CORONARY PHYSIOLOGY IN THE CATHLAB:

Pd/Pa at rest, iFR, b-SRv, resting gradient Why Can They Never Be As Good As Hyperemic Indexes

Educational Training Program ESC
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CATHARINA-ZIEKENHUIS

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Hyperemic indices:

- **FFR** *(Pijls, De Bruyne 1992)*
- **iHDPVr** *(Di mario, Serruys 1994)*
- **hSRv** *(Piek, Spaan, Siebes 1997)*

Resting indices ("FFR-light"):

- **resting transtenotic gradient** *(Gruentzig, 1977)*
- **Pd/Pa *at rest, +/- diastolic*** *(Gould,Meier, 1981)*
- **iFR** *(Sen, Davies 2011)*
- **i-FFR** *(Andersson, 2013)*
- **bSRv** *(Verhoef, Siebes 2012)*

Virtual Hyperemic Index: **FFR_{CT}** *(Min, Koo, 2009)*

“FFR - light ”

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

Why Are Resting Indices Insufficient ?

- ***Limited Clinical Significance***

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

- Resting Conditions Are Very Hard to Obtain
  - uncertainty if resting condition is present in cath lab, large variation
  - most “resting” indices vary with level of hyperemia
  - the only condition which can be reliably obtained, is maximum hyperemia

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**)*

Why Are Resting Indices Insufficient ?

- **Limited Clinical Significance**

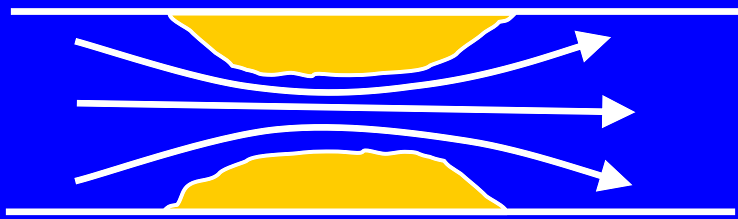
- ***Limited Physiological Meaning***
  - poor scientific background
  - no experimental validation
  - deny the fluid-dynamic equation

Similar baseline gradients can lead to large differences during hyperemia as a result of:

- geometry of the stenosis (fluid dynamics equation)
- different extent of the distal perfusion area
- age of the patient
- hemodynamic conditions like blood pressure, heart rate and contractility

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

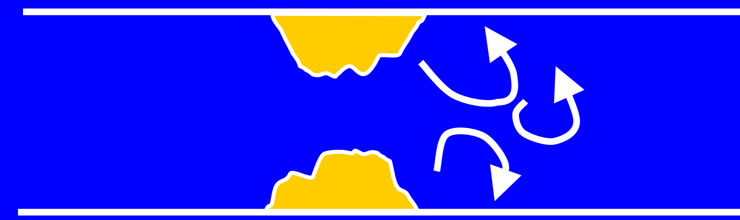
f = friction coefficient



Moderate gradient at rest

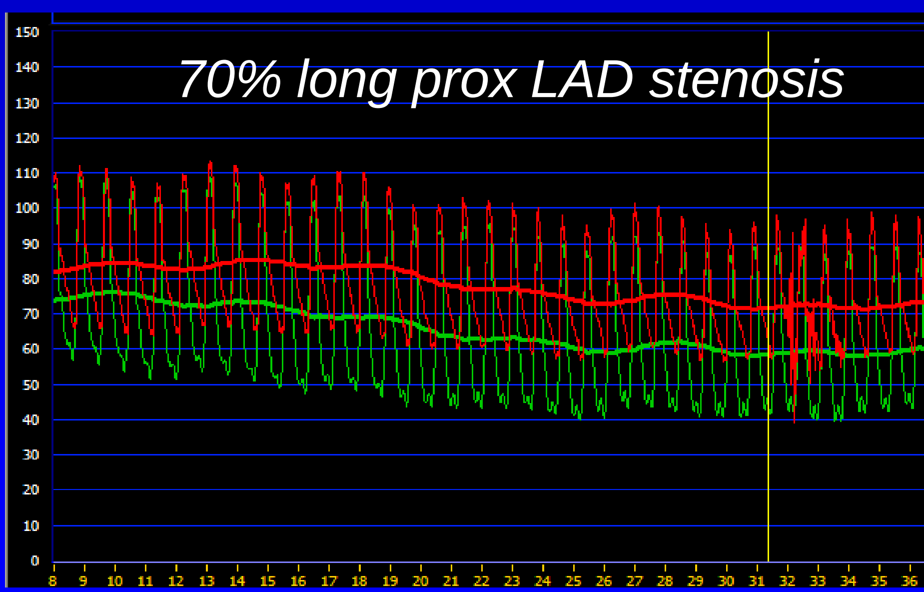
Moderate increment at hyperemia

s = separation coefficient

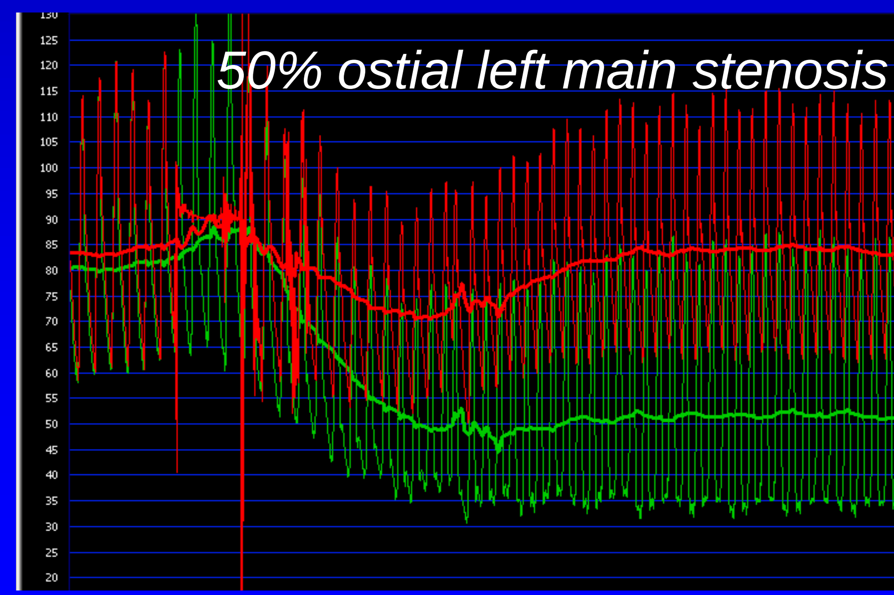


Small gradient at rest

Large gradient at hyperemia



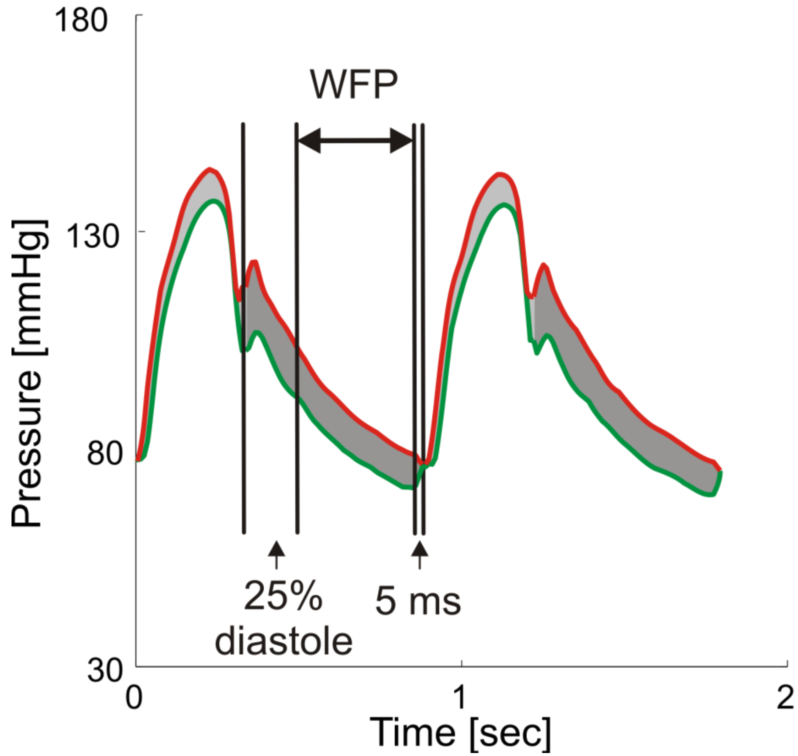
iFR = 0.89 FFR = 0.85



iFR = 0.94 FFR = 0.57

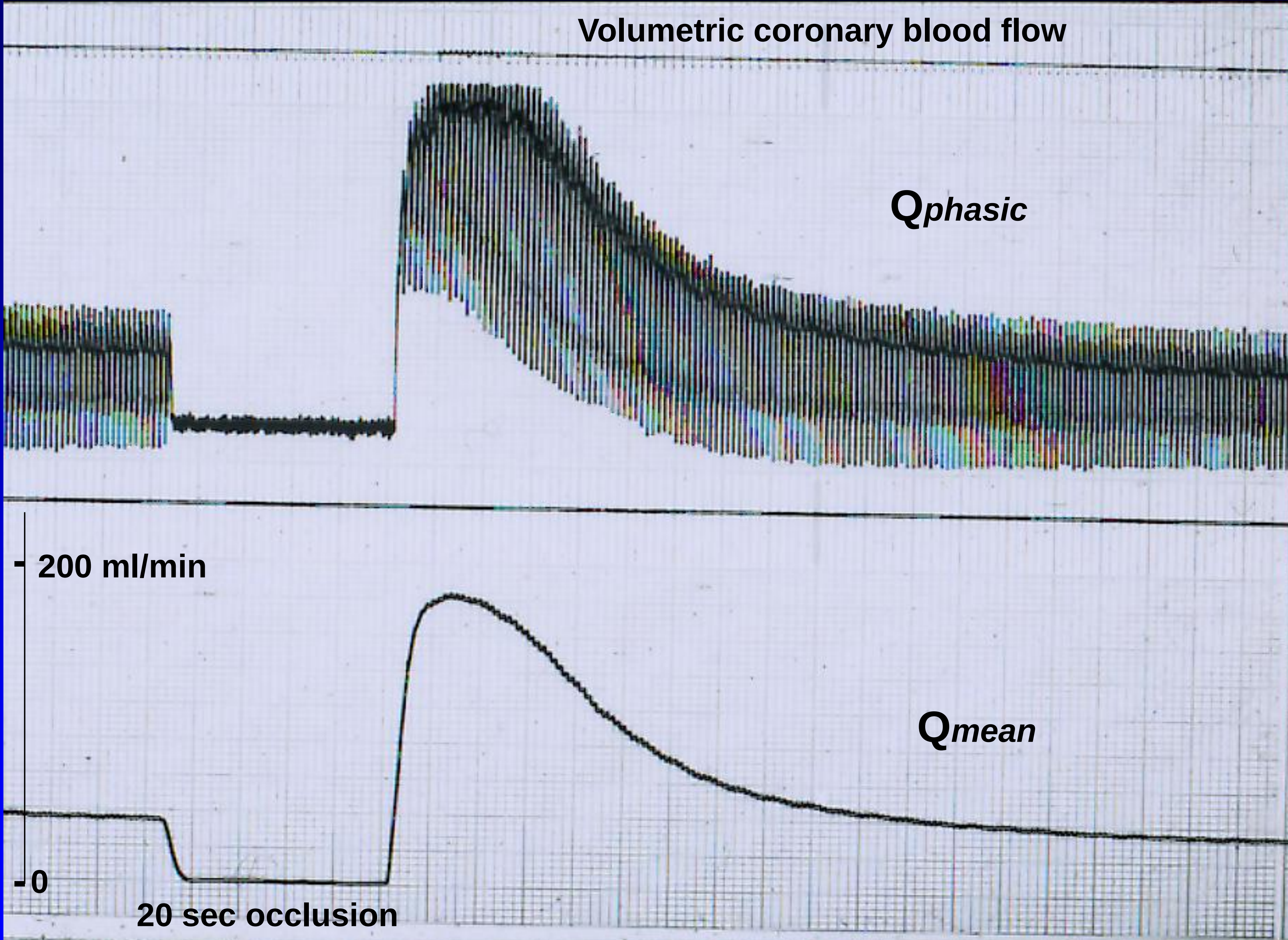
In addition, some resting indexes have no or poor scientific basis and lack experimental validation

REST



iFR = Pd / Pa at rest during WFP ***(Sen et al, JACC 2012)***

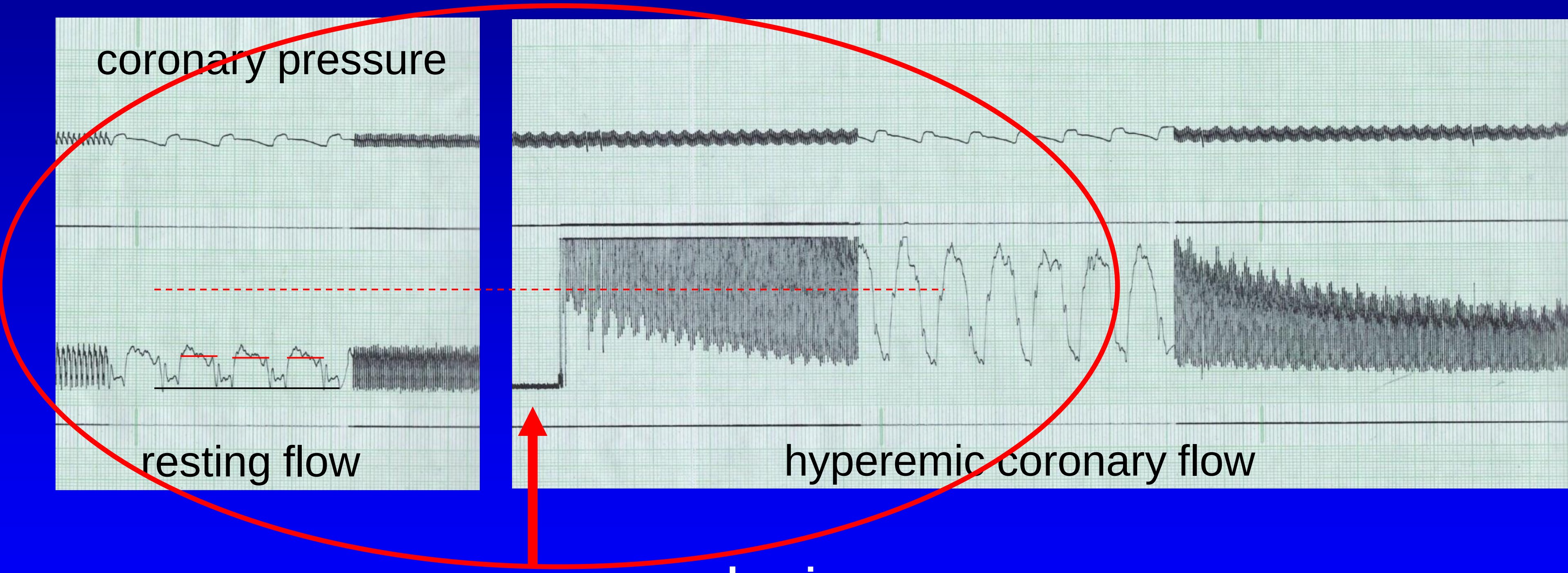
basic assumptions: 1. resistance during WFP at rest equals average hyperemic resistance
2. iFR is claimed to be "hyperemia-free"



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

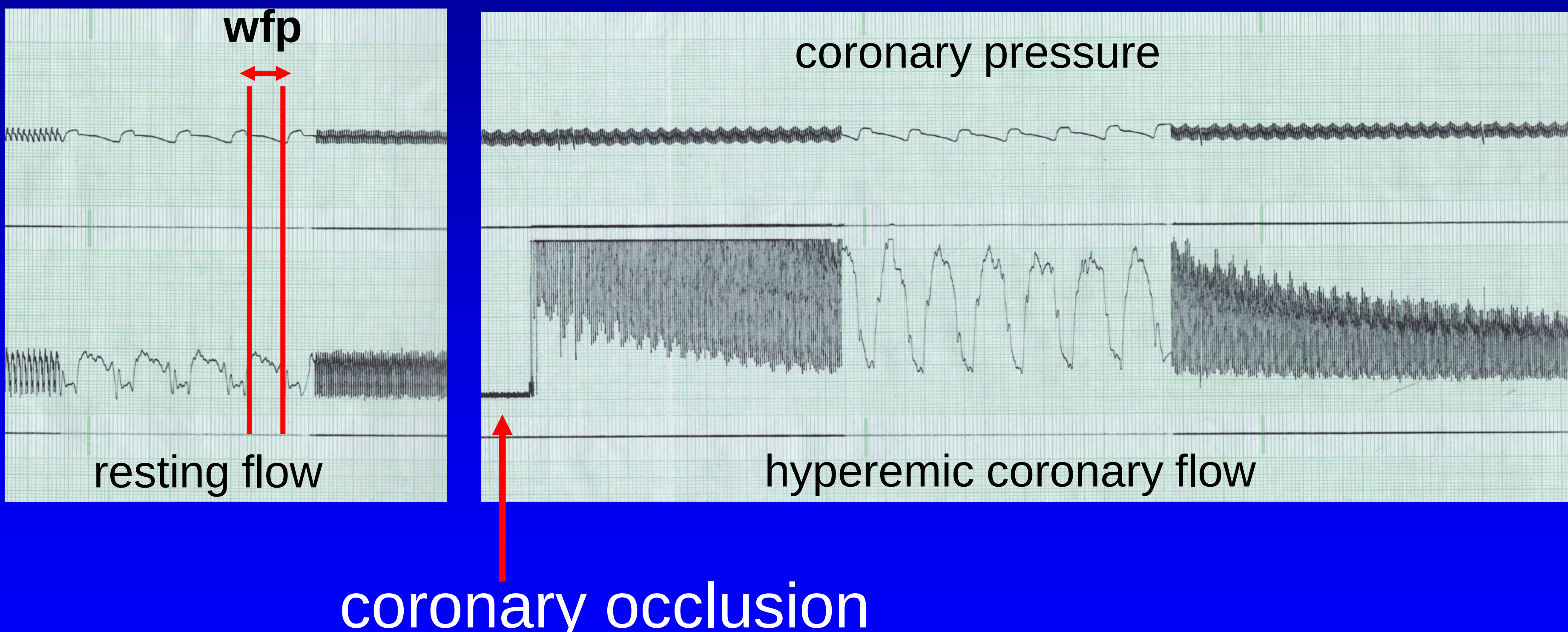
In the presence of constant coronary pressure

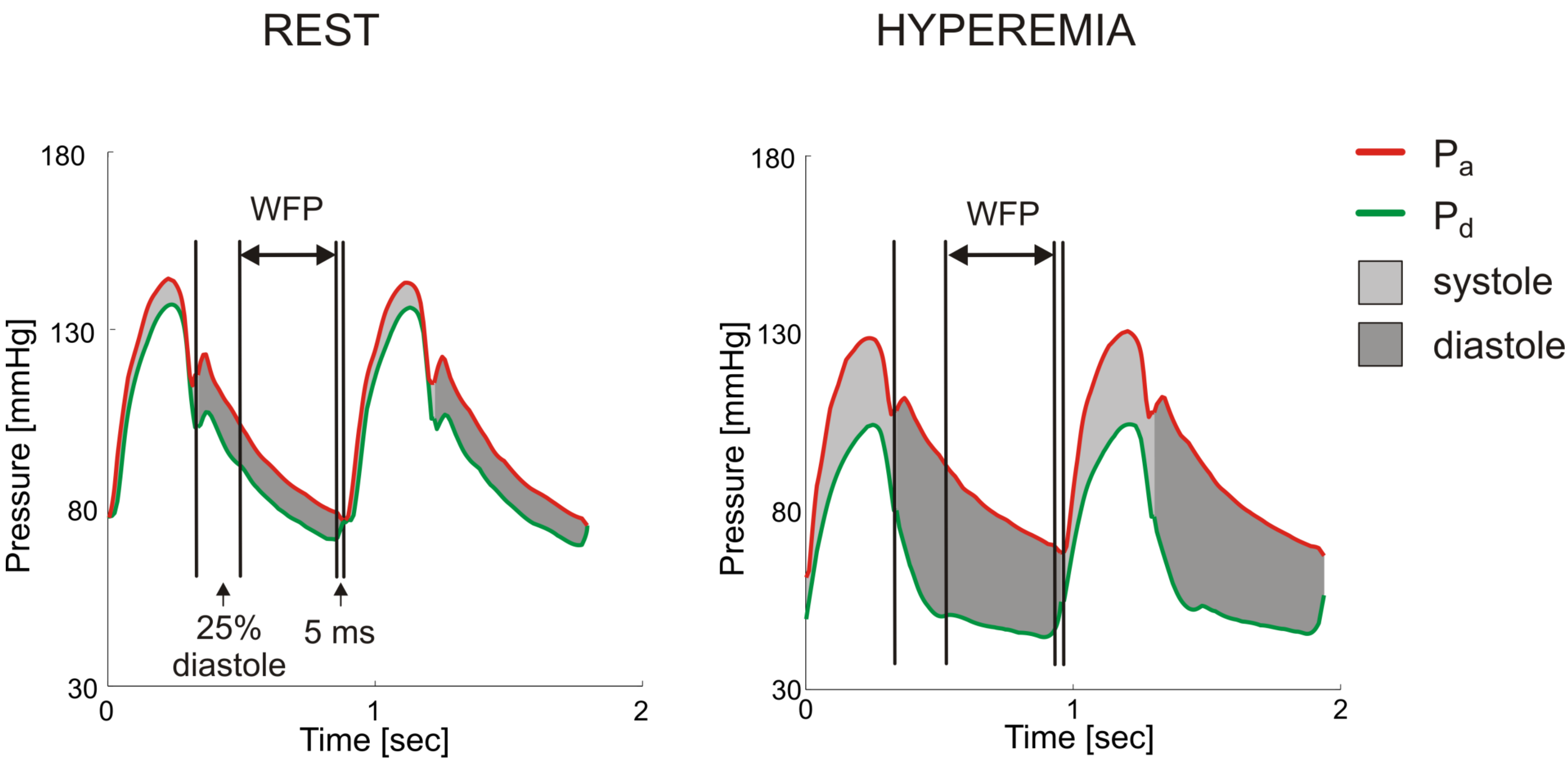
→ R ~ 1 / Flow



coronary occlusion

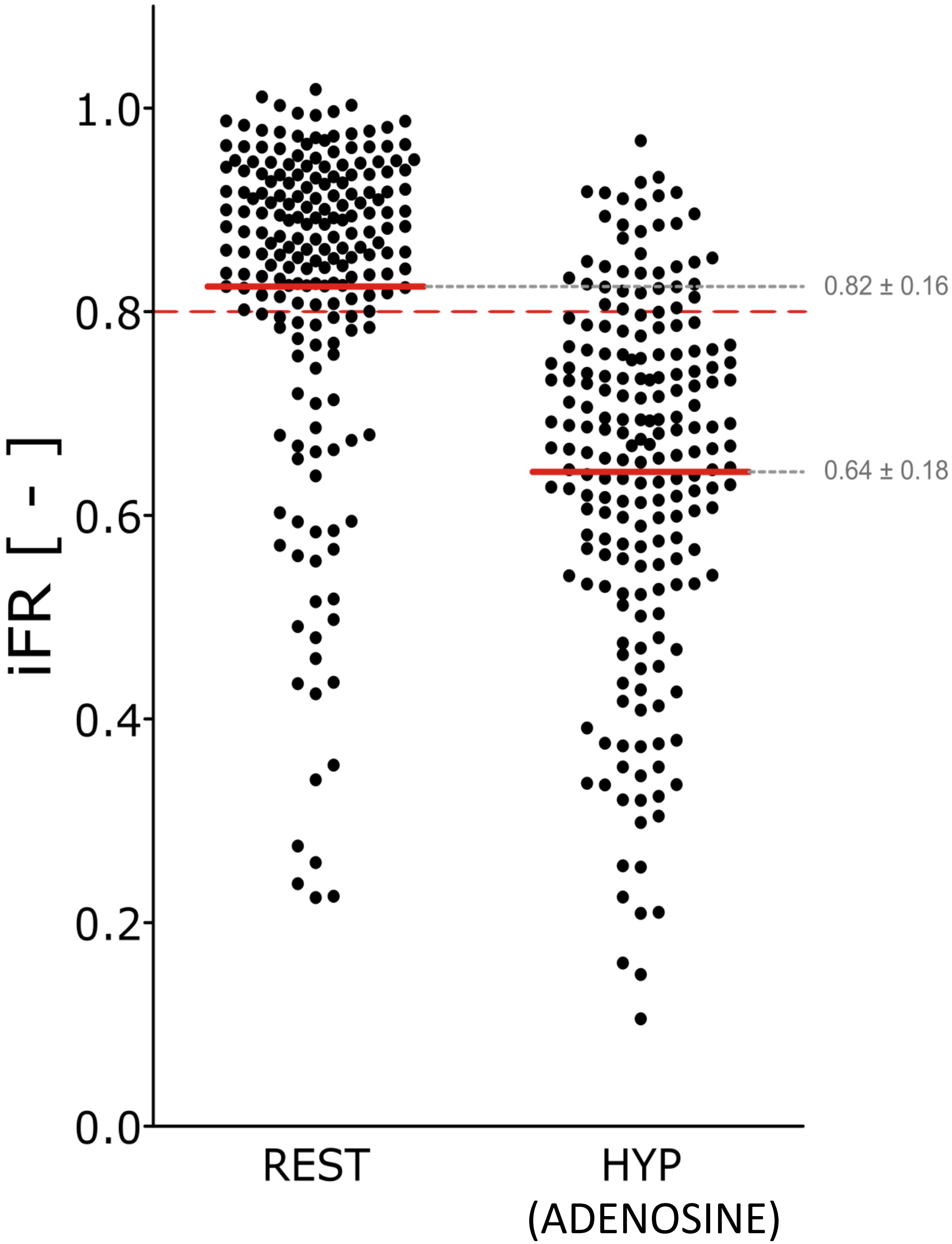
minimal myocardial resistance during the so-called "wave-free period" is ~ 250 % higher than average myocardial resistance at maximum hyperemia in all dogs and swine





