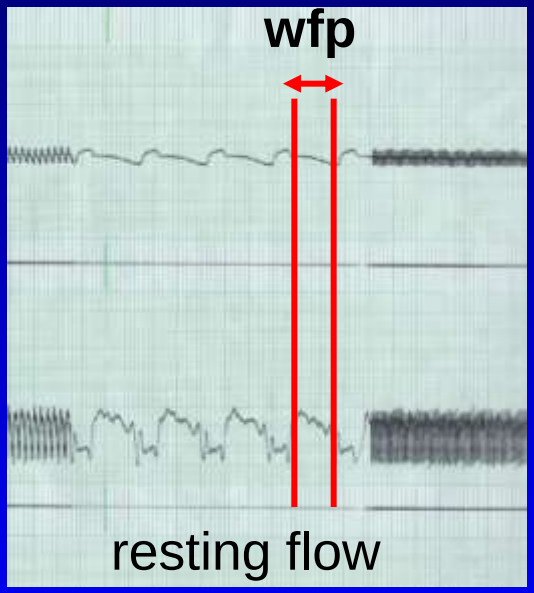
In the presence of constant coronary pressure

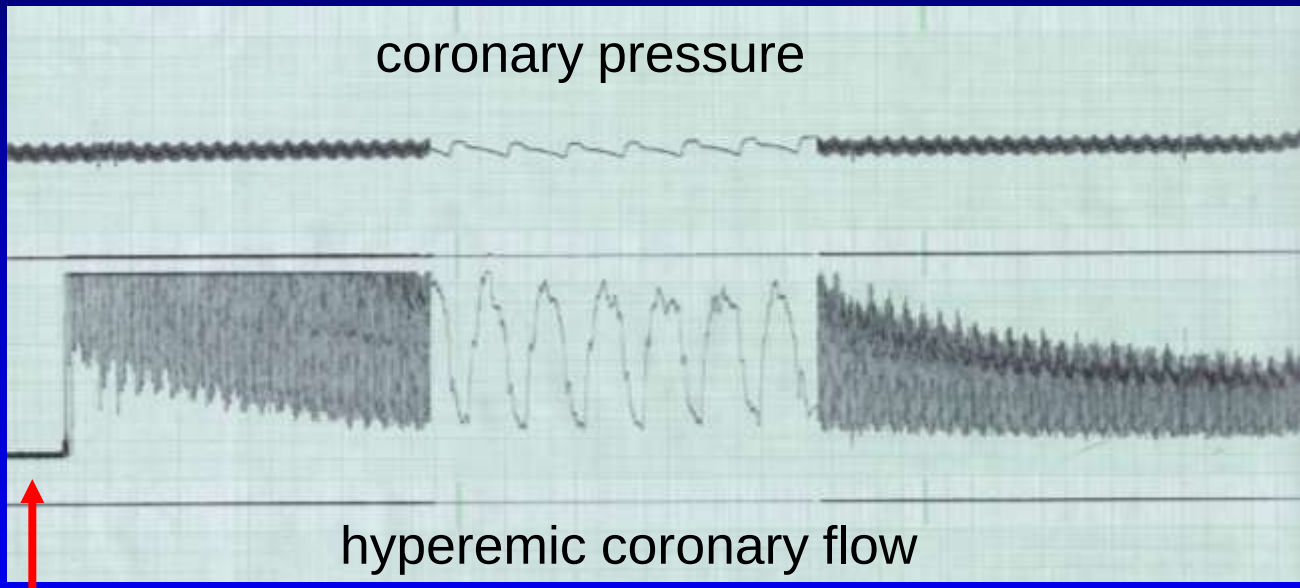
⟶ R ~ 1 / Flow



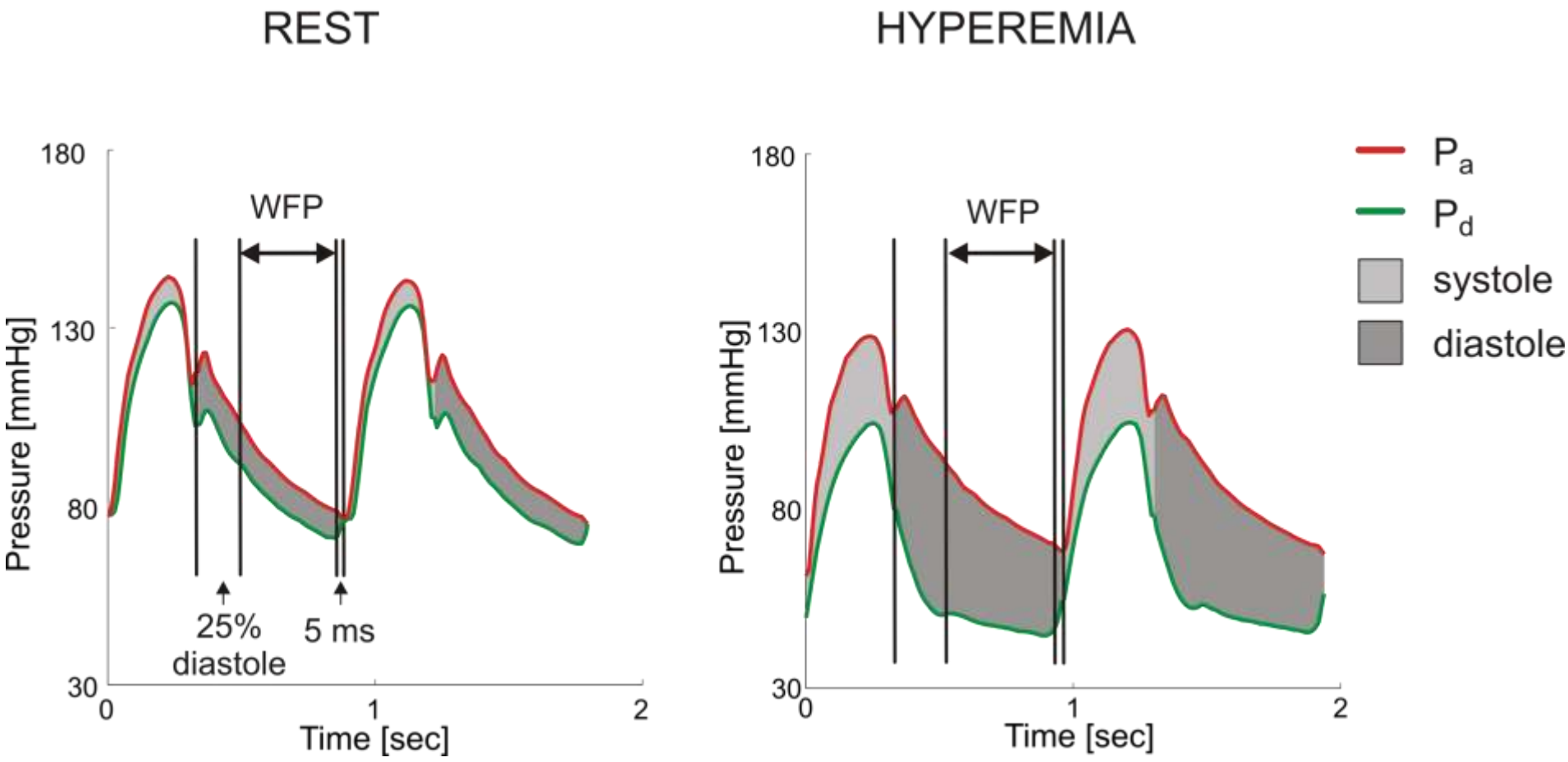
coronary occlusion

minimal myocardial resistance during the so-called "wave-free period" is ~ 250 % higher than average myocardial resistance at maximum hyperemia in all dogs and swine