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”

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

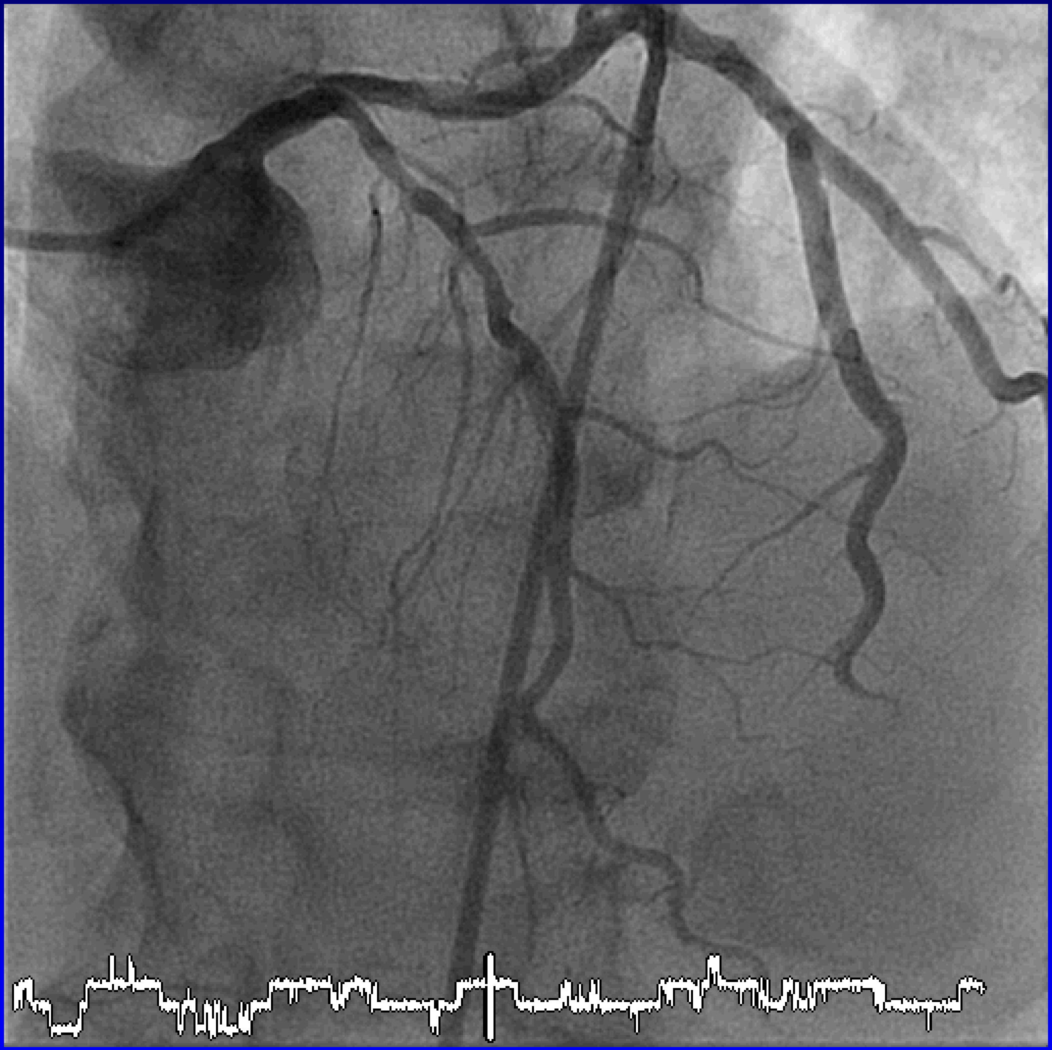
VERIFY study,Colin et al, JACC 2012, in press

Why Are Resting Indices Insufficient ?

- **Limited Clinical Significance**

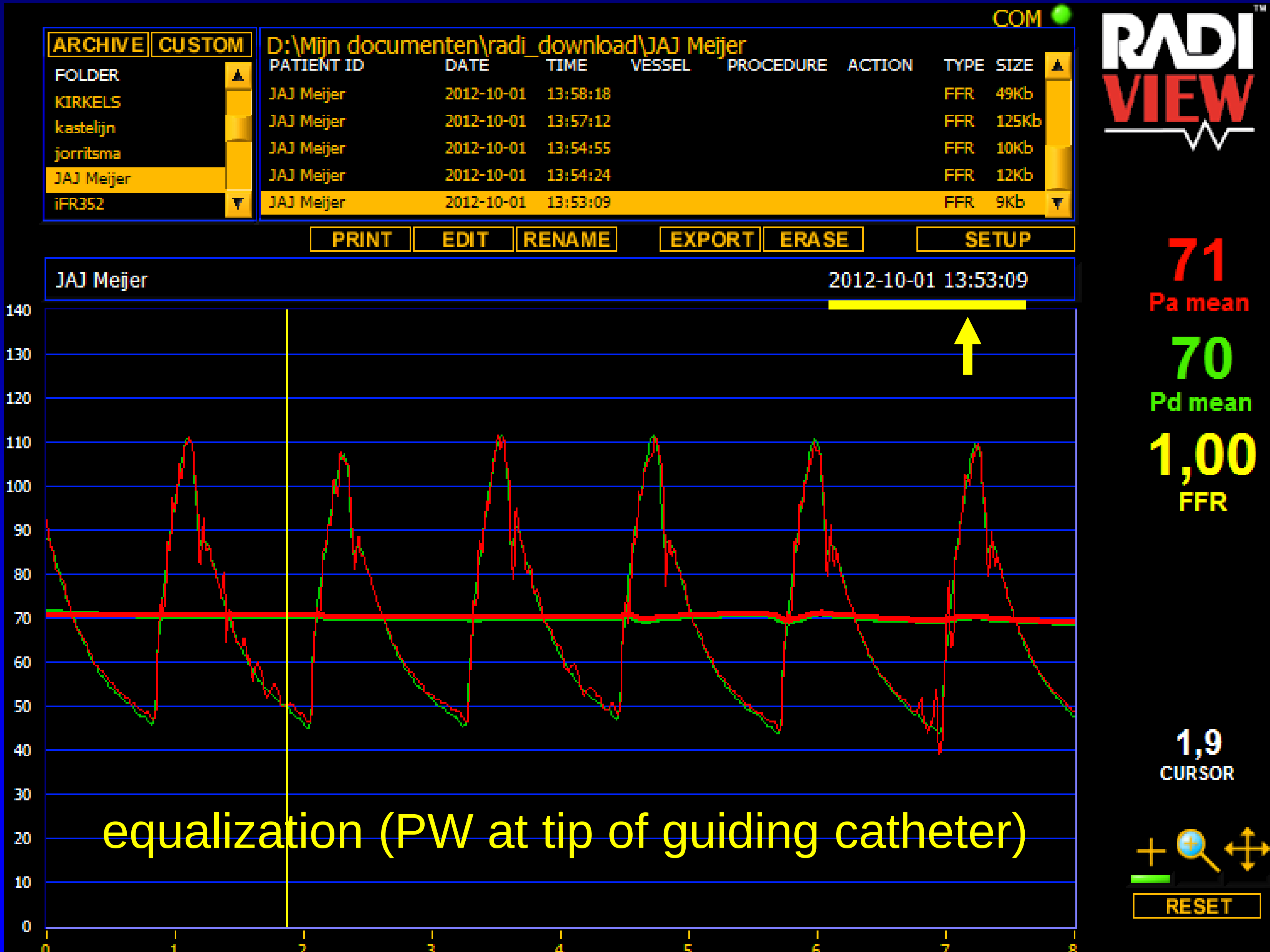
- **Limited Physiological Meaning**
  - poor scientific background
  - no experimental validation
  - fluid-dynamic equation

- ***Resting Conditions Are Very Hard to Obtain***
  - uncertainty if resting condition is present in cath lab → large fluctuations
  - most "resting" indices vary considerably
  - in fact, the only condition which can be reliably obtained in the cathlab, is ***maximum hyperemia***

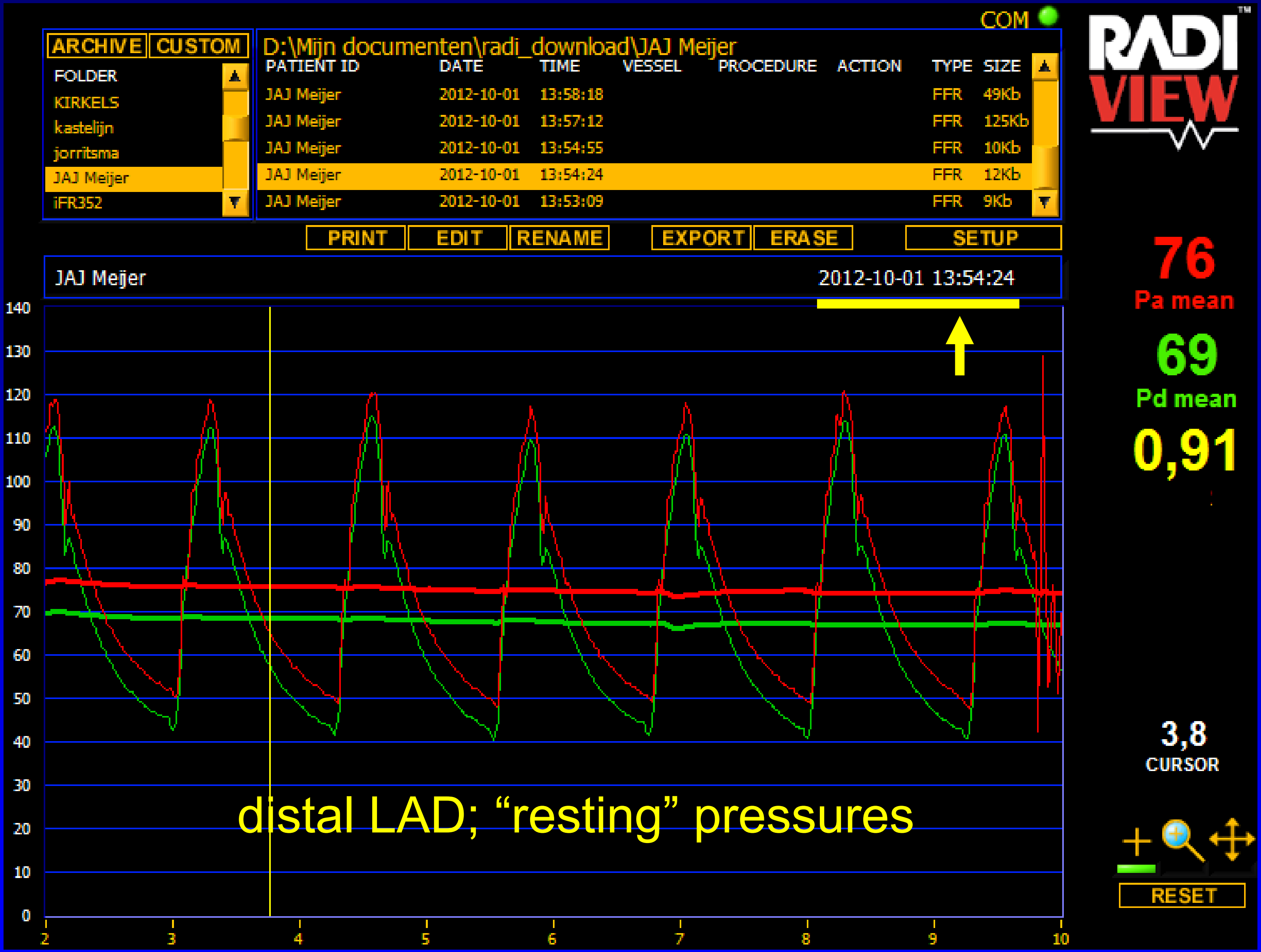


Mr M, born 26-03-1937,

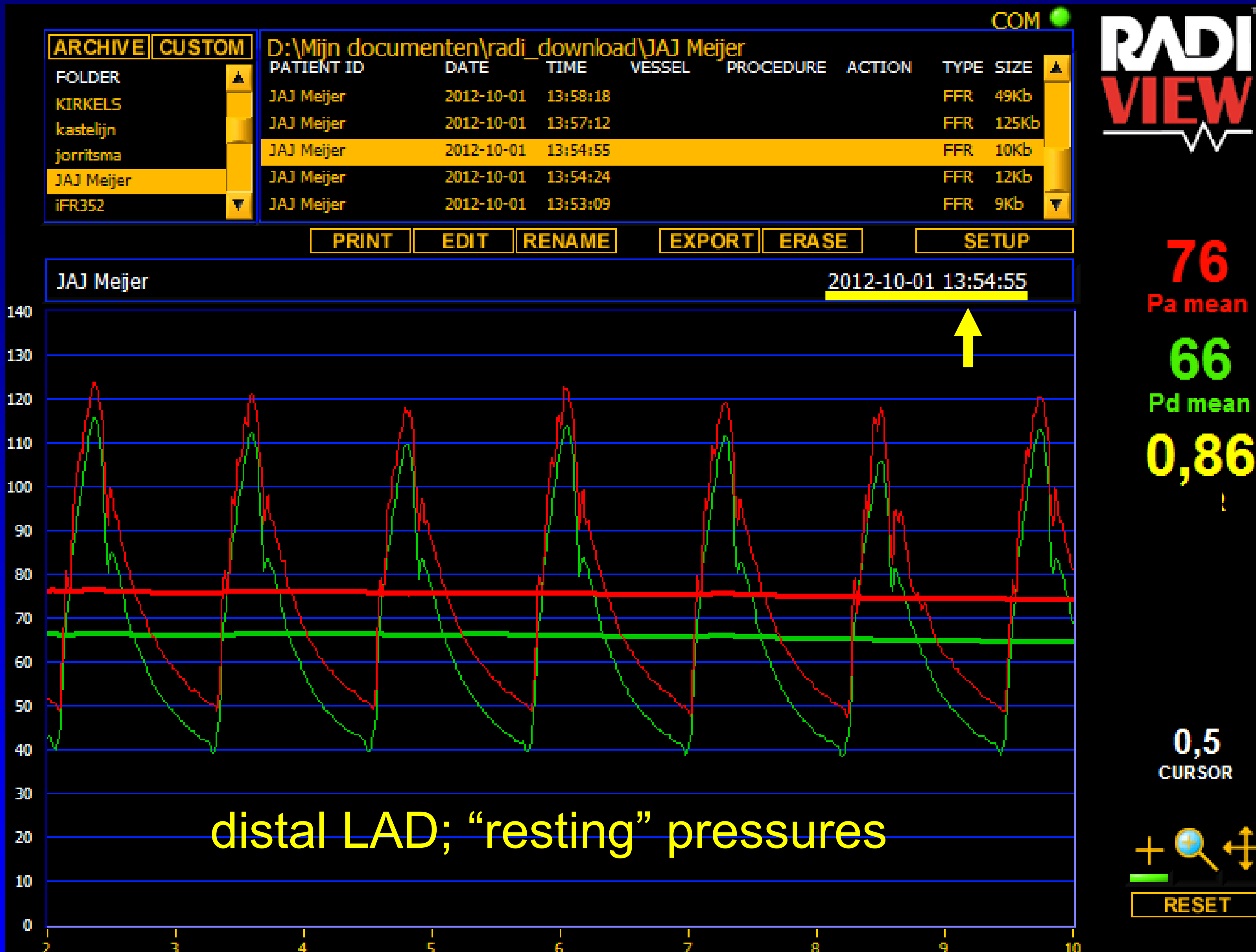
long mild/moderate proximal LAD lesion



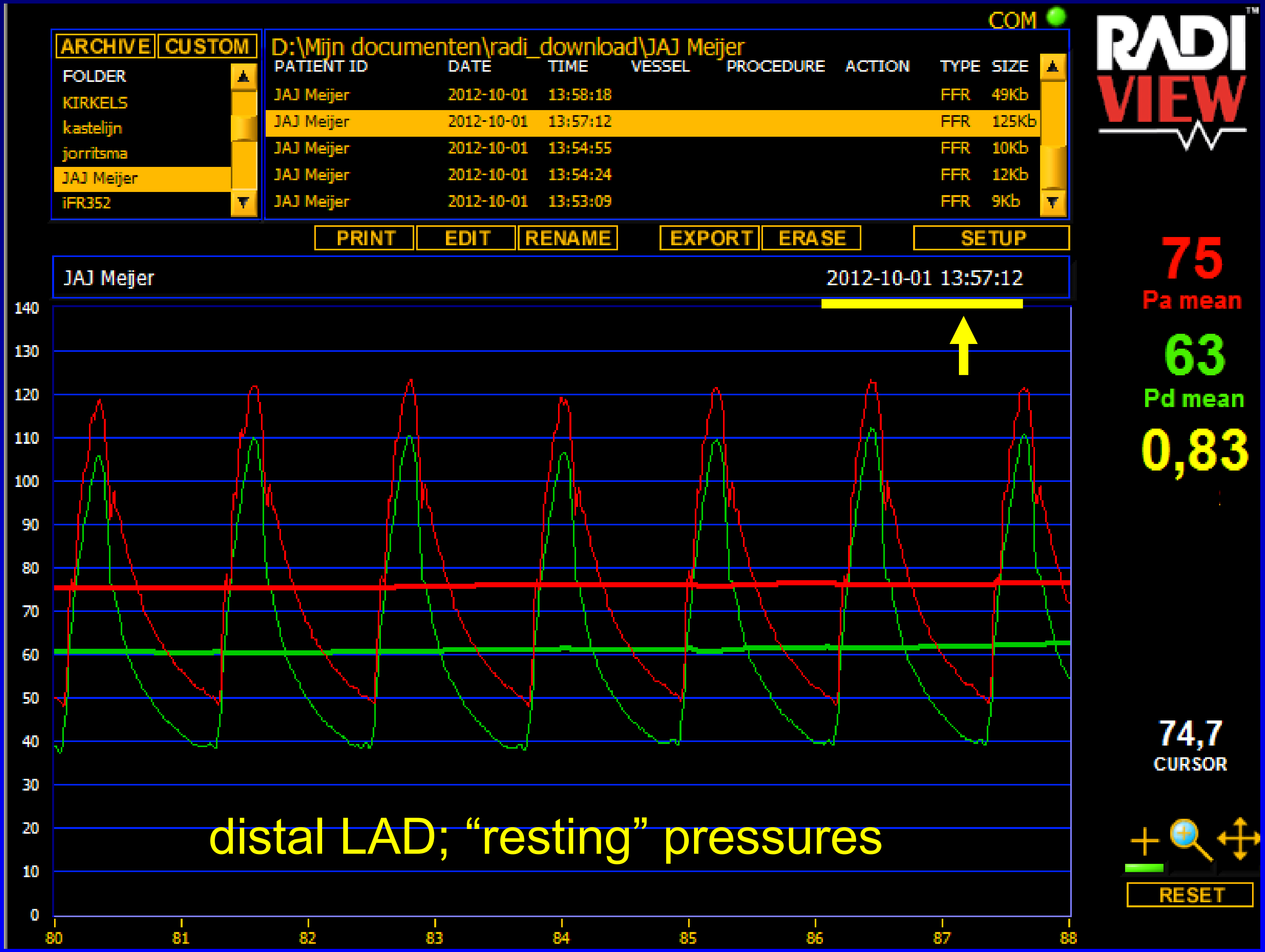
long moderate proximal LAD lesion; equalization



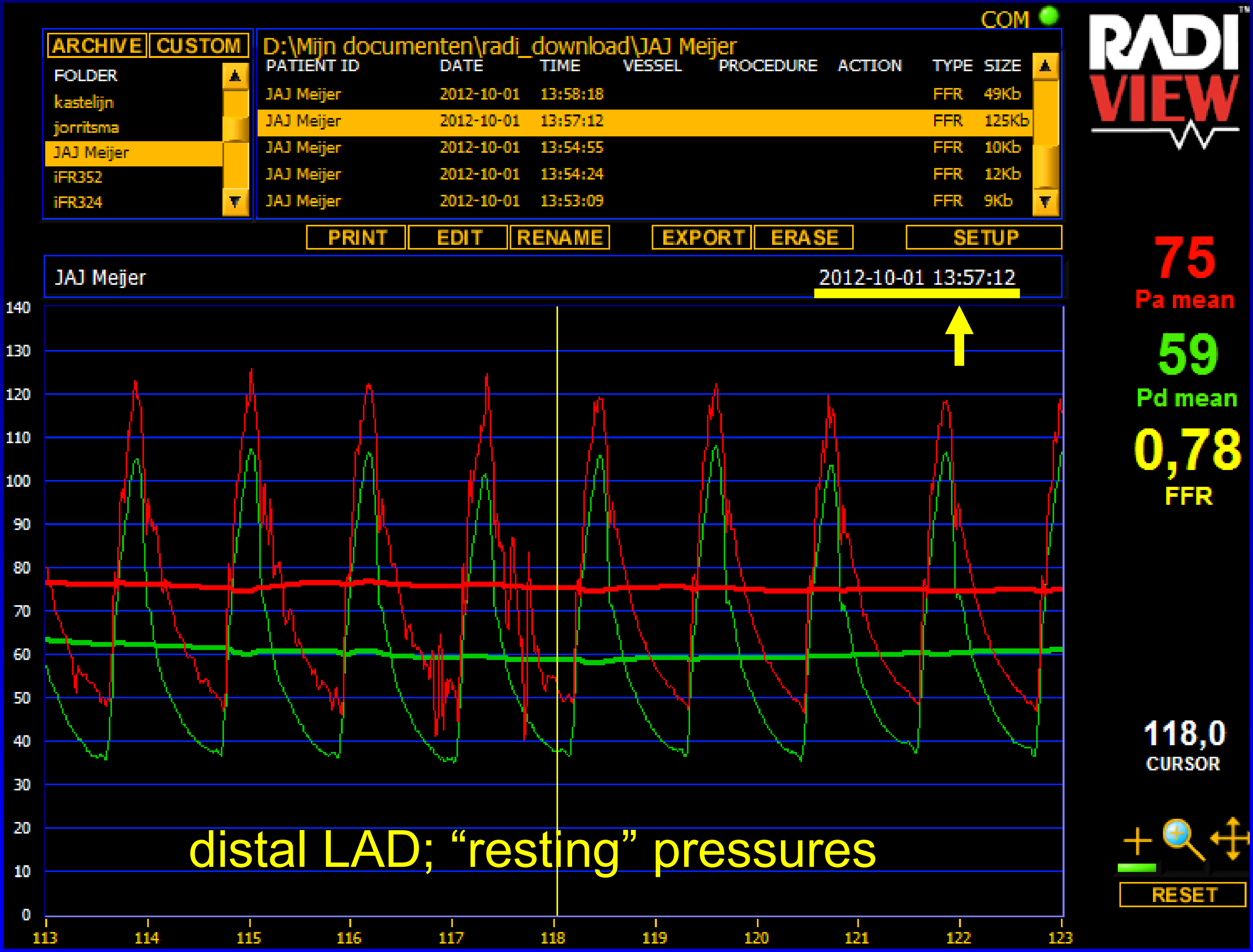
PW in distal LAD; patient “asleep” (relaxed)



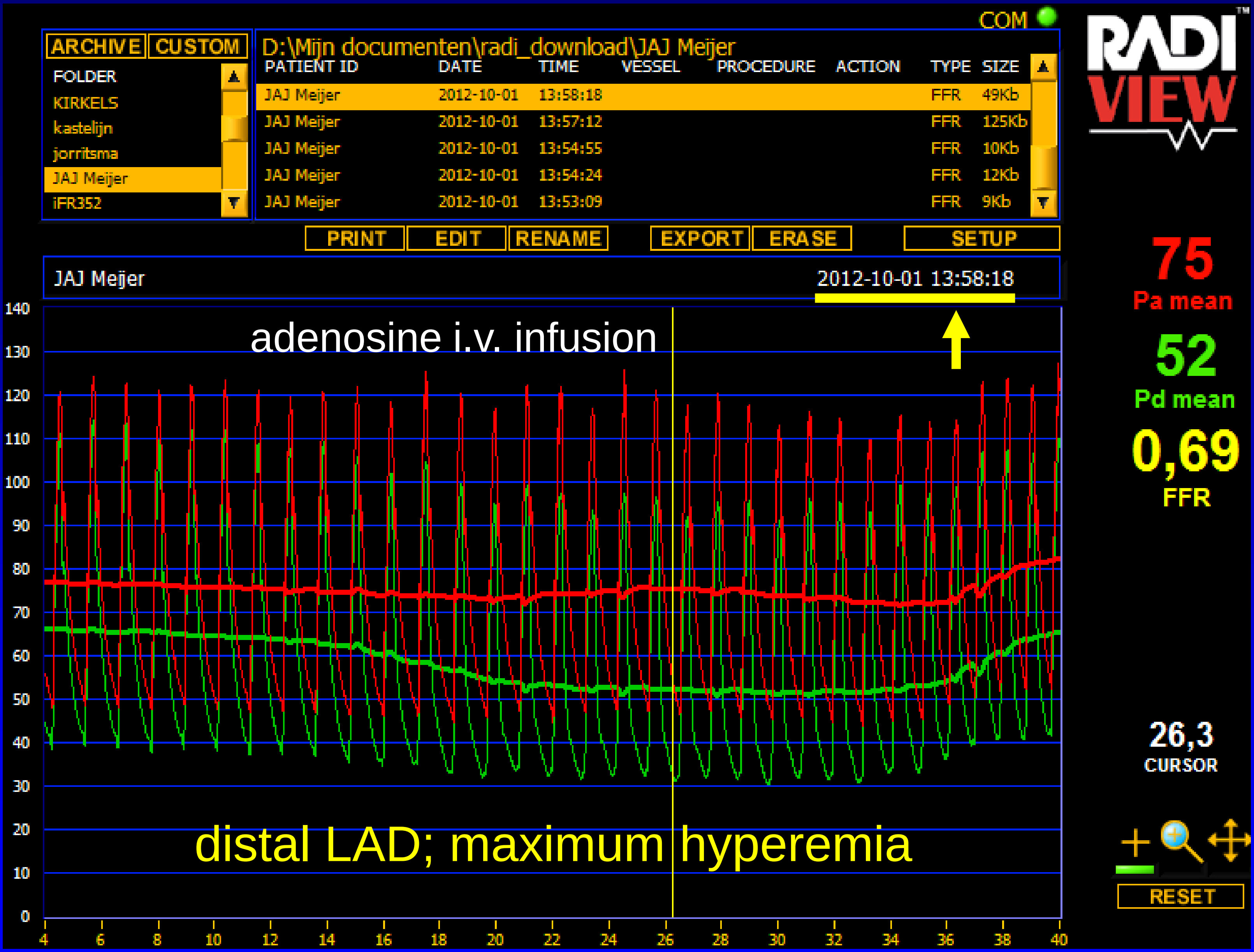
PW in distal LAD; patient “awake”



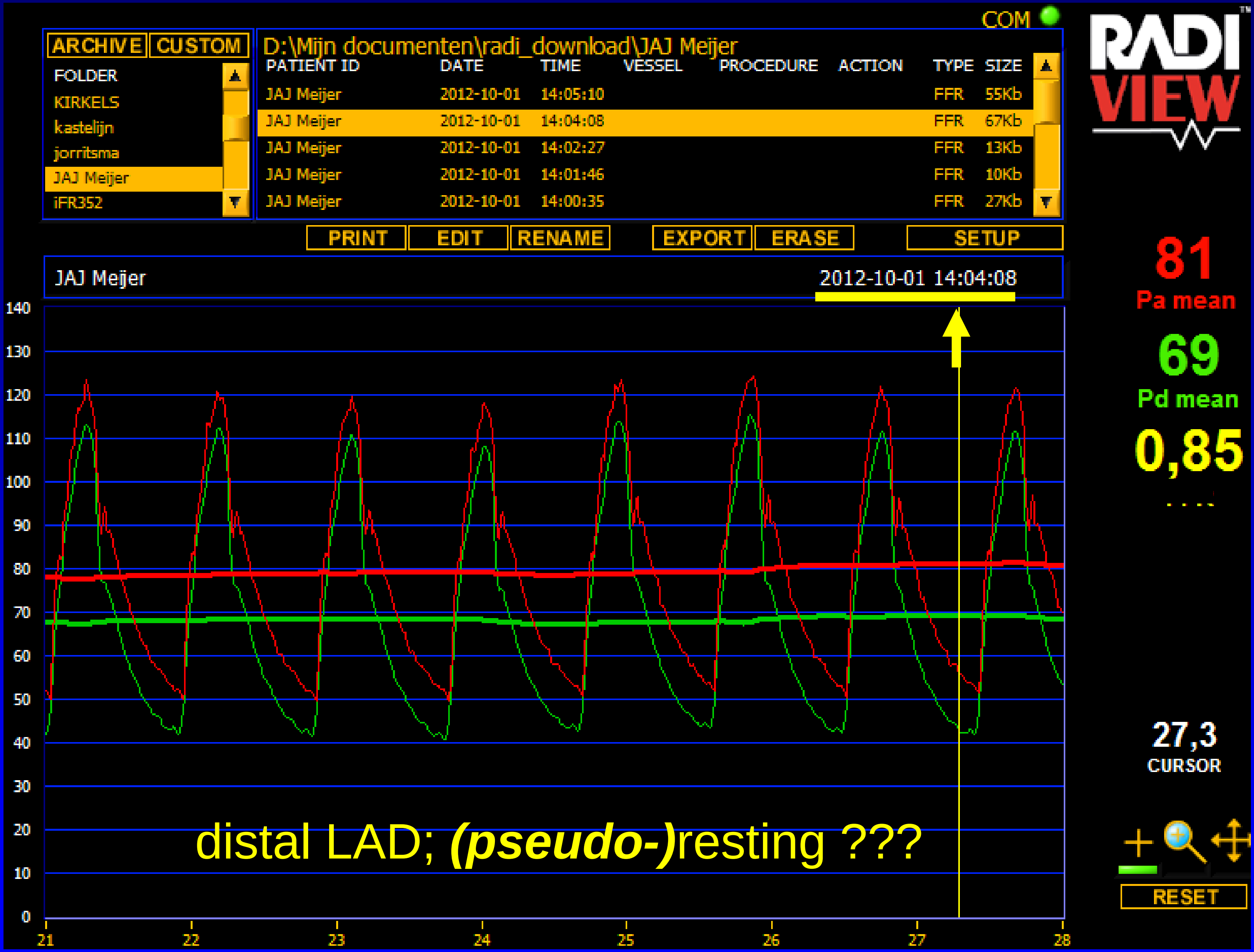
prior to adenosine: explanation to patient what is going to happen



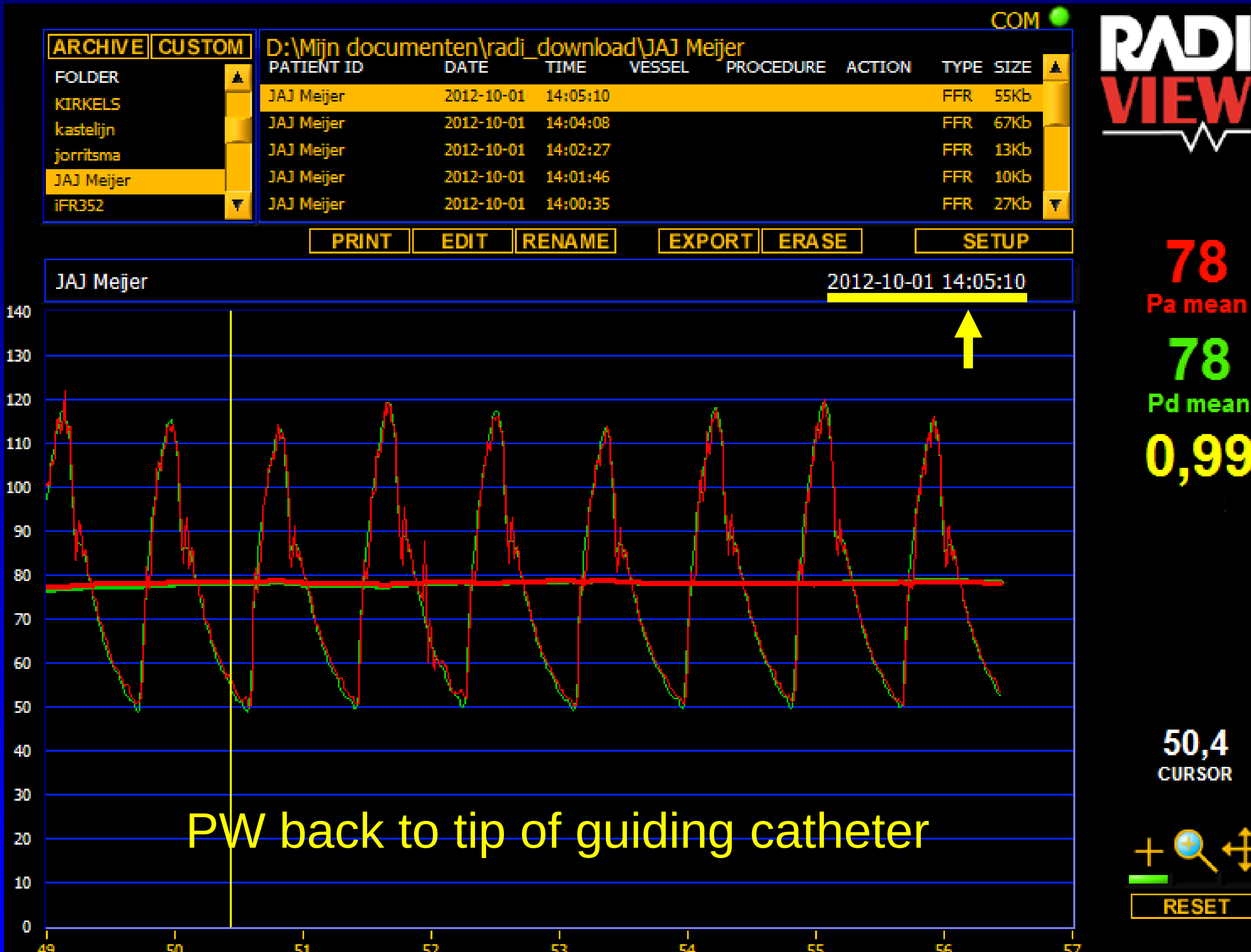
advancing the wire 2 cm and pulling it back again



Measurement of FFR



After waiting for 5 minutes, not touching anything

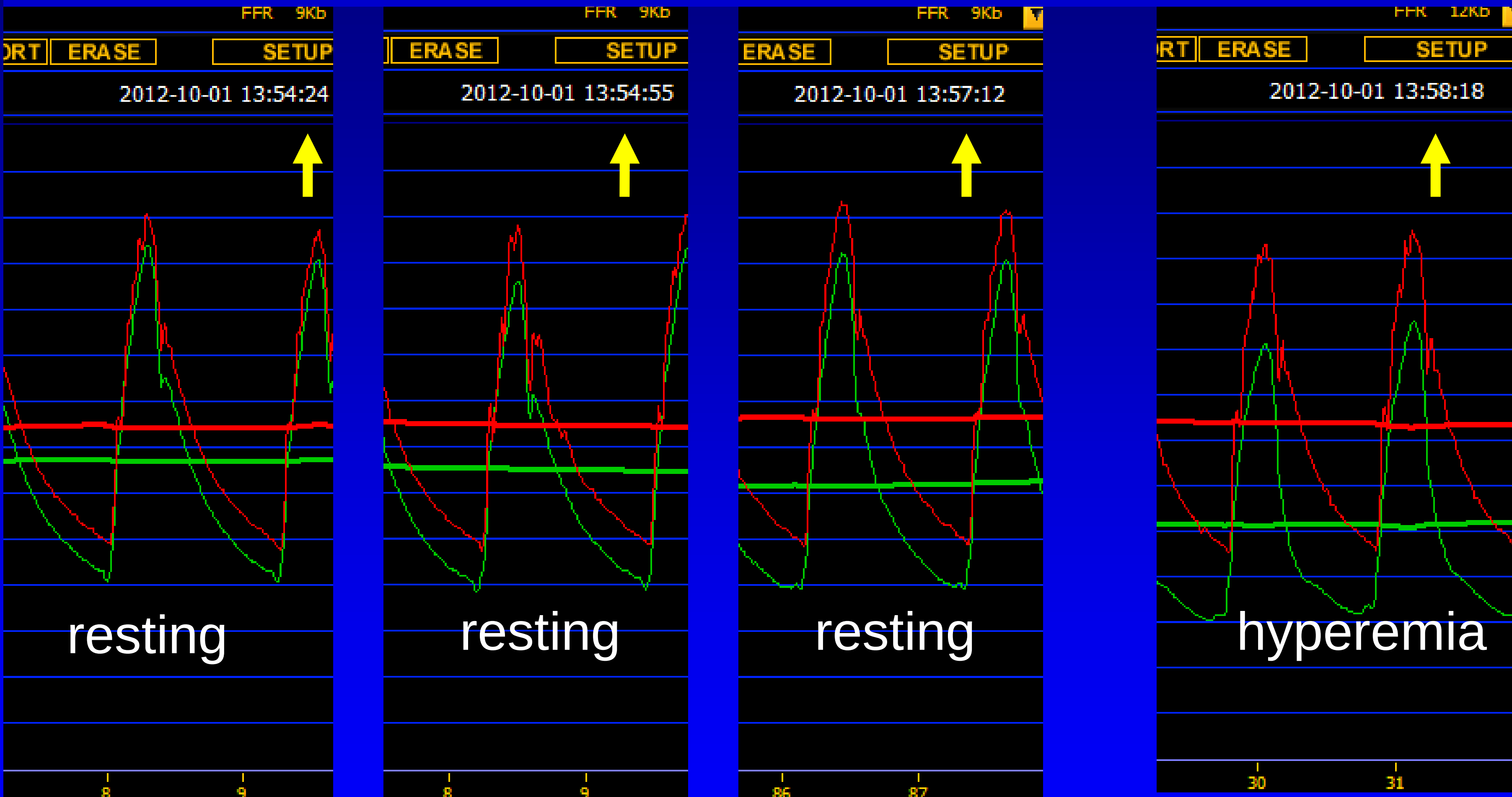


verification of equal pressures and absence of drift iFR = 0.89 P_d/P_a=0.90

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 room, is often an illusion

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

Traditional CFR: 1.7 – 2.0 – 2.5 – 3.5

CFR = 4.0 / 1.0 = 4 , but: 4.0 / 1.5 = 2.7

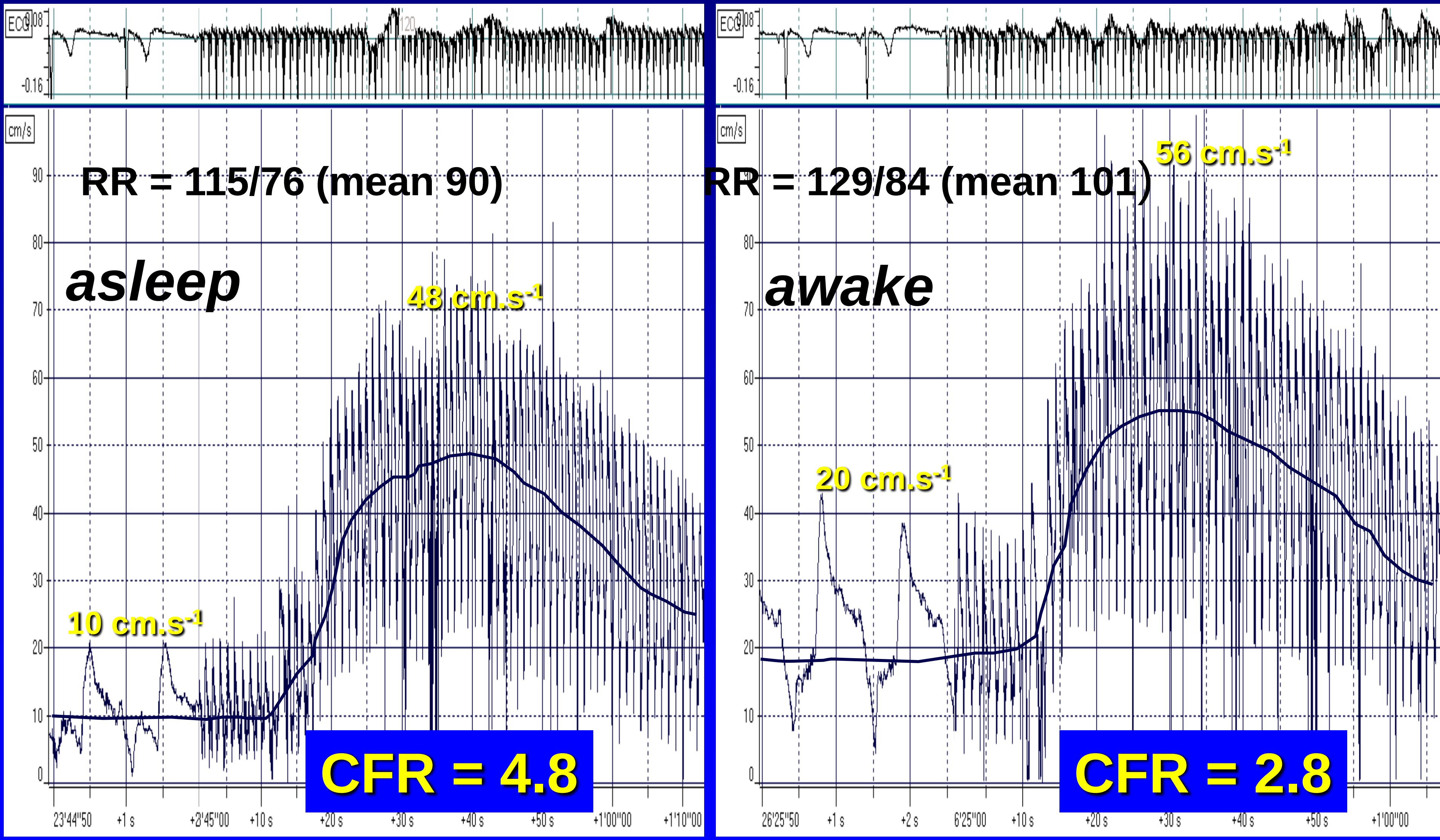
iFR: 0.83 (Advise study, Sen et al)
0.88 (Koo et al)
0.90 (Jeremias et al, resolve registry))

Similar for all indexes which rely upon resting value of flow

Jongen Egidius

Resting flow in the cath lab is an illusion:

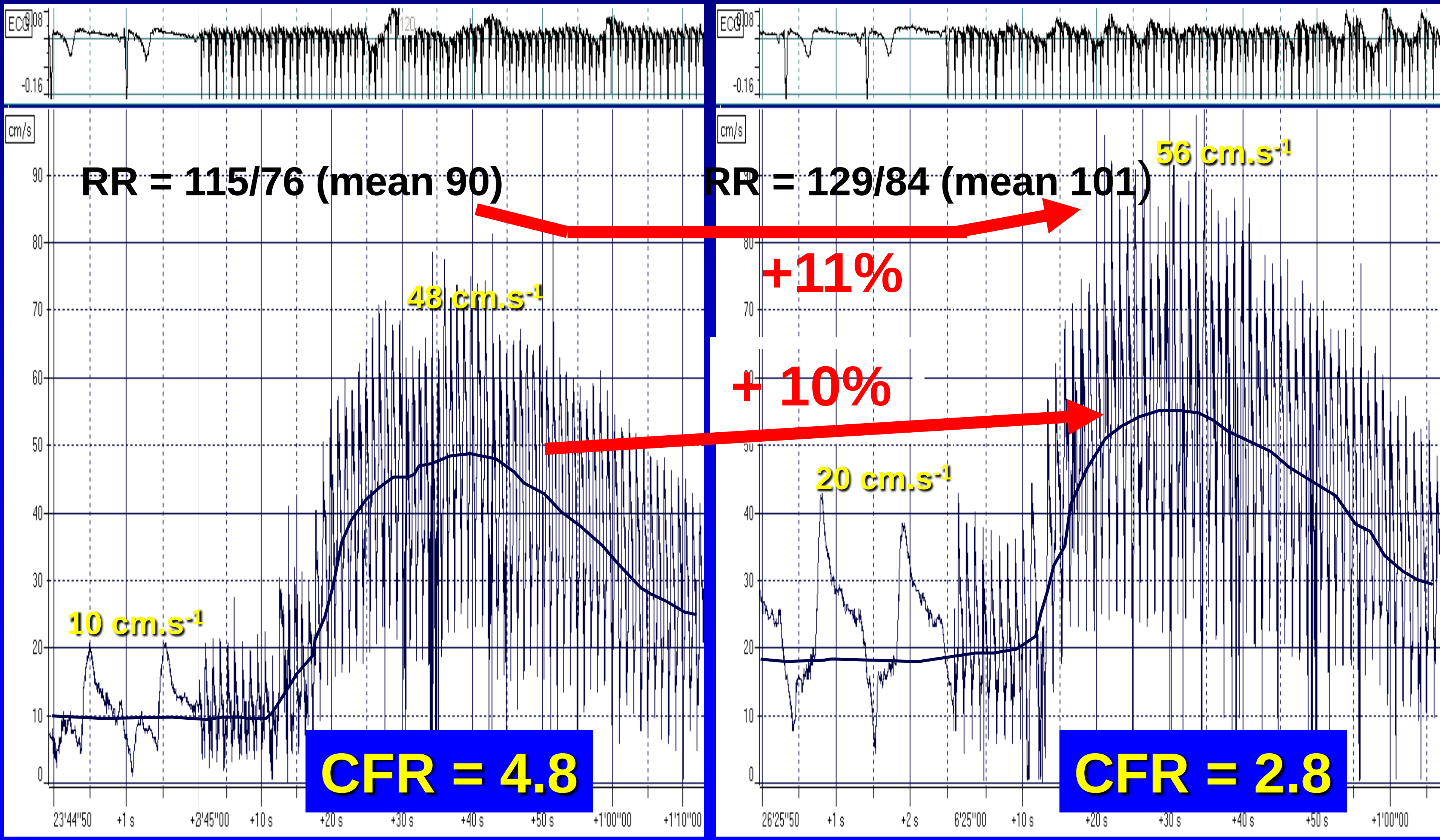
Influence of the "Resting Flow" on CFR



Jongen Egidius

Resting flow in the cath lab is an illusion:

FFR IS NOT AFFECTED !



Cut-off
=
0.83

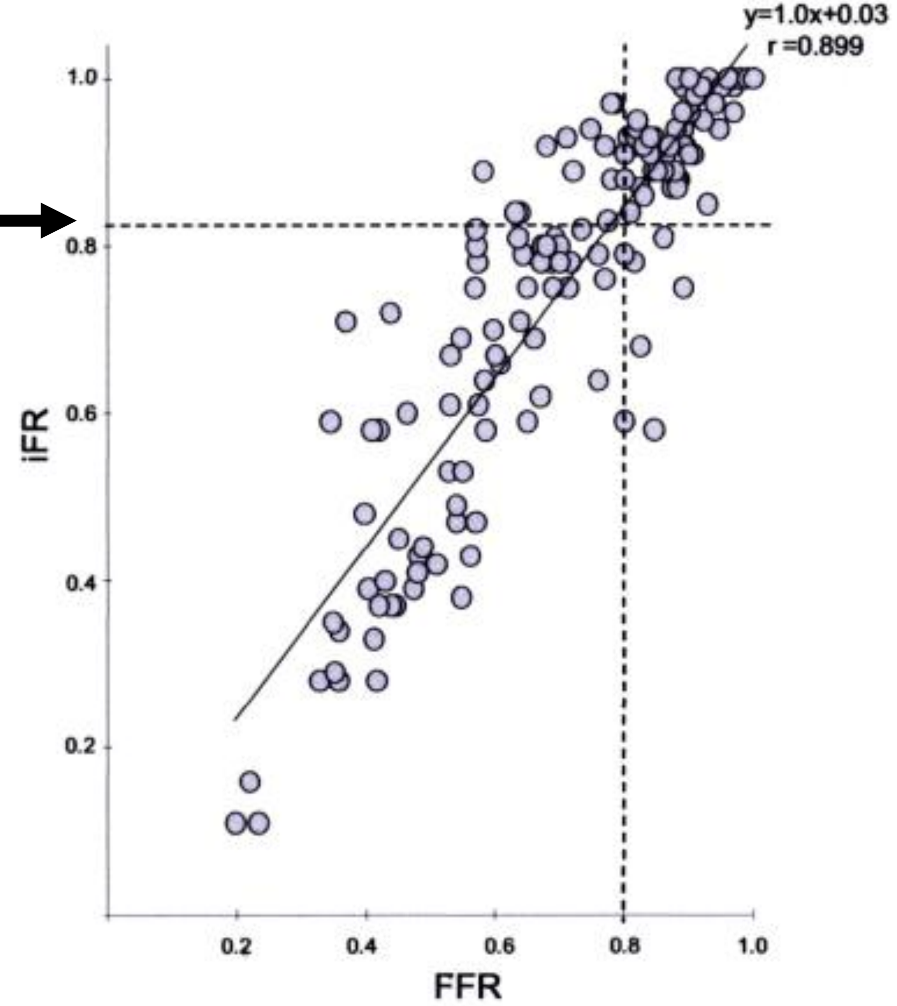
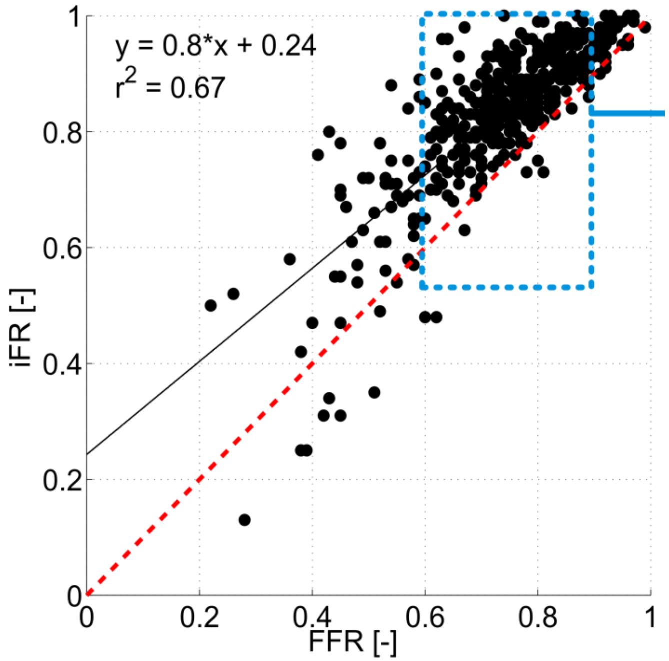


Figure 5:

ADVISE STUDY (N= 131)

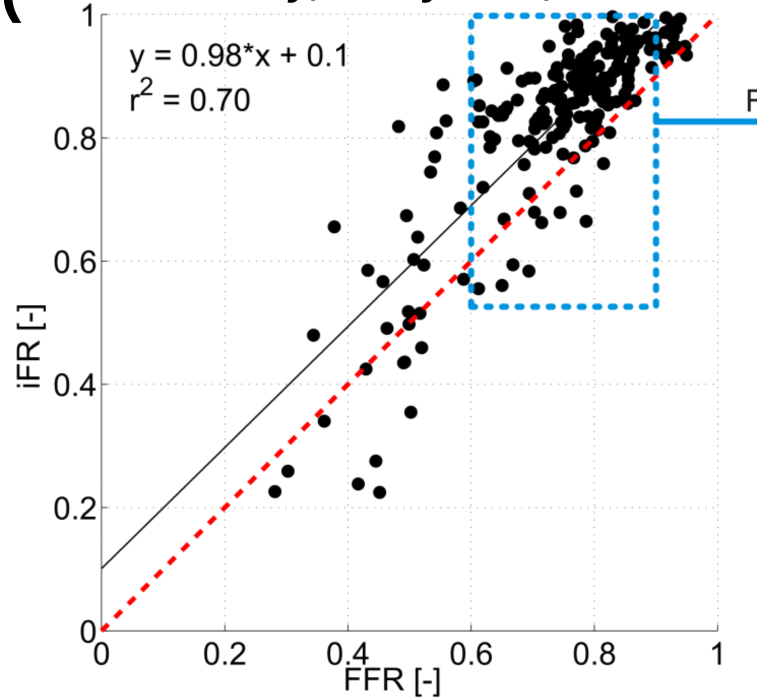
From:
Sen, Davies, et al
JACC 2011

Retrospective analysis
IFR versus FFR in 500 patients
(***VERIFY study, Berry et al, JACC 2013)***

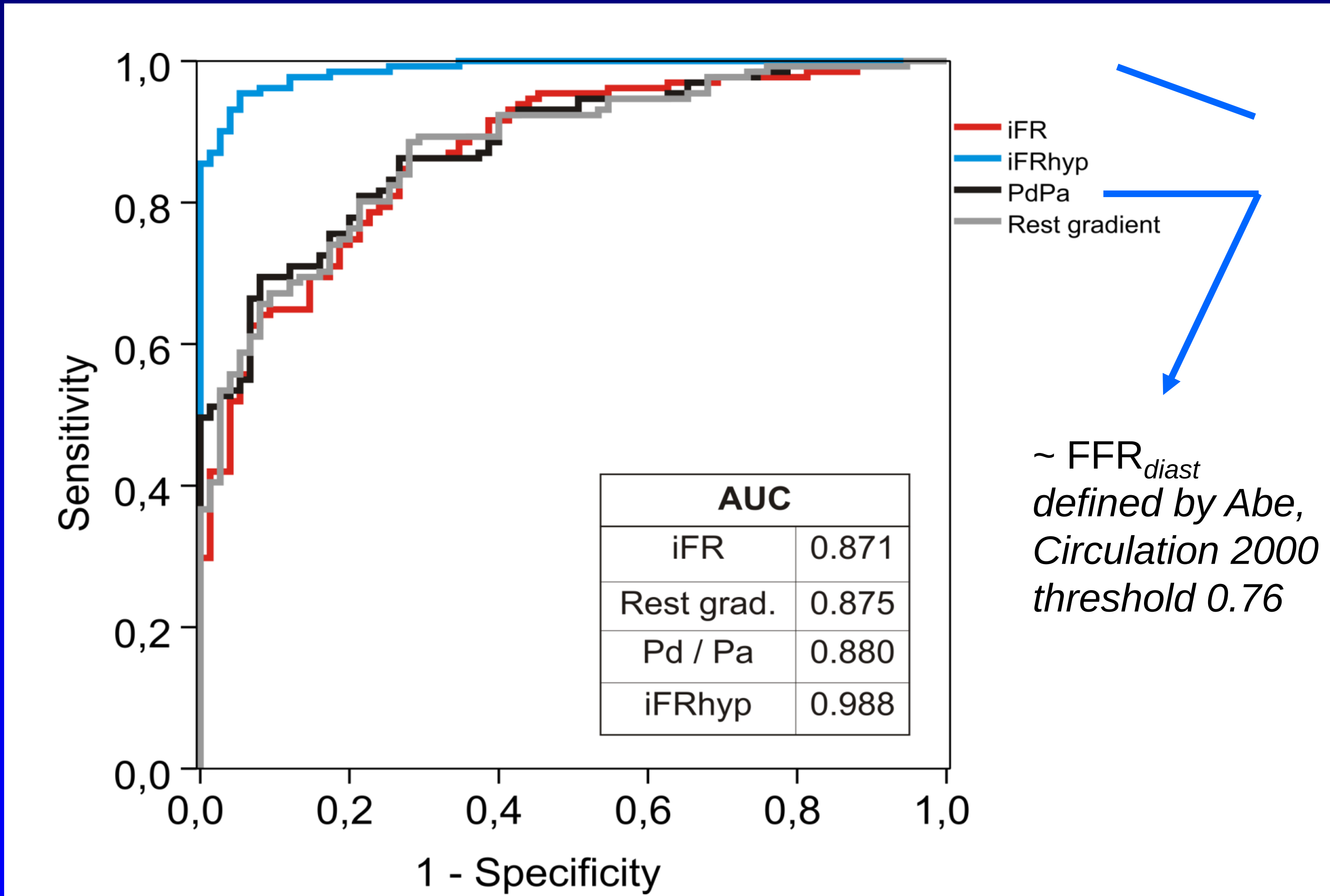


$R^2 = 0.67$
diagn accuracy = 66 %

Prospective analysis
IFR versus FFR in 205 patients
(***VERIFY study, Berry et al, JACC 2013)***



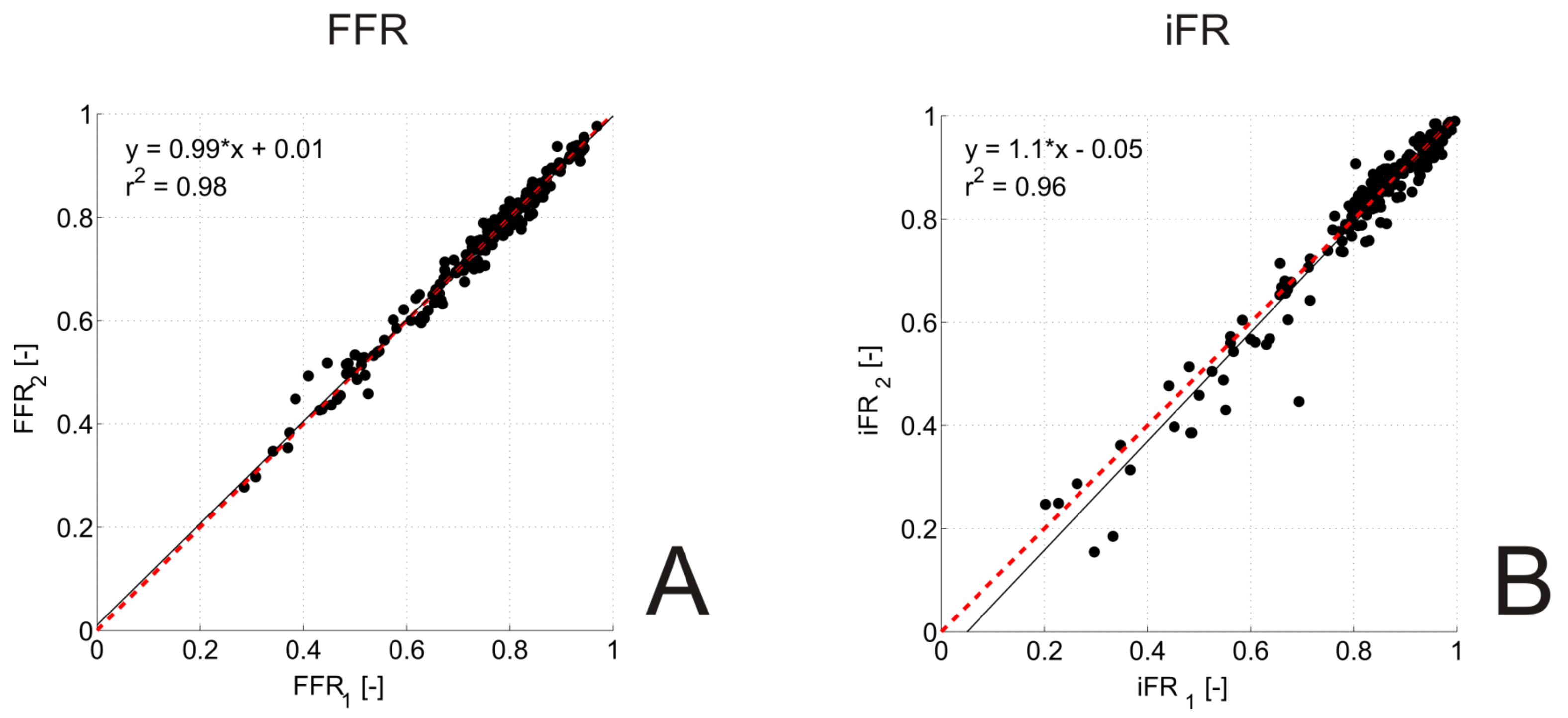
$R^2 = 0.70$
diagn accuracy = 67 %



AUC	
iFR	0.871
Rest grad.	0.875
Pd / Pa	0.880
iFRhyp	0.988

Colin et al, JACC 2012, in press; Johnson et al JACC 2012, in press; Koo et al, JaccCVI

Reproducibilty of FFR and iFR



From VERIFY study, Berry et al, JACC 2013

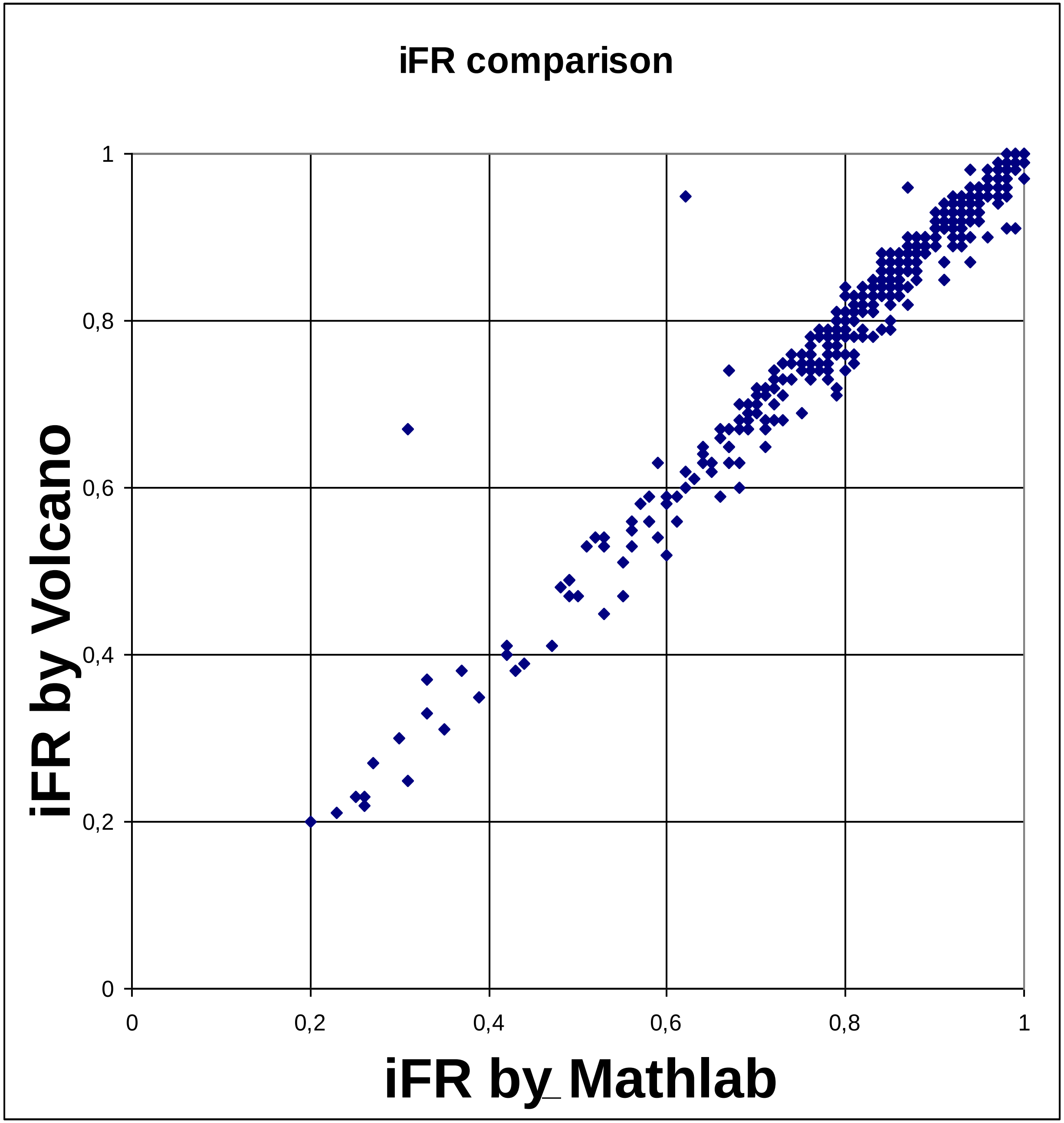
CALCULATION OF iFR: VOLCANO BOX vs MATLAB *DOES IT MATTER ?*

VERIFY STUDY: 705 resting and hyperemic tracings

Calculation by Mathlab (free available computer program) blinded for results by the Volcano algorhitm (University of Technology, BME dept)

Calculation by the Volcano algorhitm blinded for the results by Mathlab (CRF, New York)

From:
VERIFY
N=705



Berry et al
JACC 2013;