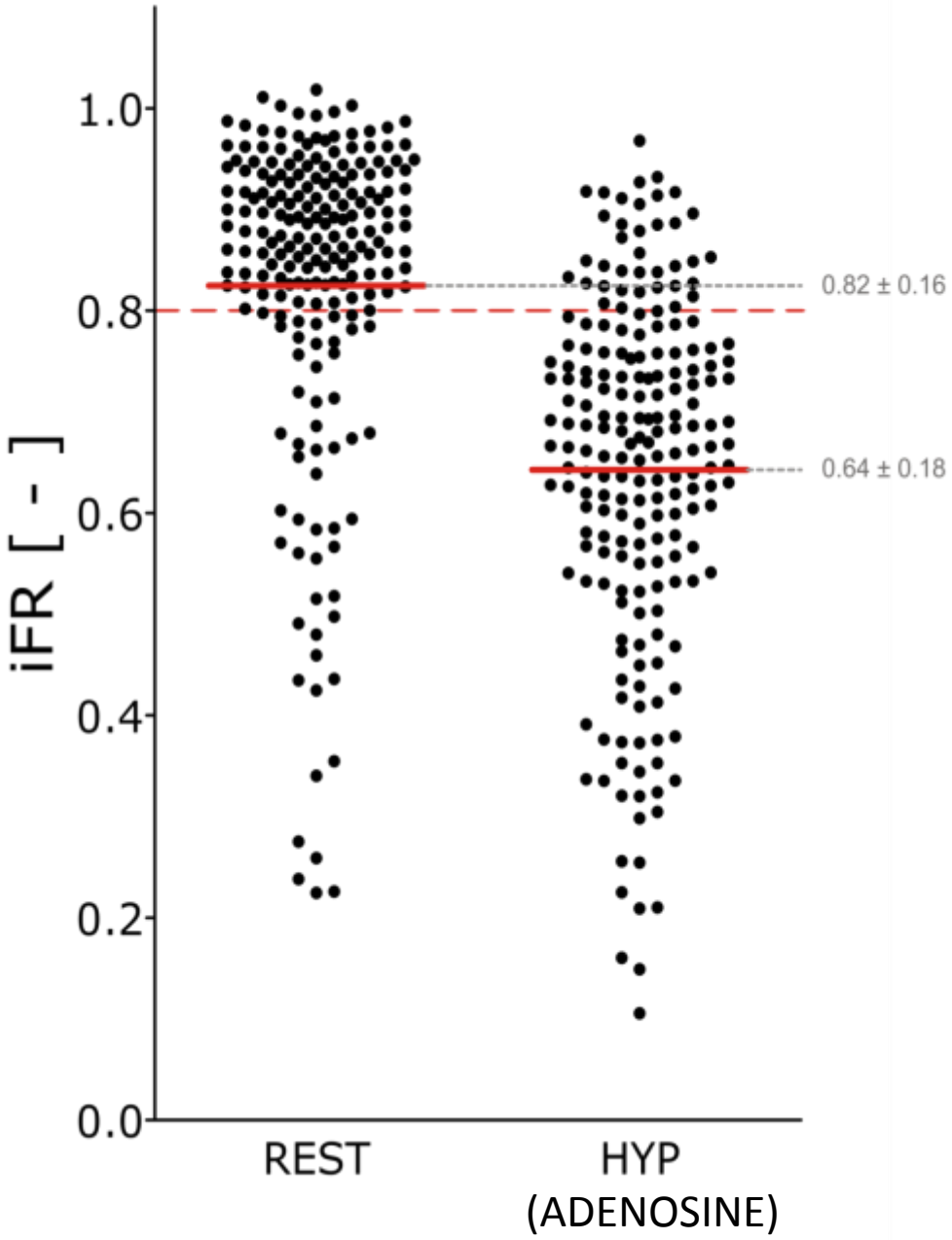


coronary occlusion



iFR = Pd / Pa during WFP → strongly dependent on hyperemia