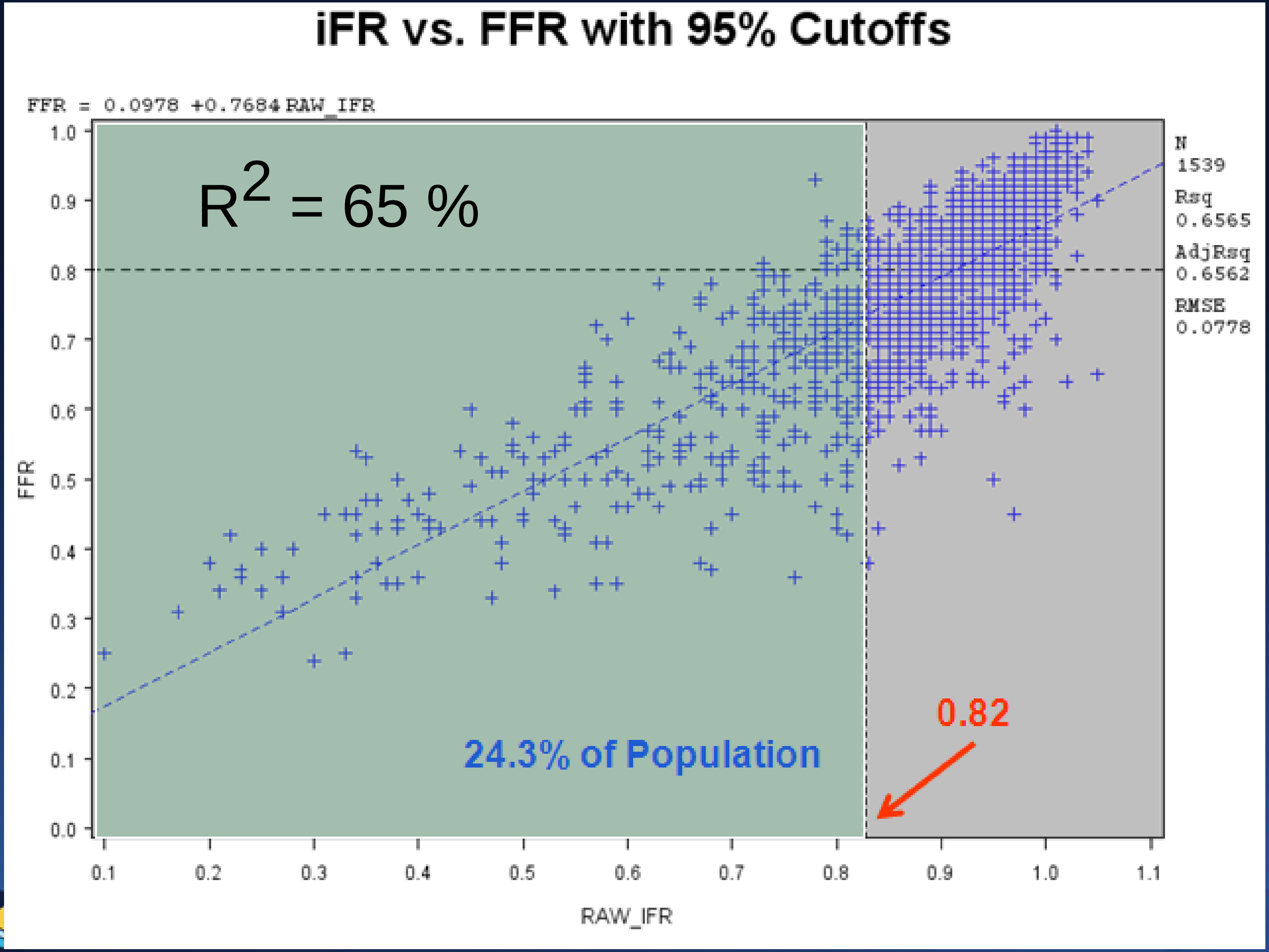
RESOLVE REGISTRY (TCT 2012, Jeremias et al)

Data Contribution

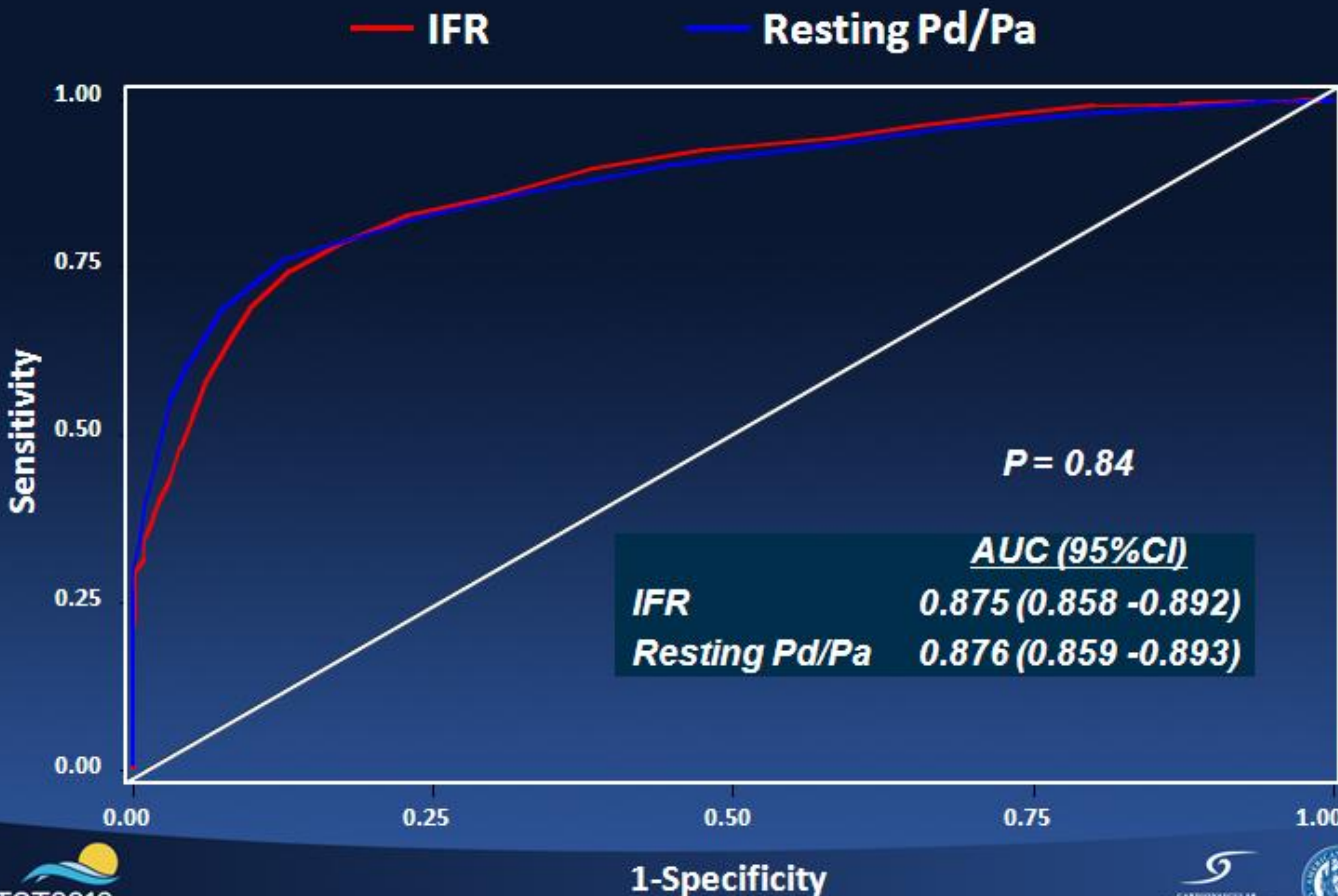
	Patients	Lesions
ADVISE/ADVISE Registry	528	528
VERIFY Prospective Cohort	202	202
VERIFY Retrospective Cohort	592	592
Seoul National University	180	184
UT Houston	136	144
Stony Brook University	164	200
Total	*1802*	*1850*

TCT2012

Correlation FFR and iFR



ROC Curve iFR and Pd/Pa Based on FFR 0.80



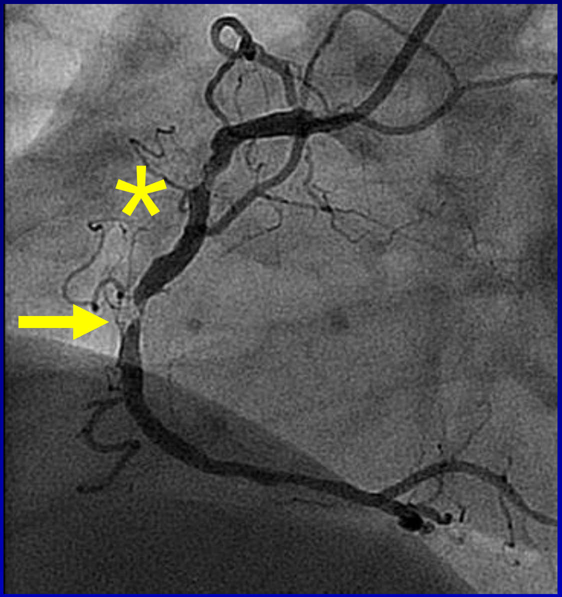
	AUC (95%CI)
IFR	0.875 (0.858 -0.892)
Resting Pd/Pa	0.876 (0.859 -0.893)

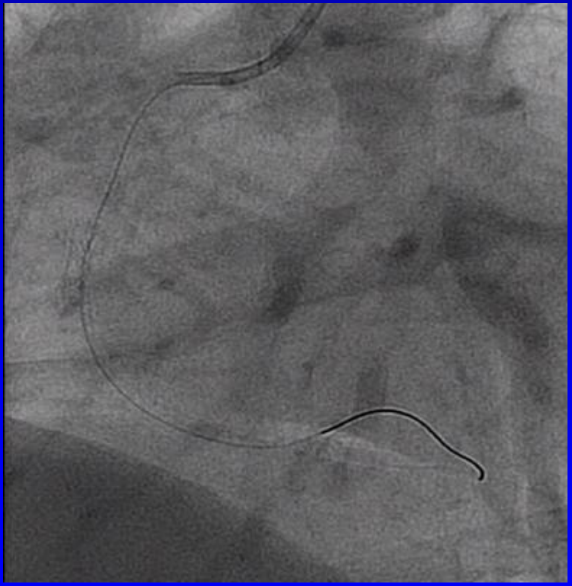
necessity of hyperemia

- If Pd/Pa at rest (or comparable indices) 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 and FRR , you cannot judge how much a patient improved by stenting: "*did FFR go from 0.78 to 0.91 or from 0.65 to 0.91 ?*"

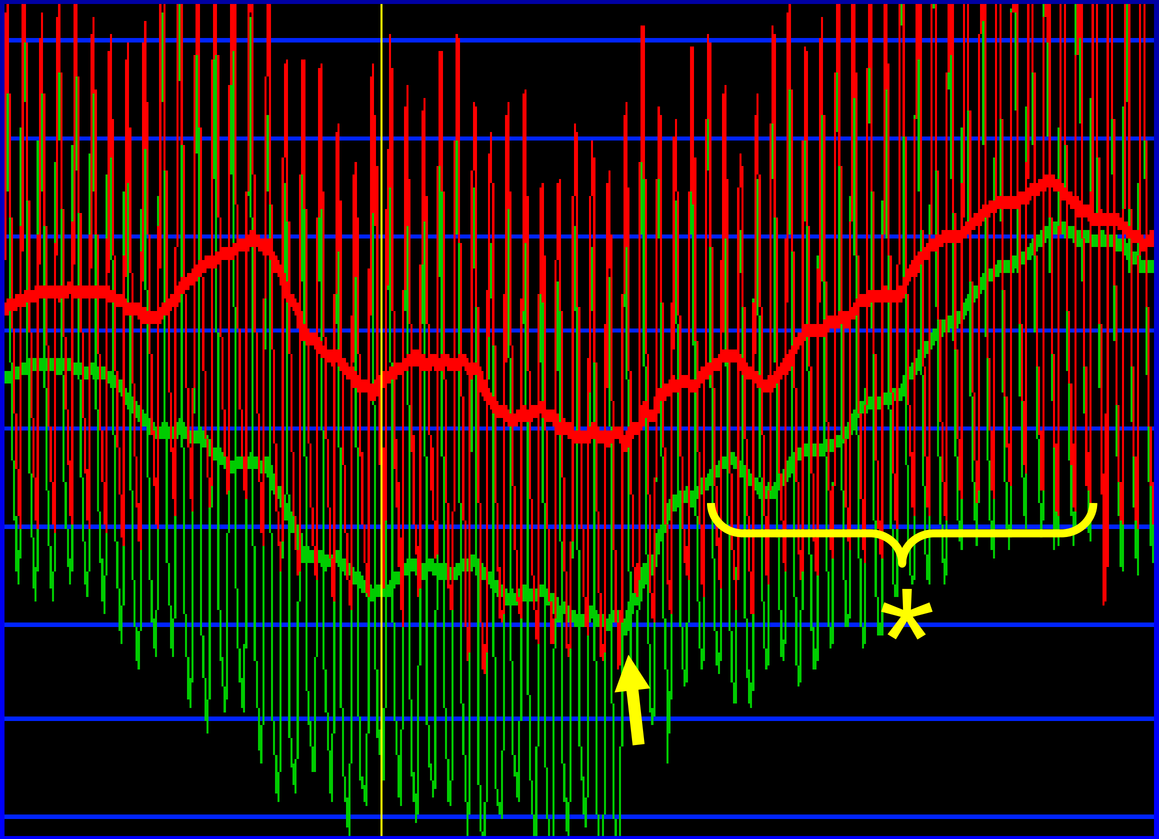
- And without hyperemia, you cannot make a meaningful *pull-back recording* and you are loosing a lot of valuable information





“hyperemic pull back recording”

in case of diffuse disease or multiple lesions: ***how would you believe to get this information without hyperemia ?***



AVOIDING HYPEREMIA IS PROHIBITIVE FOR STENT EVALUATION

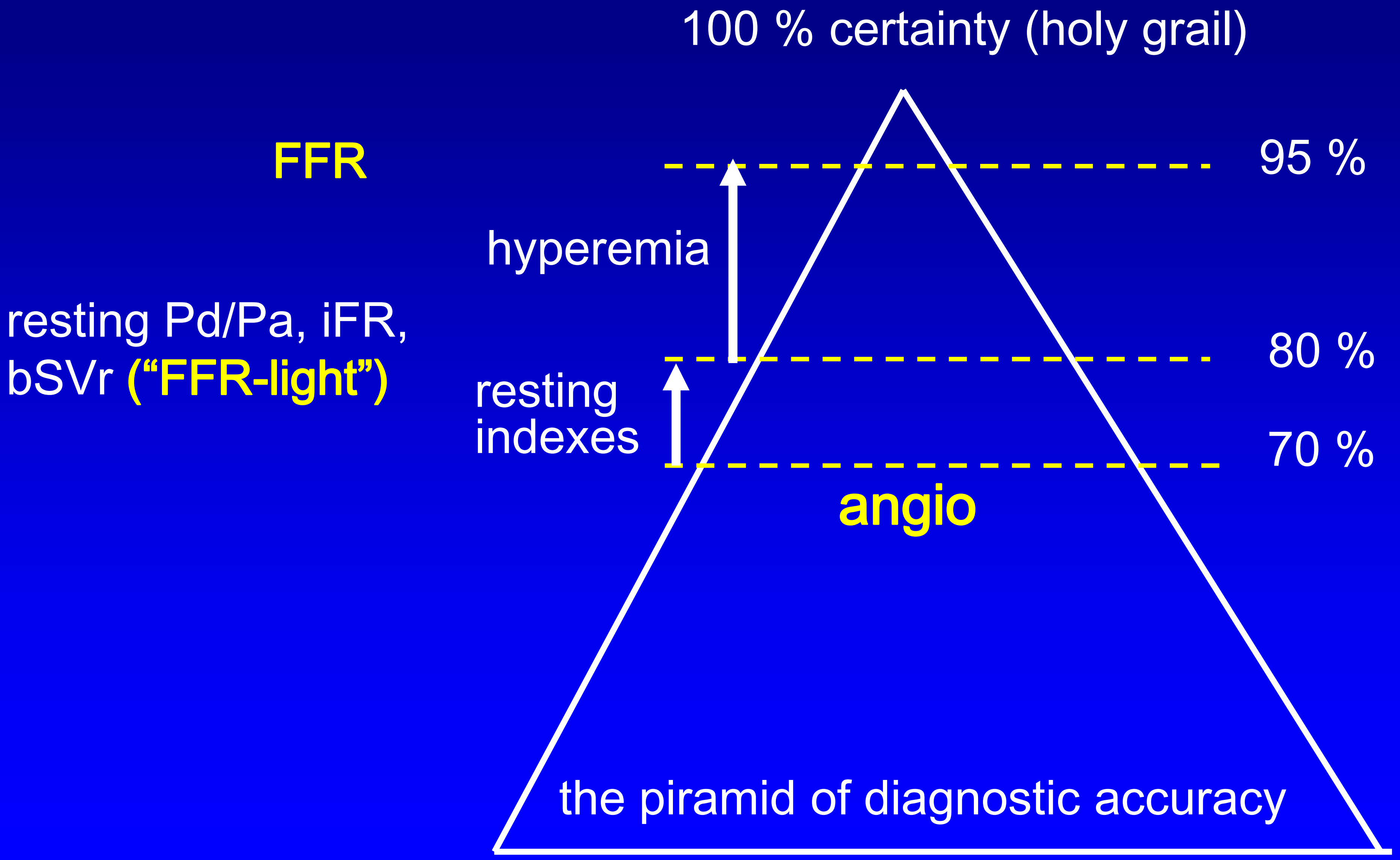
After stenting, in the majority of patients no resting conditions are obtained anymore and "semi-hyperemic" status persists, with a lot of inter-individual variation.

It often takes > 30 minutes to achieve "baseline" again

As a consequence, "resting" Pd/Pa (and iFR) are often *lower after stenting than before* *("paradoxical deterioration of iFR or resting Pd/Pa").*

To evaluate improvement by stenting, you need to compare FFR after and before stenting

Correct Classification of Ischemic Stenosis



CONCLUSIONS

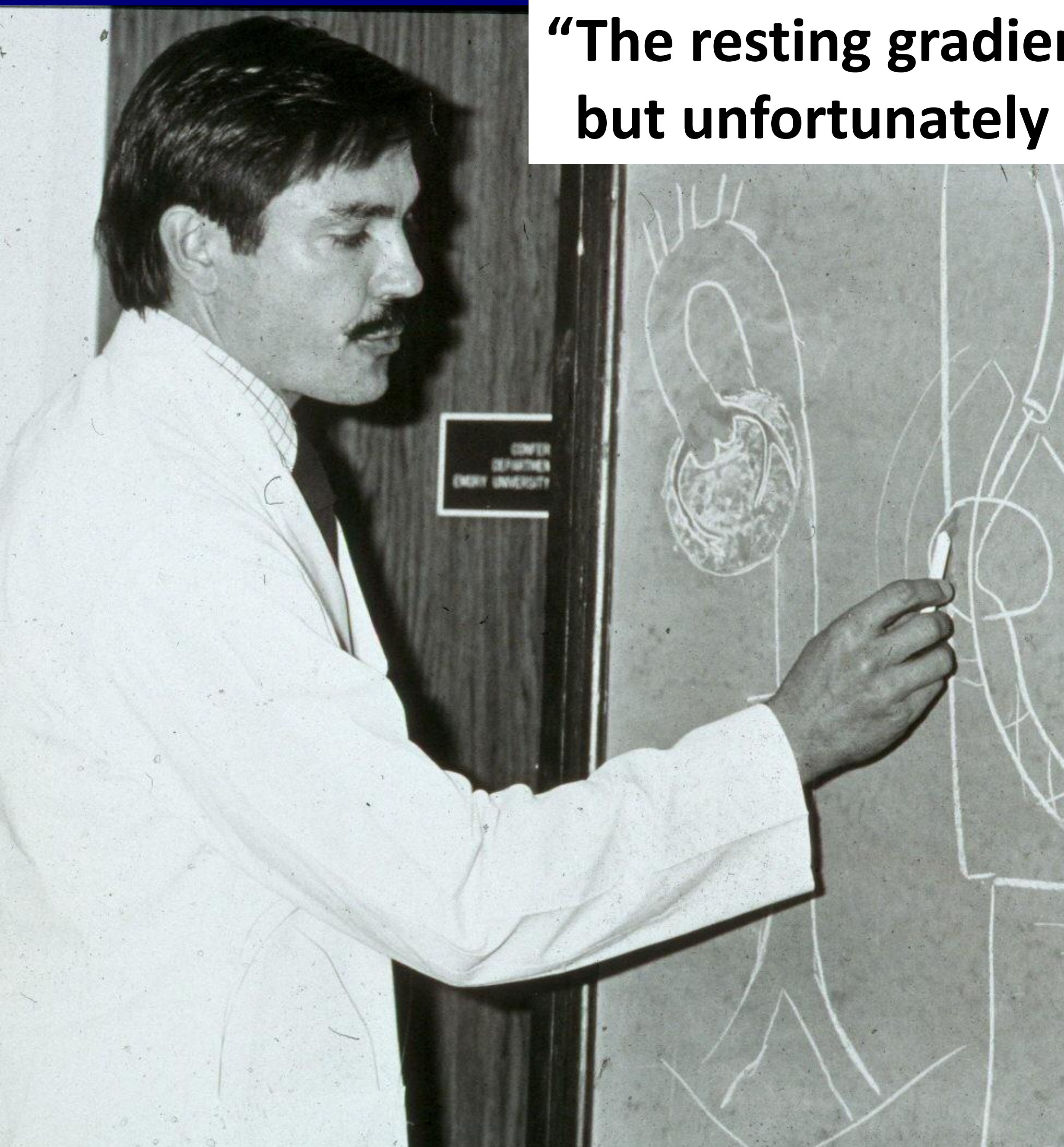
- the physiologic basis for using resting indices is flawed and based upon unproven assumptions
- the experimental validation is lacking and experiments in dogs and swine in fact reject those assumptions
- none of these resting indexes has been independently validated
- the accuracy of all of these resting indices (whether **ΔP,** Pd/Pa *at rest*, or iFR) in clinical studies is similar for all of them and ~ < 80 % only when compared to FFR
- It is questionable if you should accept 80% certainty in your patients if you can get 95%

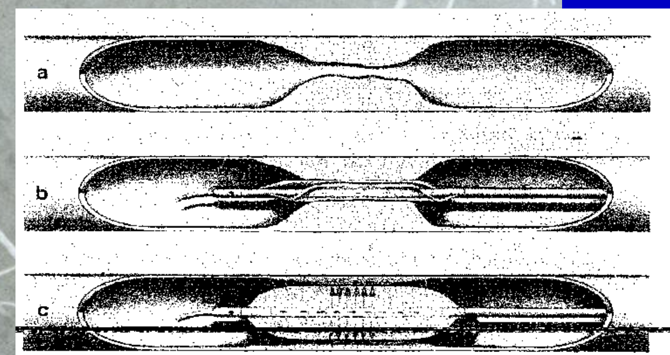
CONCLUSIONS

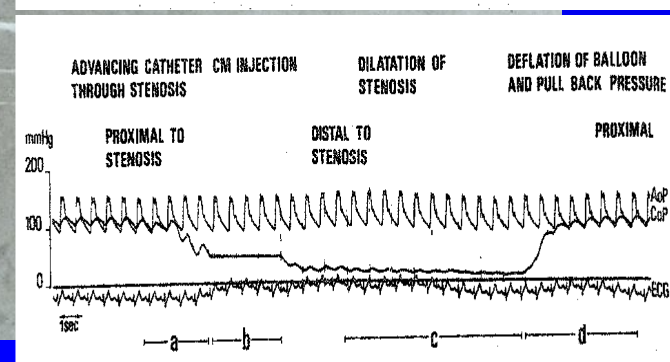
- using resting indices is like testing in a wind tunnel without wind
- the physiologic basis for using resting indices is flawed and based upon unproven assumptions
- the experimental validation is completely absent and in fact experiments in dogs and swine reject their validity incontrovertably
- the accuracy of all resting indices (whether **ΔP,** Pd/Pa *at rest*, or iFR) in clinical studies is similar and ~ 80 % only, versus 95 % for (hyperemic) FFR

→ ***relying upon resting indexes only, means a wrong decision in 1 out of every 5 patients***

"The resting gradient is far from enough but unfortunately it's all I have now".