Colin et al, JACC 2012, in press
Johnson et al JACC 2012, in press



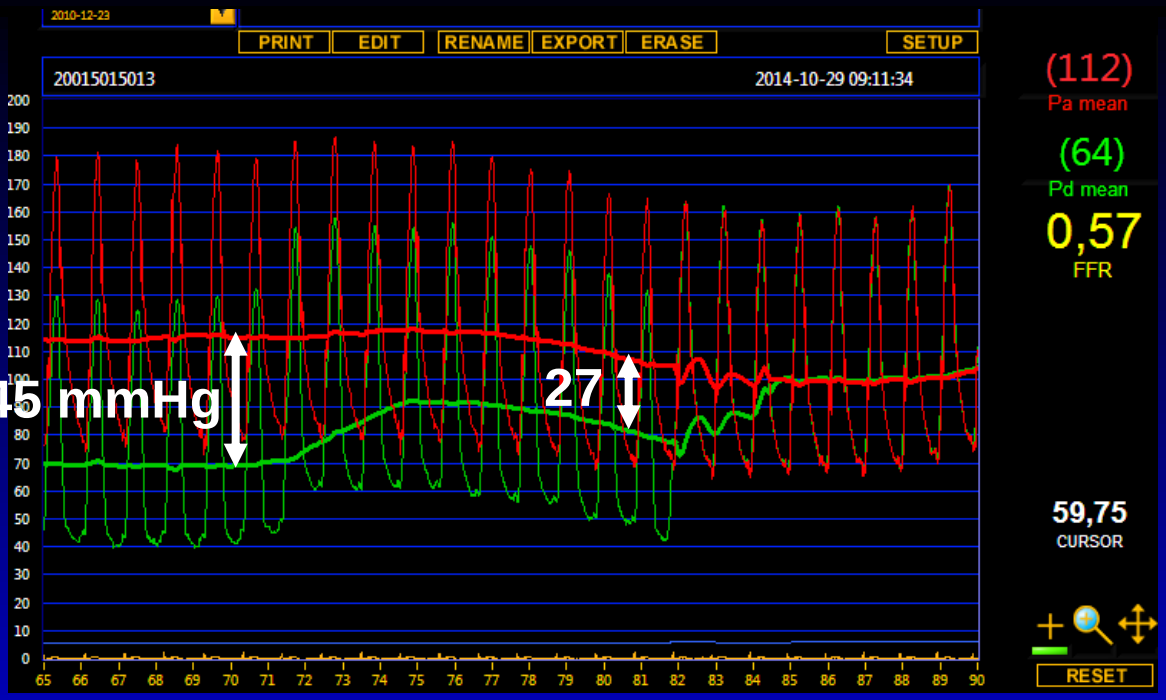
profound influence of hyperemia on iFR:

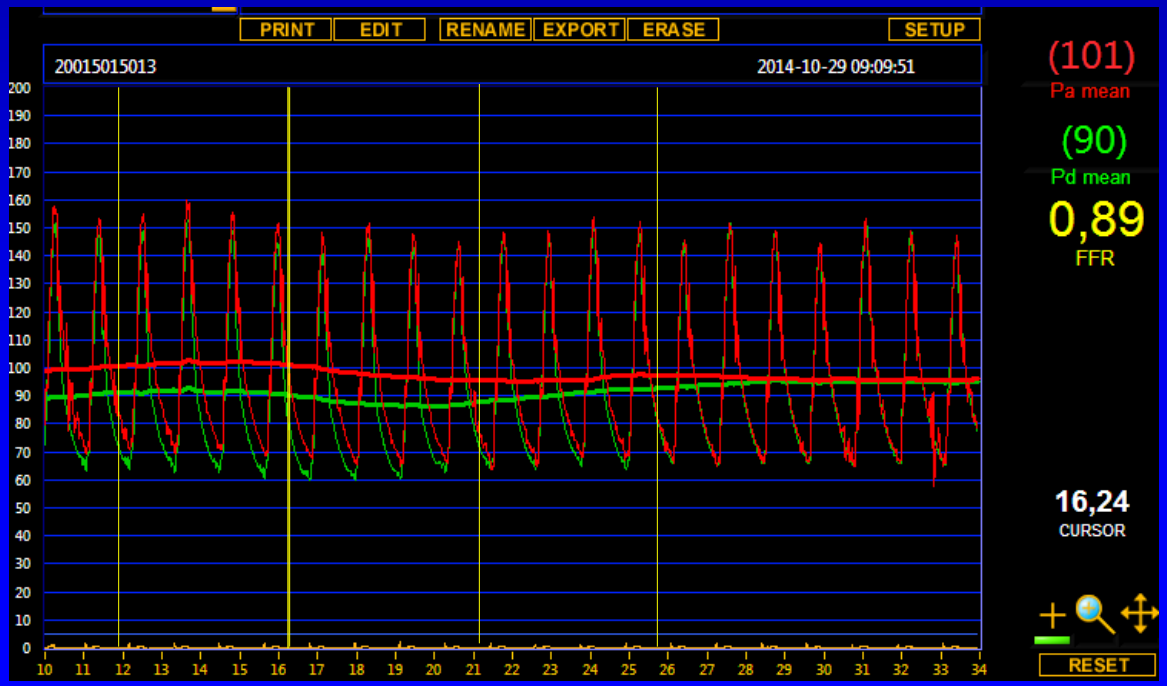
"iFRhyp" *was already called diastolic FFR by Abe et al in Circulation, 1996)*

estimated decrease of resistance during "wave-free period"