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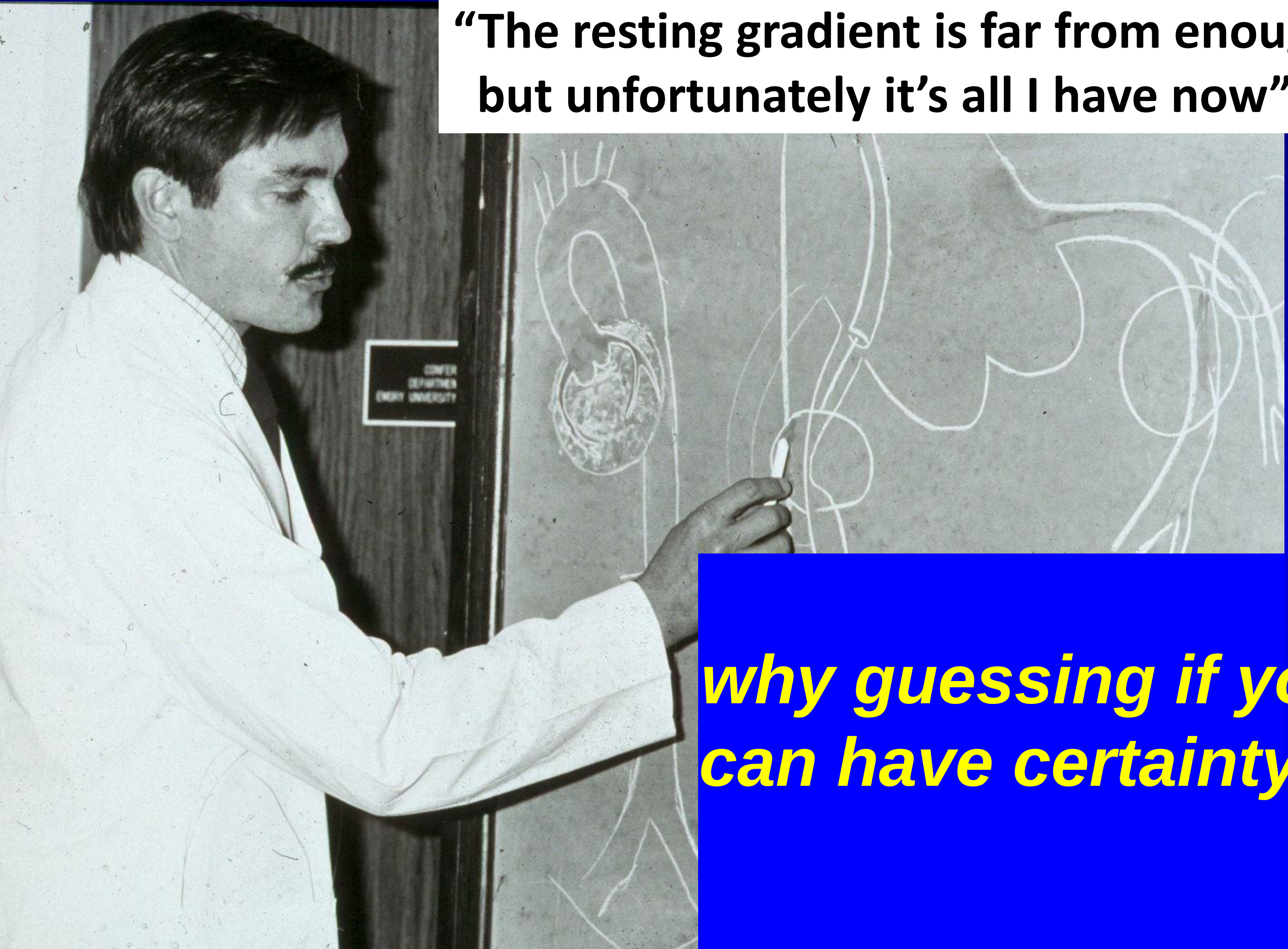


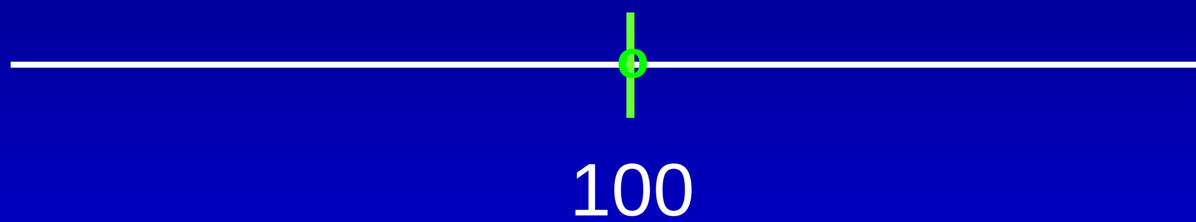
why guessing if you can have certainty ?

Neem als basis
TCT 2012 (soortgelijke voordracht)
Budapest (soortgelijke voordracht)

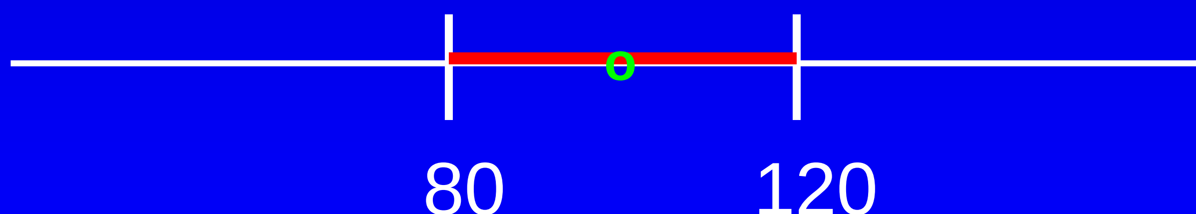
Latere data:
Dia’s met reprod heid
Inaccuracy van 80% en van 70% tov die 80%
(lijn met intervallen)
Ook Nils Johnson

Hocus-pocus with statistics (1)

true value = 100

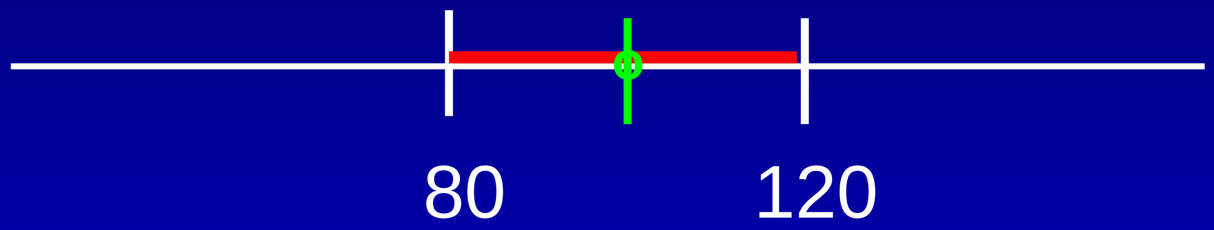


measuring methodology #1 : accuracy = 80 %

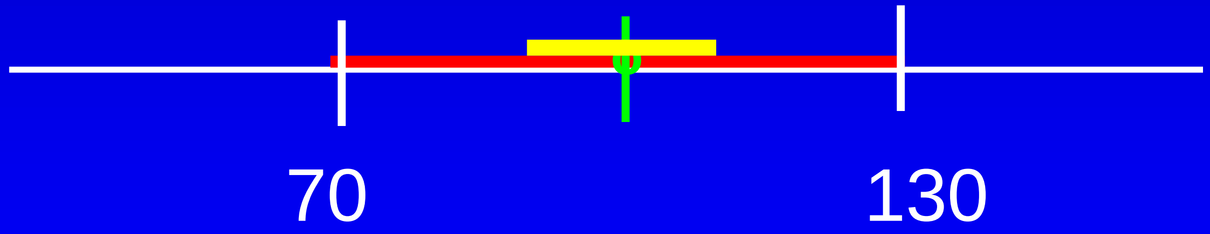


measured value between 80 and 120

measuring methodology #1 : accuracy = 80 %



measuring methodology #2 :
accuracy = 90 % compared to methodology #1



Range of uncertainty between 70 and 130
(and not between 90 and 110)

Hocus-pocus with statistics (2)

Accuracy of method #1 = 90 % compared to gold standard

Accuracy of method #2 = 80 % compared to method #1

What is the accuracy of method #2 compared to gold standard ?

→ **(0.8 x 0.9) = 0.72 (or 72 %)**

And NOT: (0.8 : 0.9) = 0.89 (or 89 %)

Hocus-pocus with statistics (3)

About reproducibility and "wrong decisions"

Or: confusing a-priori and a-posteriori knowledge

- In Catharina Hospital, 7000 invasive procedures (diagnostics and PCI) are performed annually
- Prior to a procedure, kidney function is checked
- If GFR < 60 ml/min → prehydration
- Accuracy of GFR measurement is ≤ 3ml/min *(rather good!, you don't think so?)*

Hocus-pocus with statistics (3)

About reproducibility and "wrong decisions"

Or: confusing a-priori and a-posteriori knowledge

- In the year 2012, out of the 7000 patients GFR was between 57 and 63 ml/min in 387 of them.
- In ~ 50% of these 387 patients, a second measurement would have switched them from above 60 ml to below or vice versa
- *Does this mean that you could better not determine renal function prior to PCI/ CAG, because "it is wrong In the group of patients where it matters" ???*

<u>Hocus-pocus with statistics (3)</u>

About reproducibility and "wrong decisions"

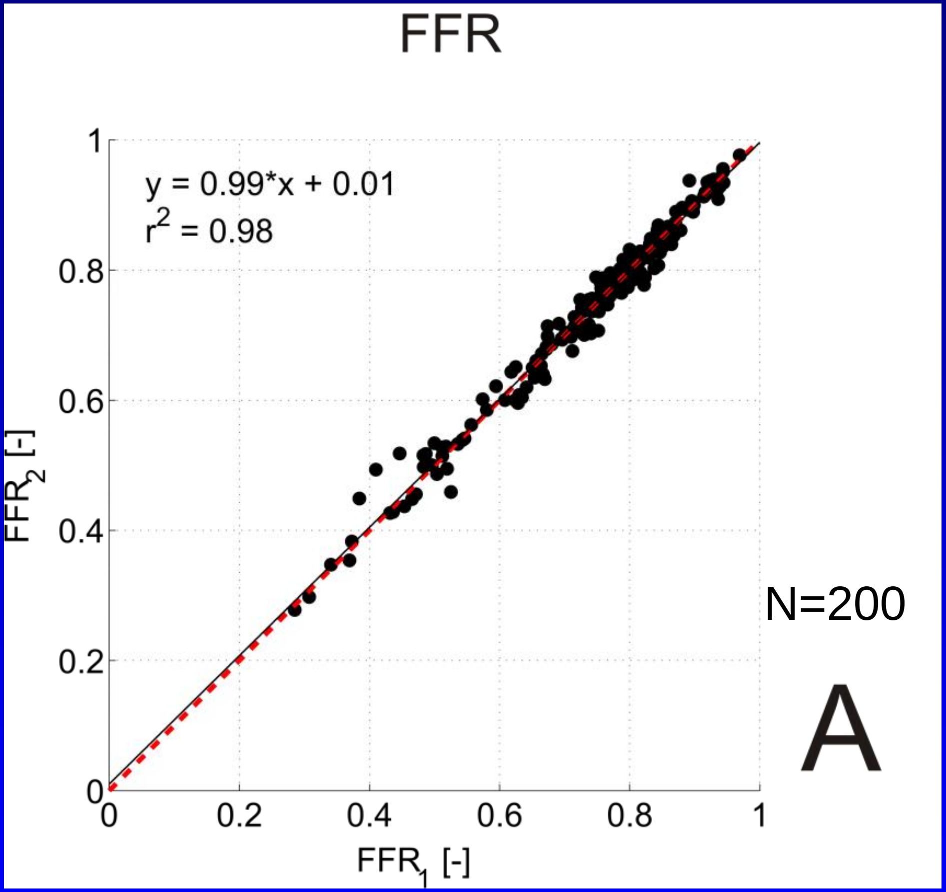
What is fundamentally wrong in this reasoning?

→ *confusing <u>a-priori</u> and <u>a-posteriori</u> knowledge*

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

→ Of the total population you need to examine, only a small percentage is close to the cut-off value and might "cross the border" (387/7000 = 6 % in case of GFR & hydration)

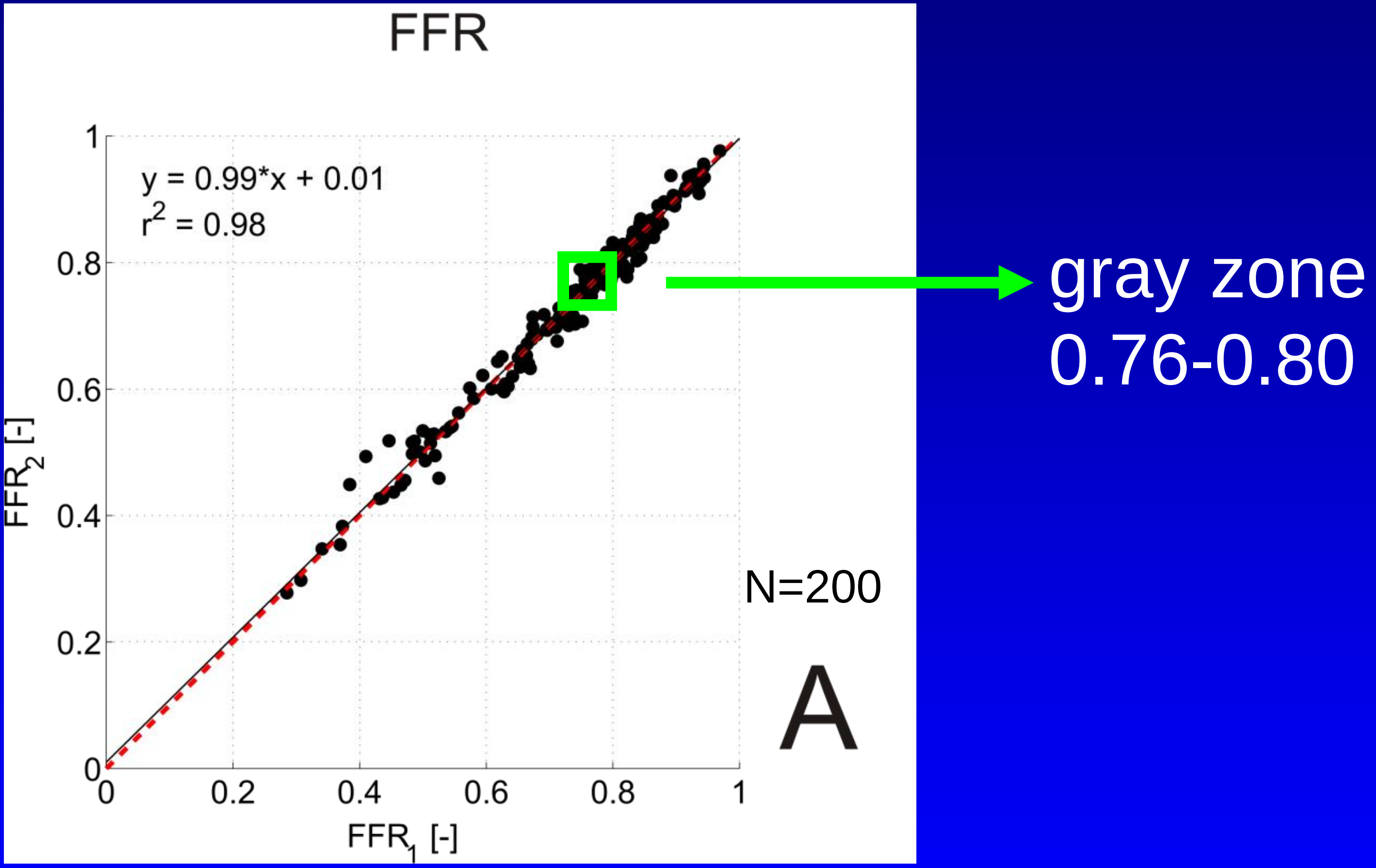
Reproducibility of FFR



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

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

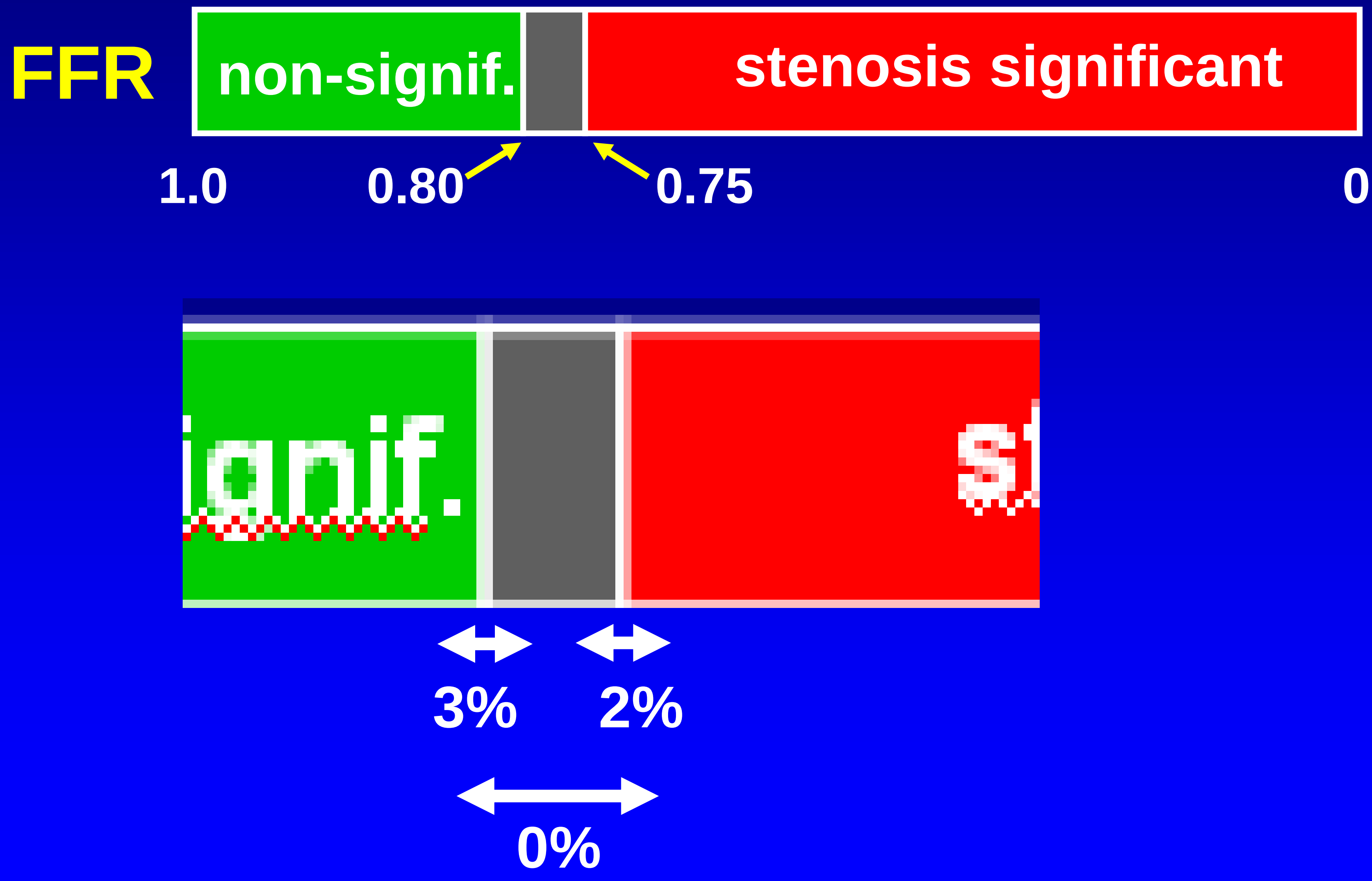
Reproducibility of FFR



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

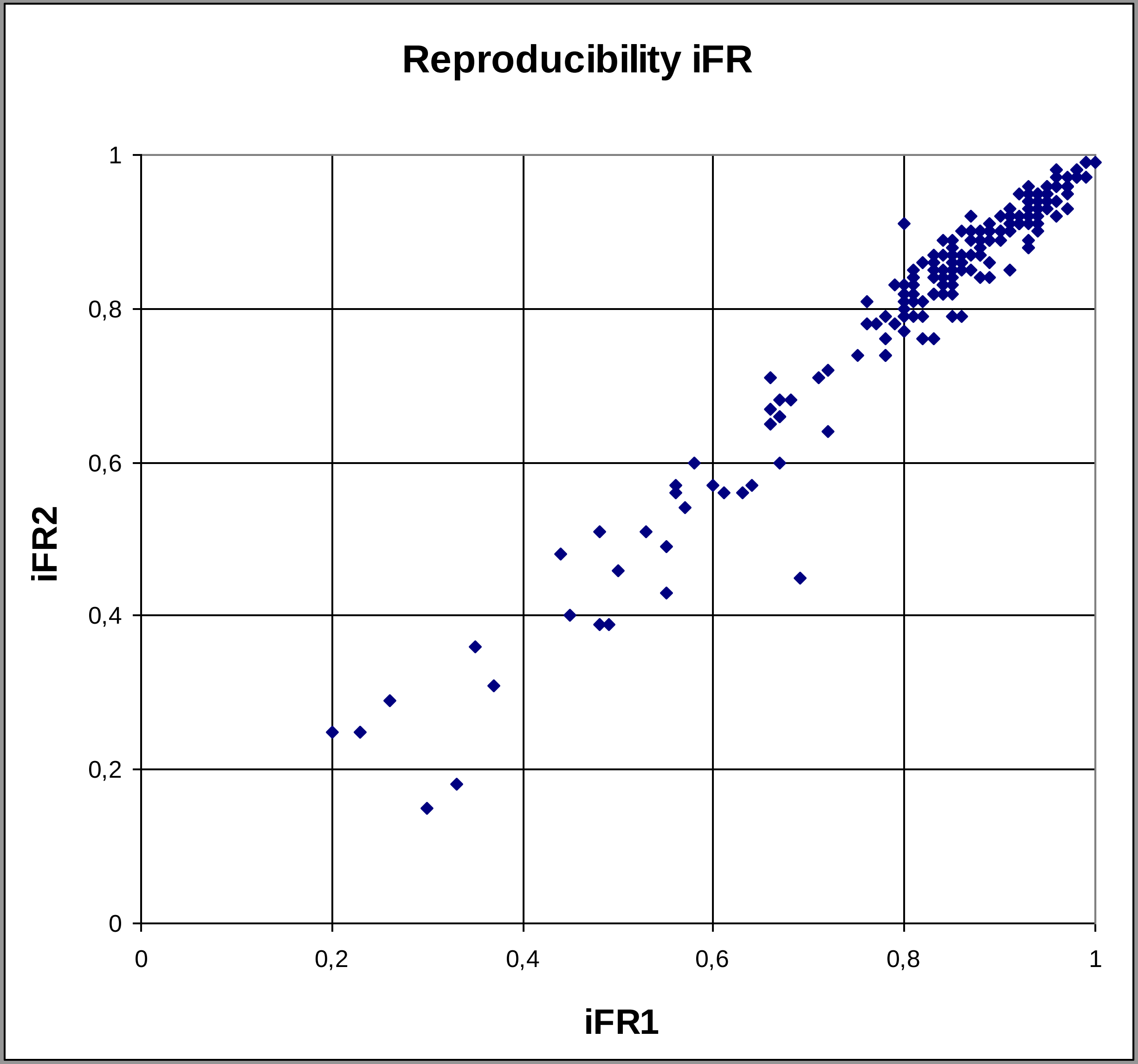
There is not any other index in physiology so reproducible as FFR