$$\frac{(1.0 - 0.64)}{(1.0 - 0.82)} = \mathbf{200\%}$$

VERIFY study,Colin et al, JACC 2012, in press


2010-12-23
PRINT
EDIT
RENAME
EXPORT
ERASE
SETUP
20015015013
2014-10-29 09:11:34
45 mmHg
27
(112)
Pa mean
(64)
Pd mean
0,57
FFR
59,75
CURSOR
RESET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SETUP
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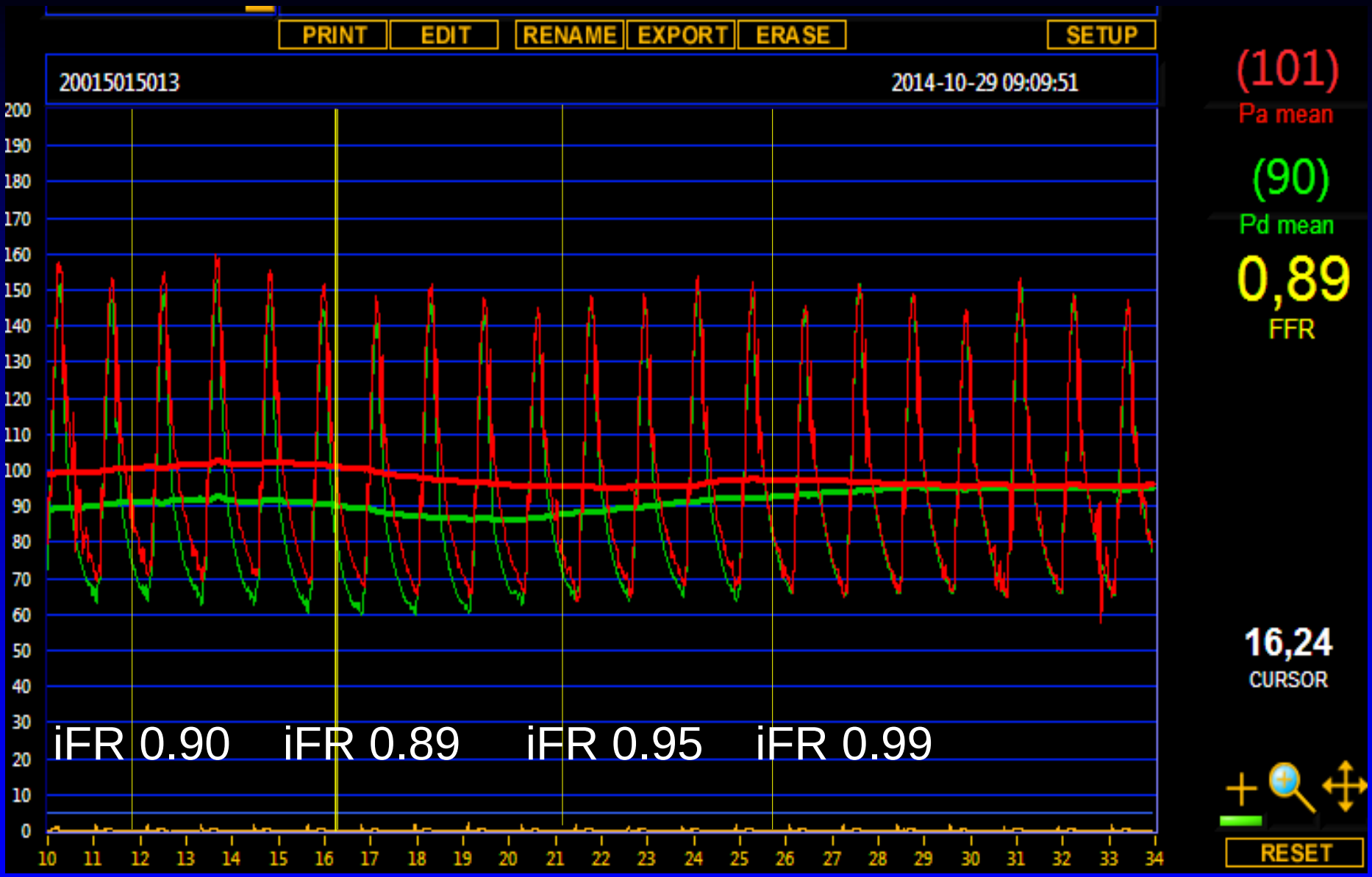
(101)
Pa mean
(90)
Pd mean
0,89
FFR
16,24
CURSOR
RESET



"resting" pullback recording with multiple iFR:

time-consuming, less reliable, poorly detailed information

Is it necessary to use hyperemia ?

Simple intermediate solution ??