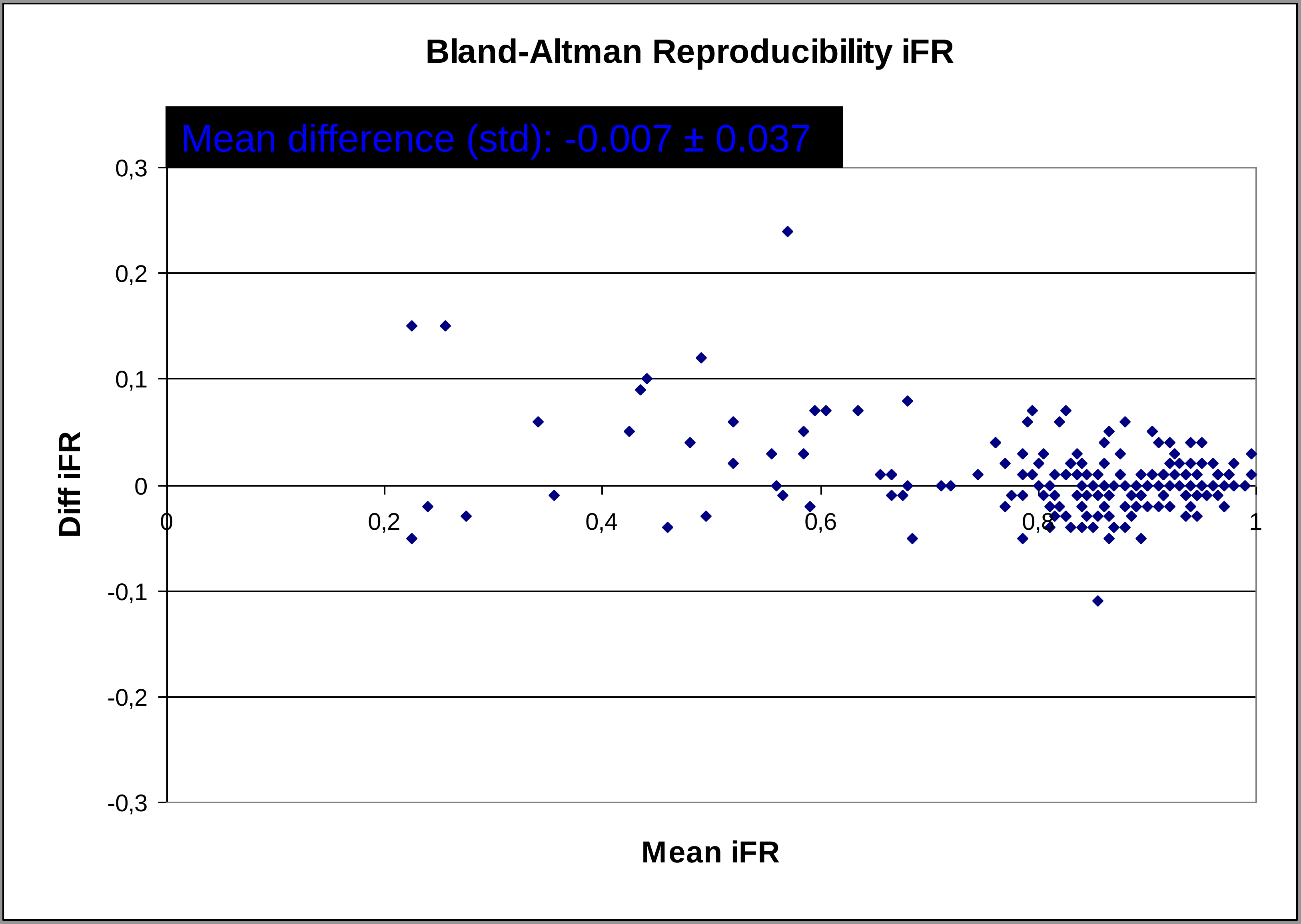
At 1200 consecutive in-duplo measurements of FFR, there was NOT ANY cross-over across the gray zone



Reproducibility iFR using matlab

Data from Verify Study


Reproducibility iFR
1
0,8
0,6
0,4
0,2
0
0
0,2
0,4
0,6
0,8
1
iFR2
iFR1

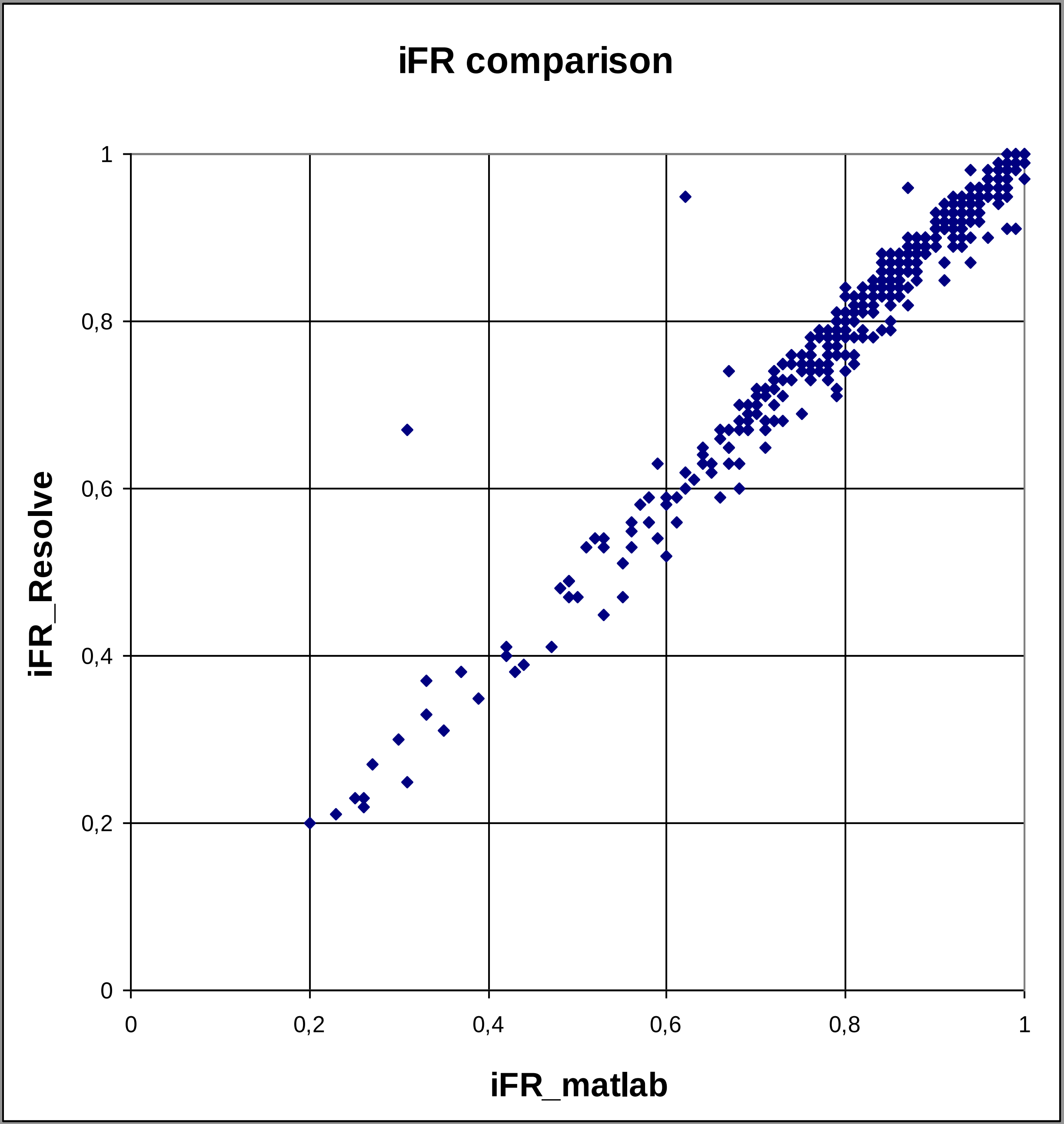


Bland-Altman Reproducibility iFR
Mean difference (std): -0.007 ± 0.037
0,3
0,2
0,1
0
-0,1
-0,2
-0,3
0
0,2
0,4
0,6
0,8
1
Diff iFR
Mean iFR

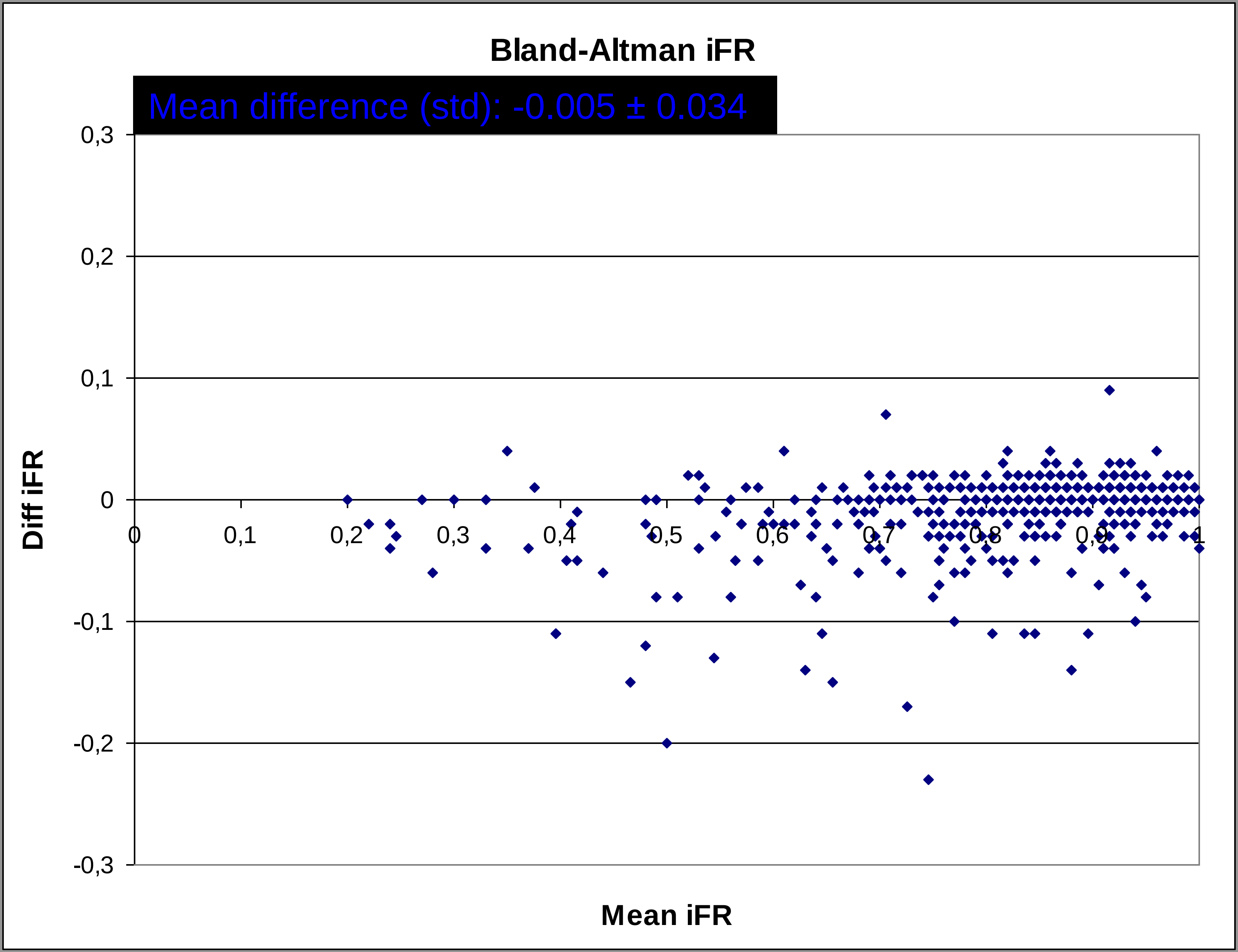
Measurements compared iFR_{matlab} vs $iFR_{volcano}$

Absolute difference 2 measurements > 0.3 (axes Bland-Altman are truncated)

All 705 measurements



iFR comparison
1
0,8
0,6
0,4
0,2
0
0
0,2
0,4
0,6
0,8
1
iFR_Resolve
iFR_matlab



Bland-Altman iFR
Mean difference (std): -0.005 ± 0.034
0,3
0,2
0,1
0
-0,1
-0,2
-0,3
Diff iFR
0
0,1
0,2
0,3
0,4
0,5
0,6
0,7
0,8
0,9
1
Mean iFR

Measurements compared iFR_{matlab} vs $iFR_{volcano}$

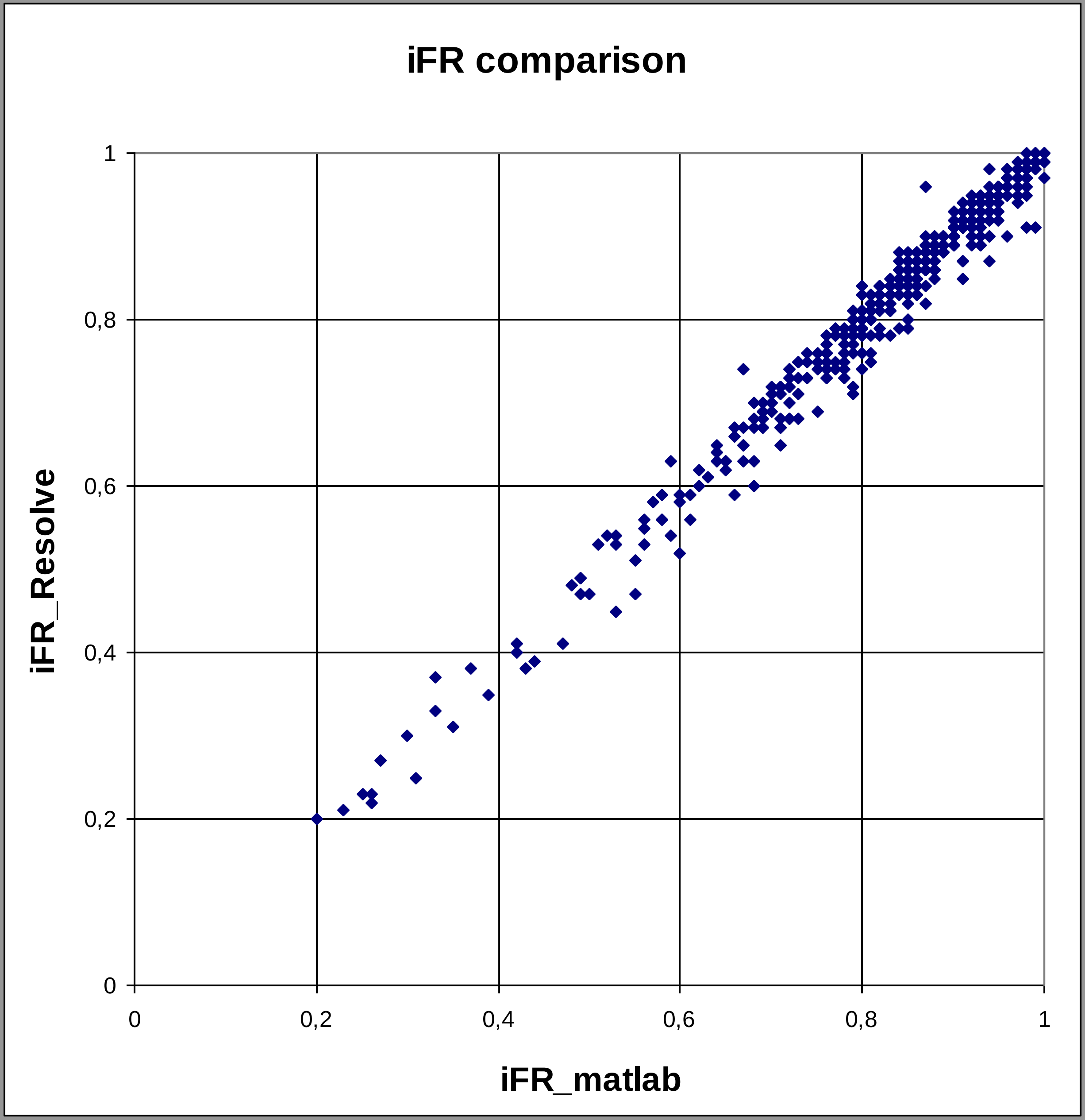
Difference of 18 measurements ≤ 0.1

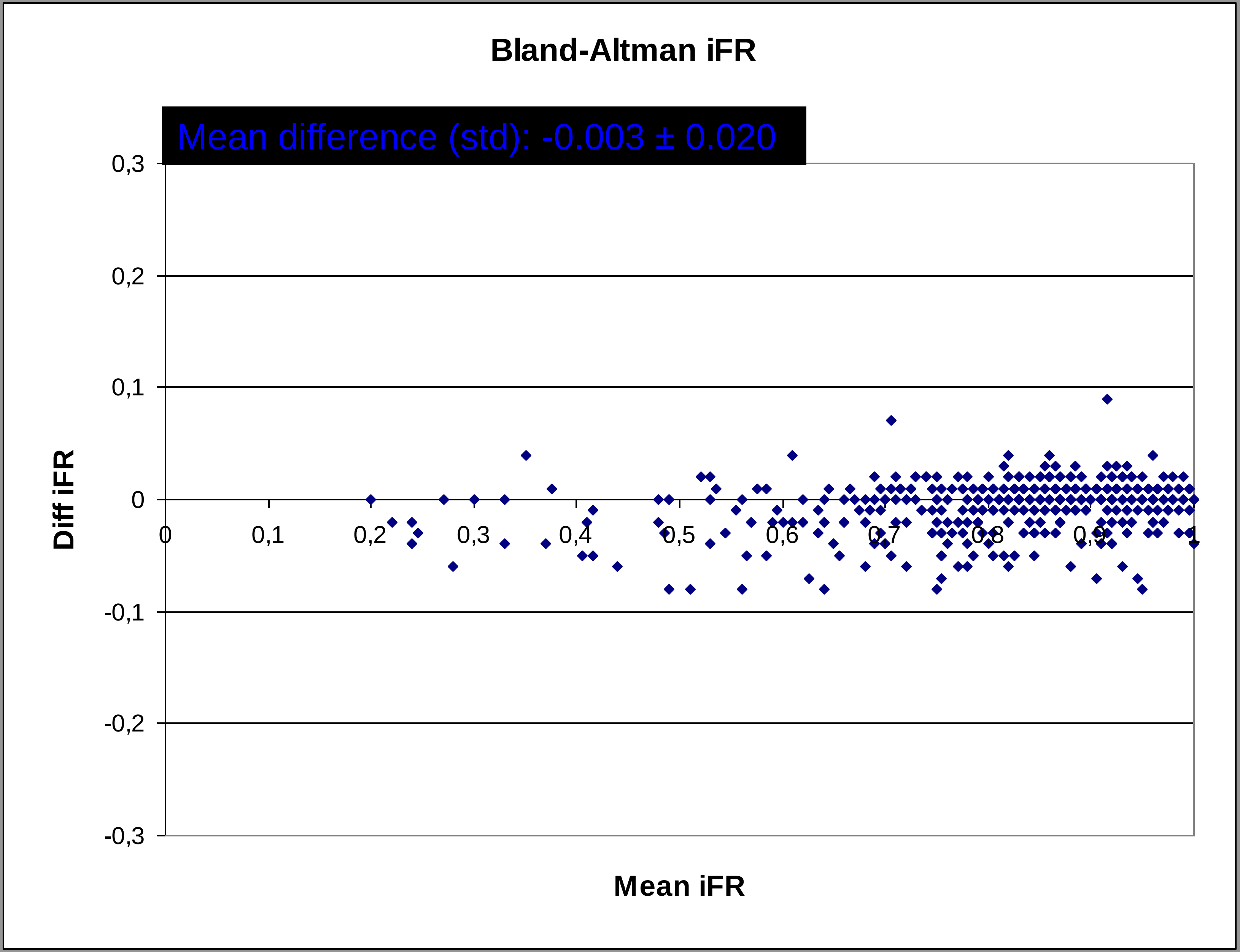
($iFR_{volcano} < iFR_{matlab}$)

Difference of 2 measurements ≥ 0.1

($iFR_{volcano} > iFR_{matlab}$)

Remain 685 measurements

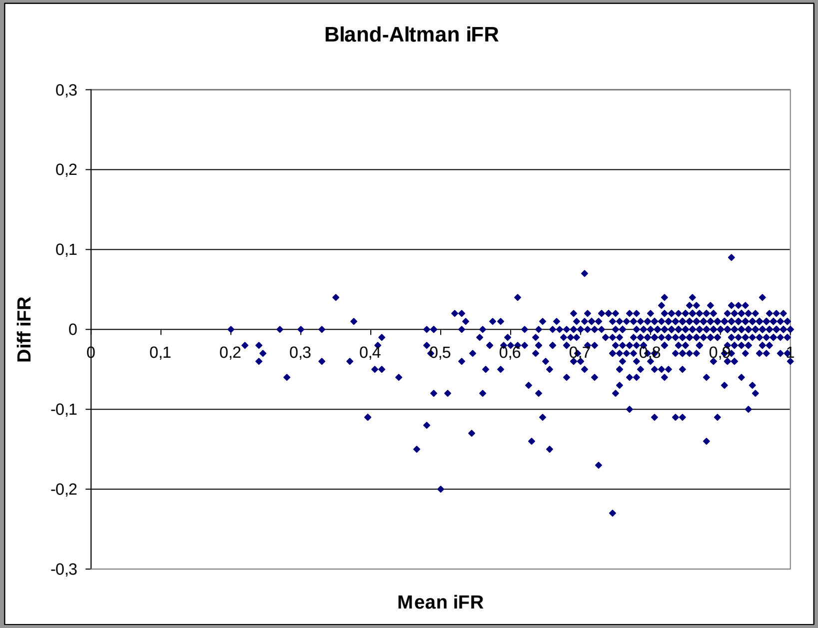

iFR comparison
iFR_Resolve
iFR_matlab
0
0,2
0,4
0,6
0,8
1



Bland-Altman iFR
Mean difference (std): -0.003 ± 0.020
0,3
0,2
0,1
0
-0,1
-0,2
-0,3
Diff iFR
0
0,1
0,2
0,3
0,4
0,5
0,6
0,7
0,8
0,9
1
Mean iFR