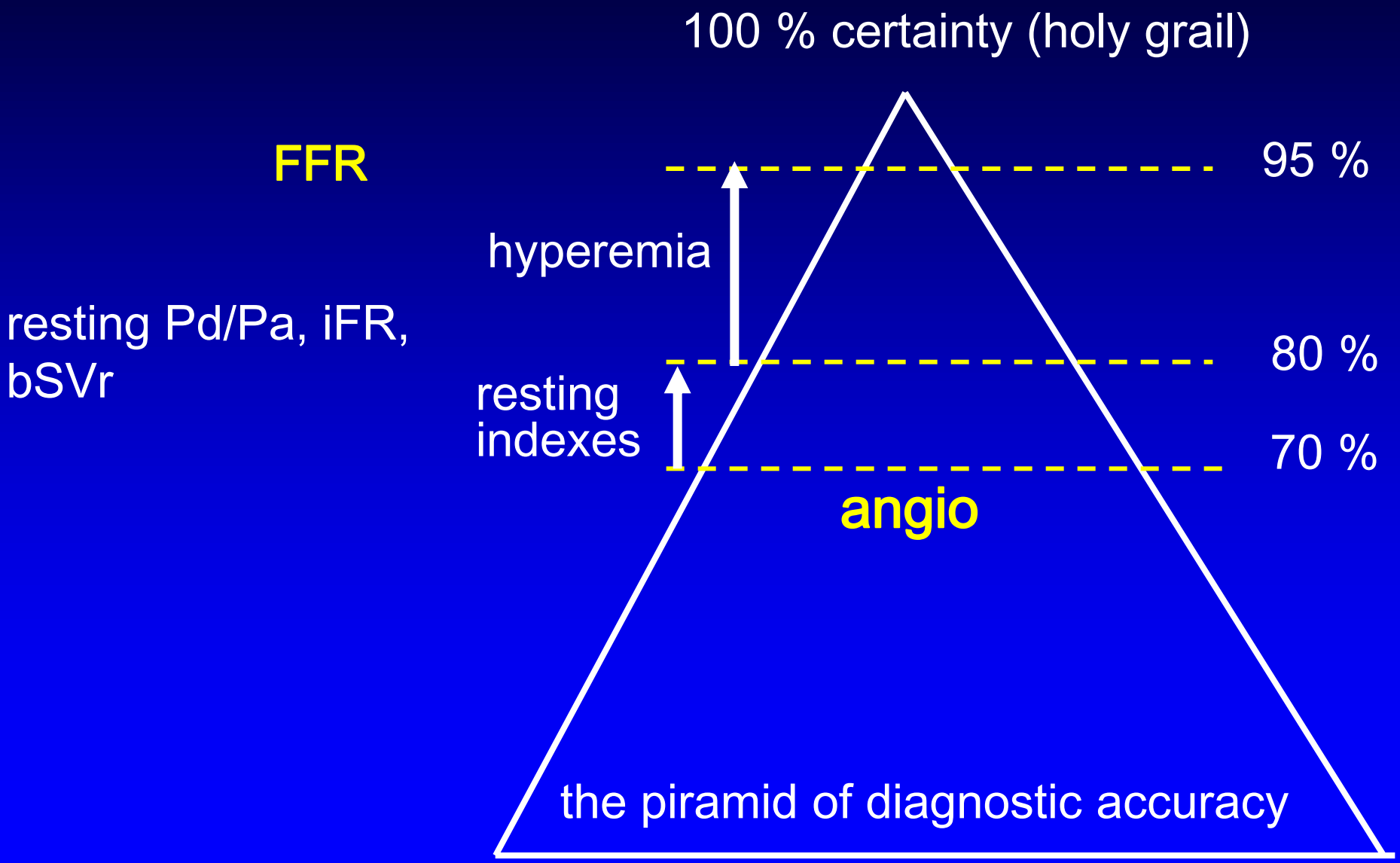
→ **Pd/Pa *contrast*®, or cFFR**

→ Several small studies presented at PCR

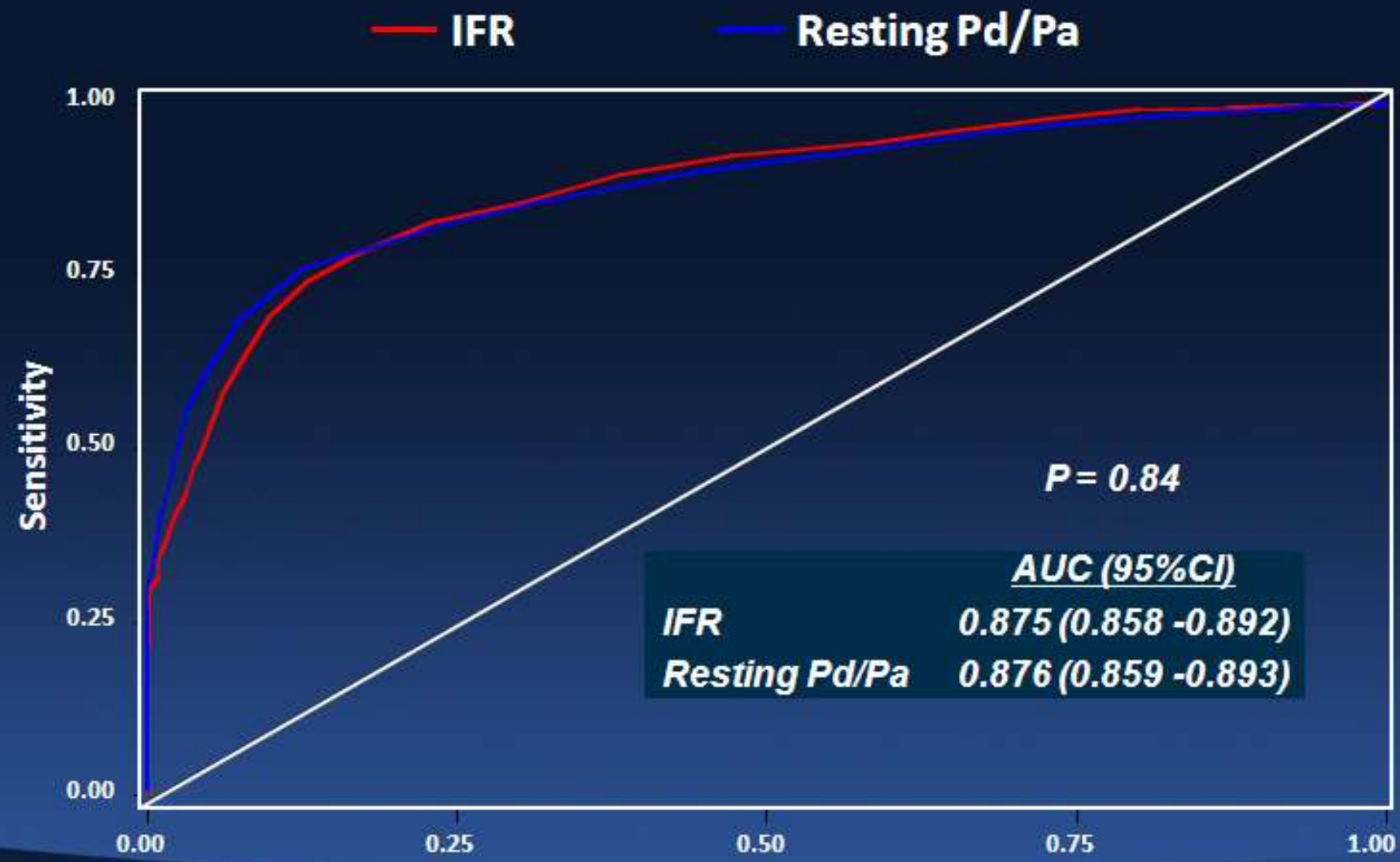
→ ***Presently ongoing CONTRAST STUDY***

Principal investigators: Dr Nils Johnson, TMC
Dr Bill Fearon, Stanford

Correct Classification of Ischemic Stenosis



ROC Curve iFR and Pd/Pa Based on FFR 0.80



TCT2012

Jeremias, JACC 2013, in press

MAXIMUM VASODILATORY STIMULI

!! Maximum hyperemia is paramount !!

- **PAPAVERINE i.c.**
- **ADENOSINE i.c.**
- **ADENOSINE i.v. infusion**
- **ATP i.c**
- **ATP i.v.**
- **REGADENOSON i.v. bolus**

Why Are Resting Indices Insufficient ?

- ***Limited Clinical Significance***

In patients with Coronary Artery Disease, resting flow and gradients have little meaning….

…Angina pectoris occurs and the myocardium becomes ischemic as soon as ***maximum achievable blood flow*** is insufficient to match oxygen demand

*Therefore, looking at maximum flow (as a fraction of normal maximum flow), makes most sense and is the basis of Fractional Flow Reserve (**FFR**)*