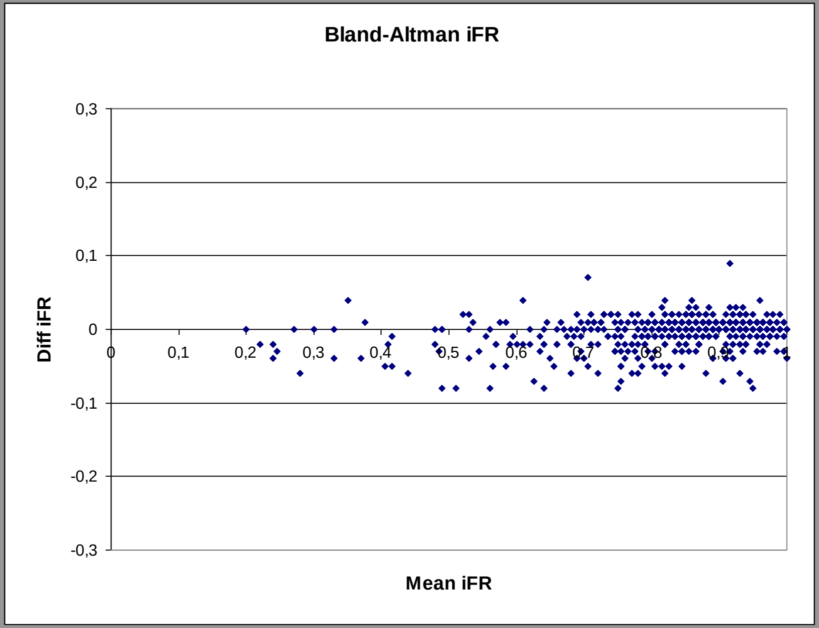
Summary

705 measurements



Mean difference (std): -0.005 ± 0.034

685 measurements



Mean difference (std): -0.003 ± 0.020

Reproducibility; difference between two iFR measurements (Verify)

Mean difference (std): -0.007 ± 0.037

Cut-off = 0.83

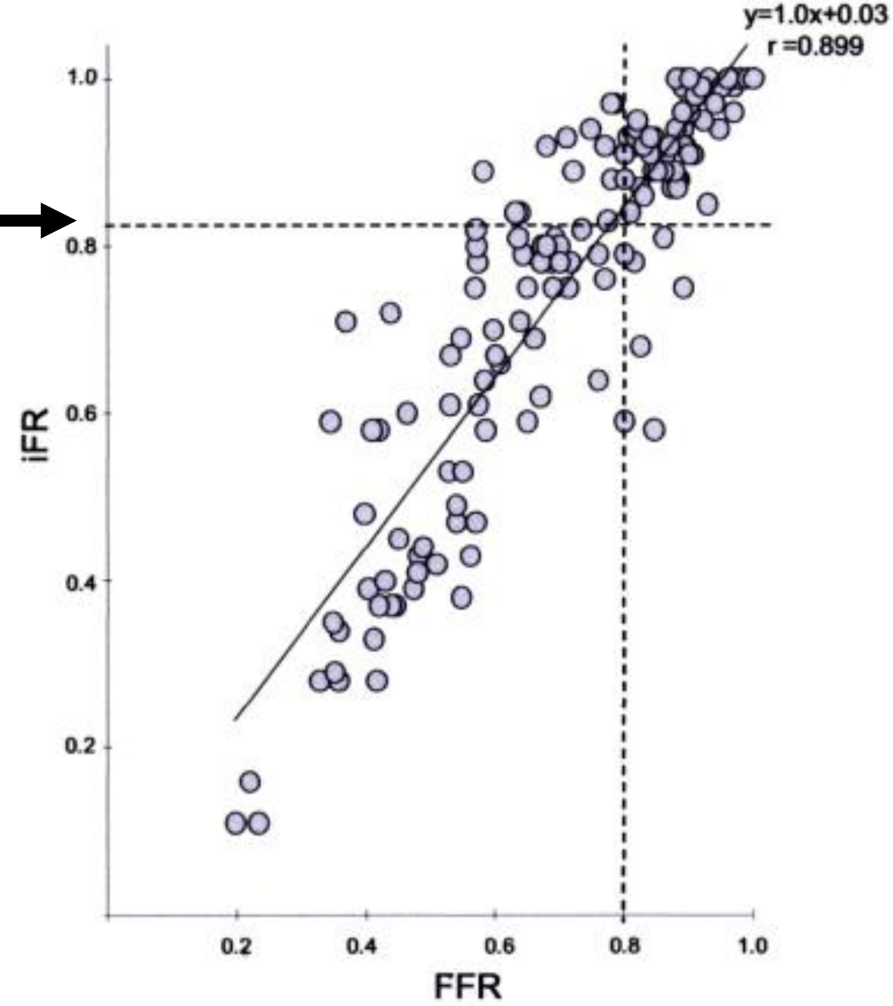


Figure 5:

ADVISE STUDY (N= 131)

From:
Sen, Davies, et al JACC 2011

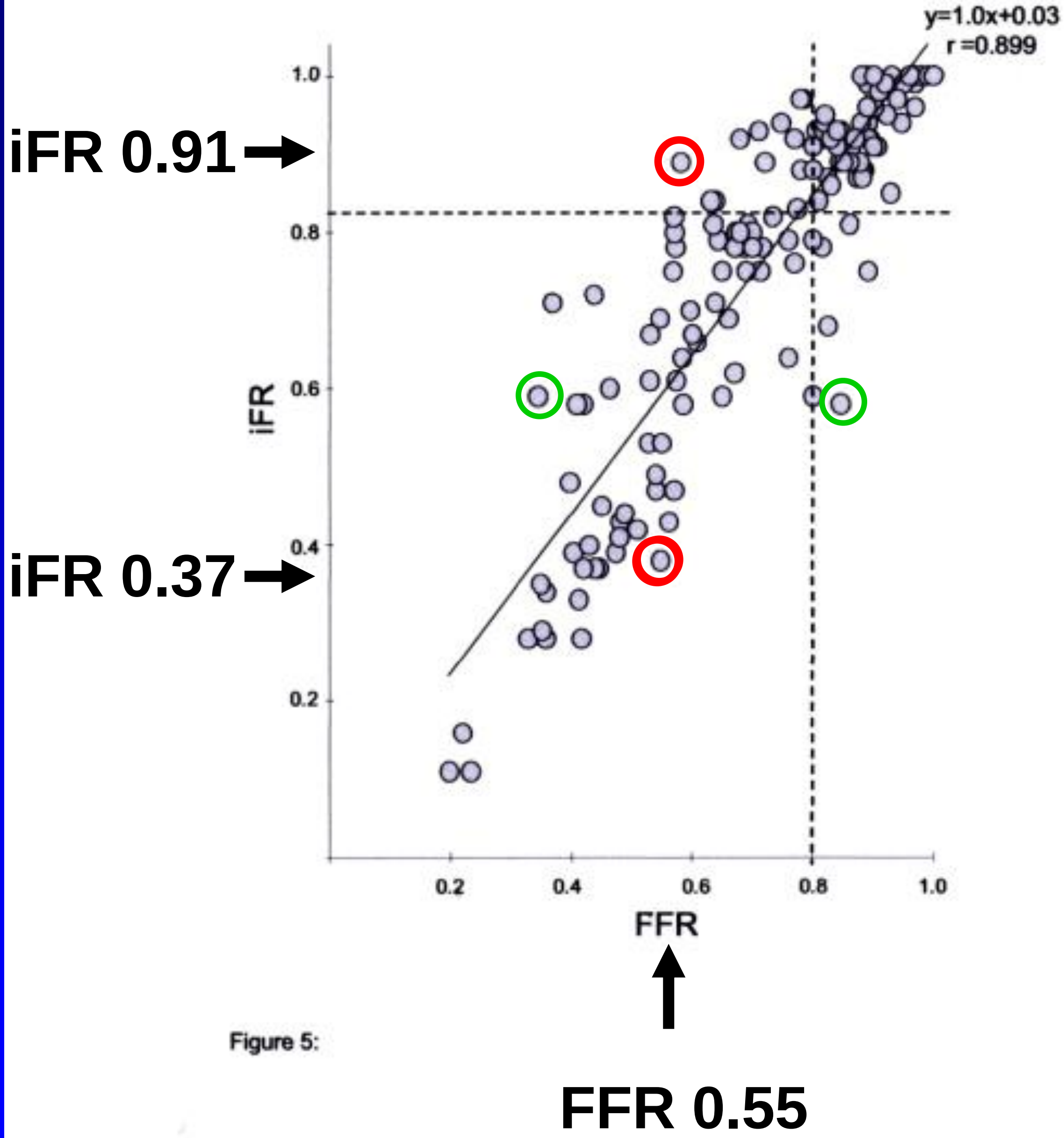


Figure 5:

ADVISE STUDY (N= 131)

From:
Sen, Davies, et al
JACC 2011

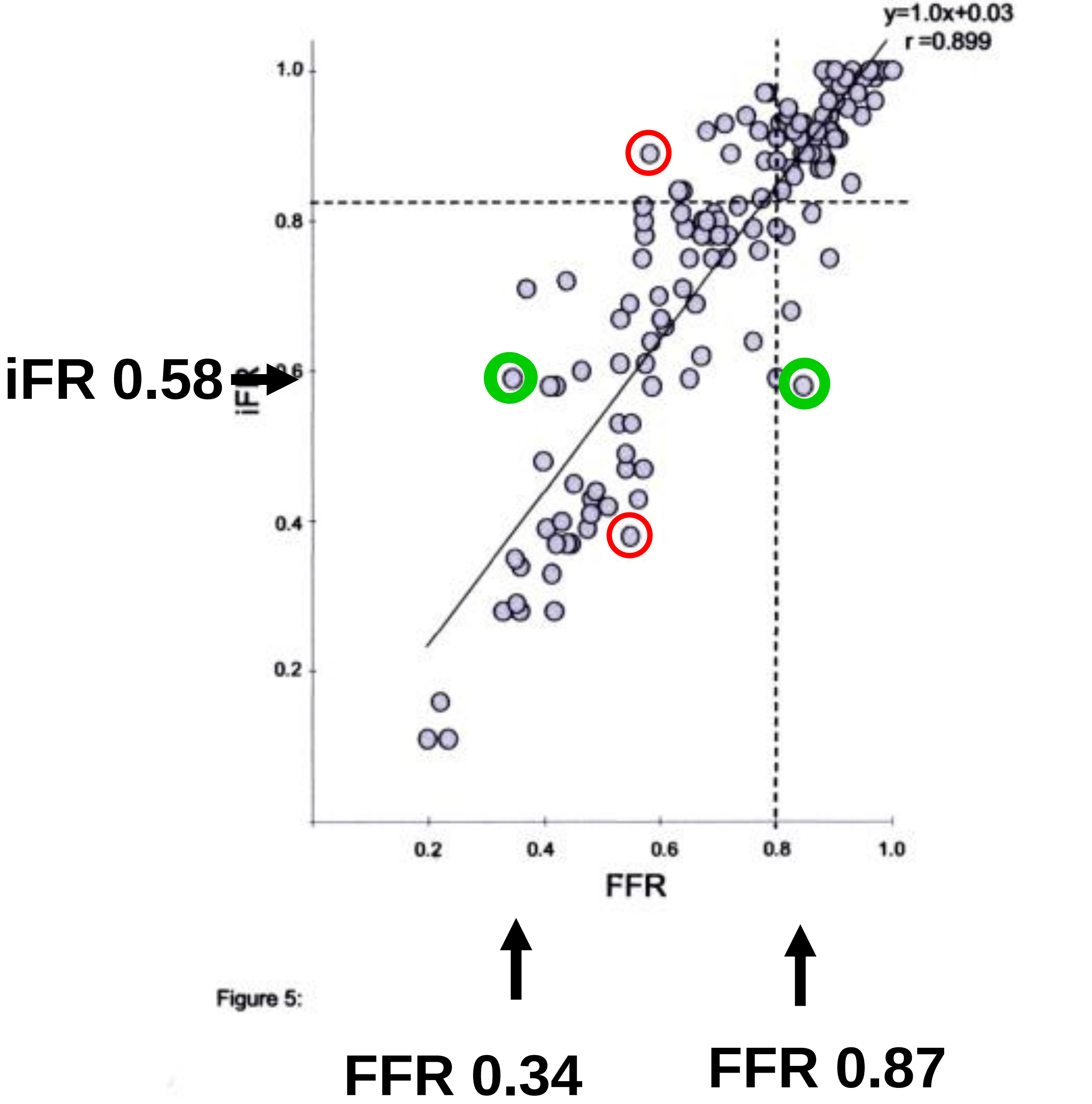
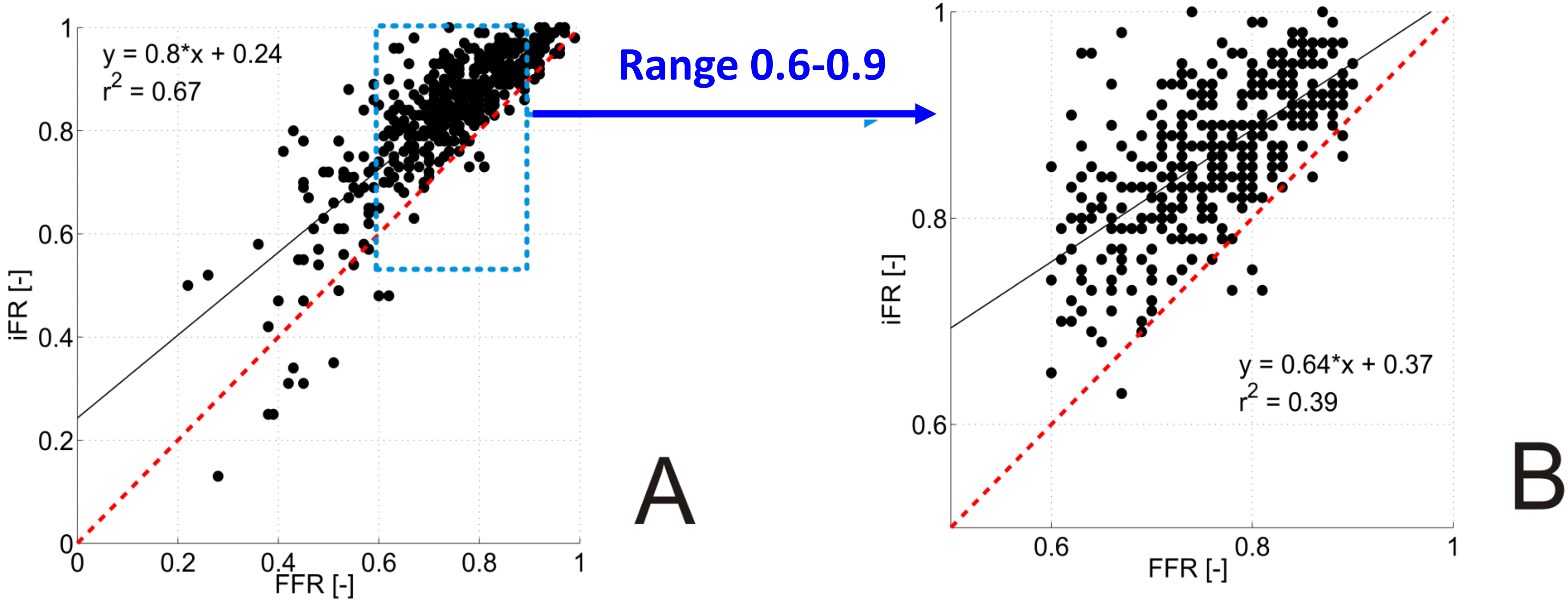


Figure 5:

ADVISE STUDY (N= 131)

From:
Sen, Davies, et al
JACC 2011

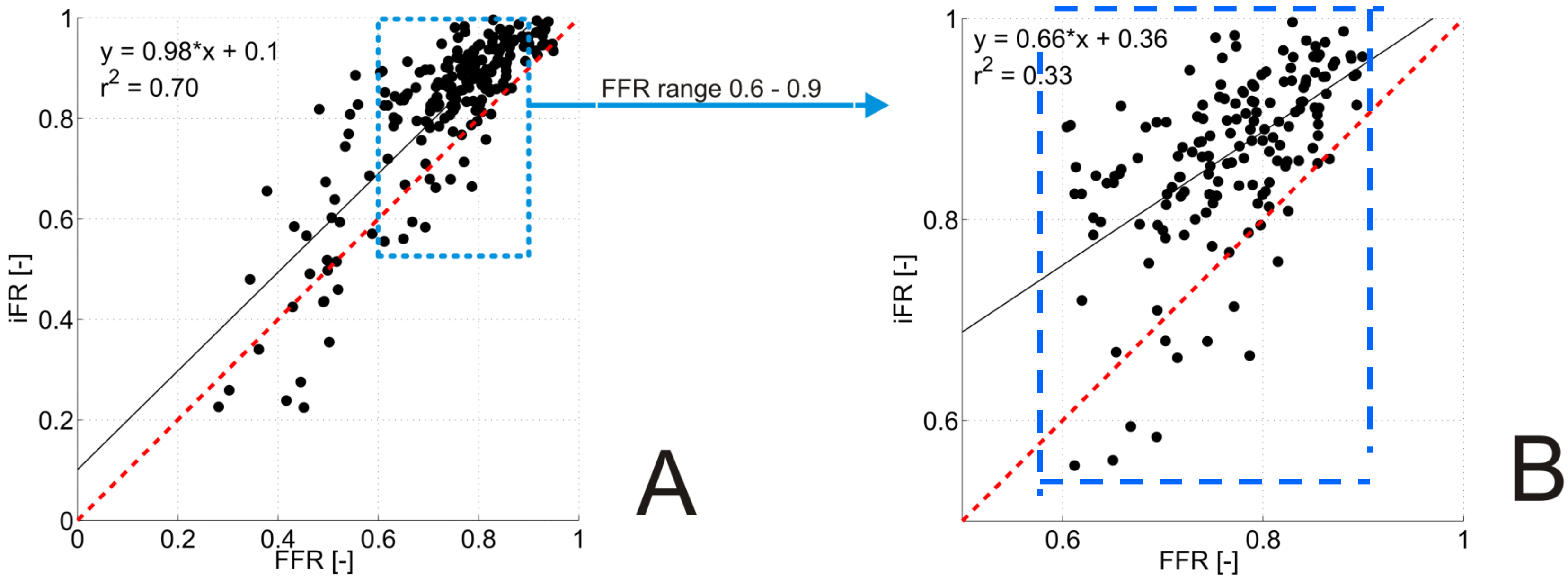
Retrospective analysis IFR versus FFR in retrospective analysis in 500 patients in Aalst and Eindhoven



all data: $R^2 = 0.67$
diagn accuracy = 66 %

FFR range 0.6-0.9: $R^2 = 0.39$
diagn accuracy = 59 %

Correlation between iFR and FFR (N=206)



diagn accuracy = 67 %

diagn accuracy = 58 %

(diagnostic accuracy of flipping a coin = 50 %)

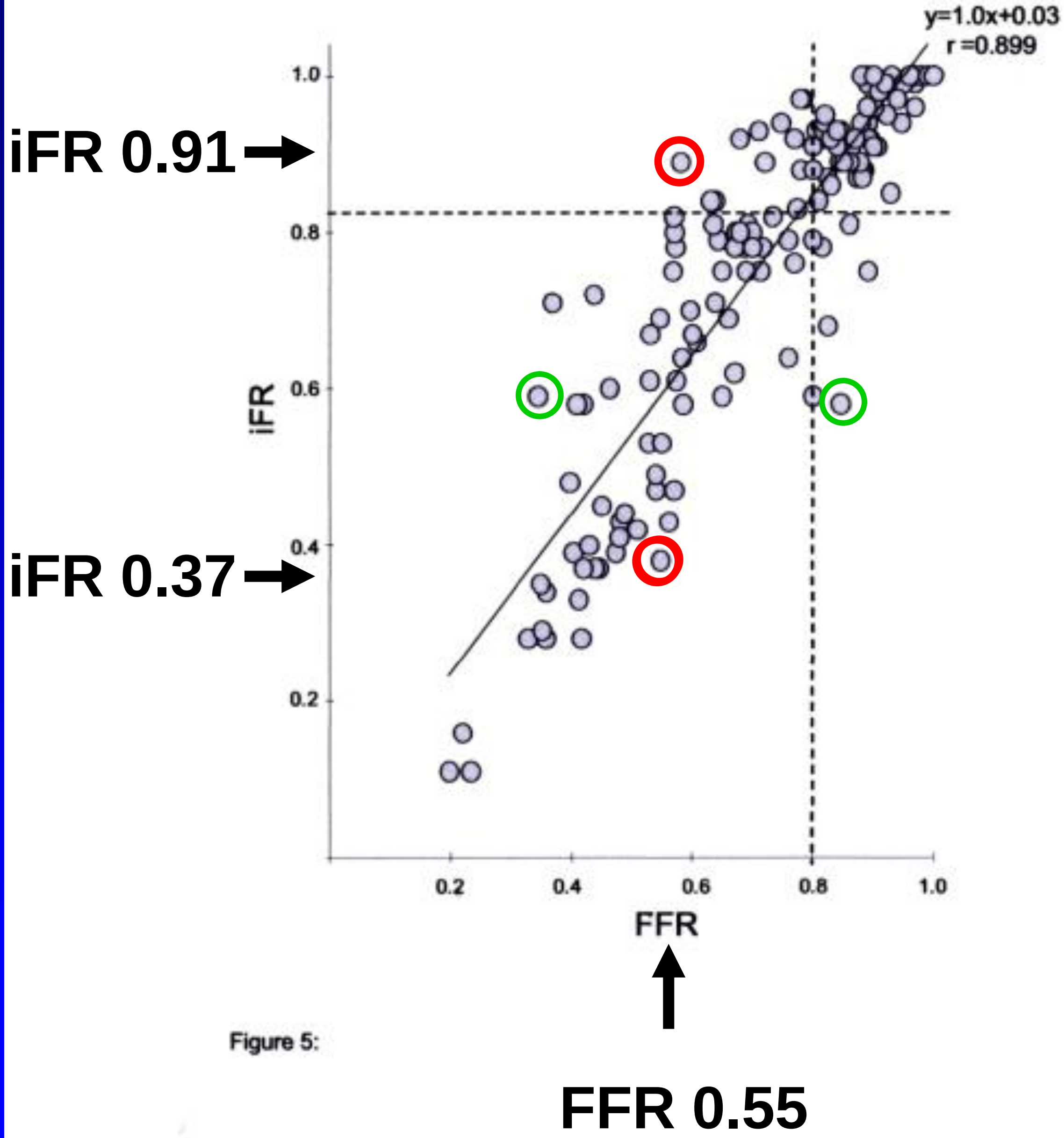
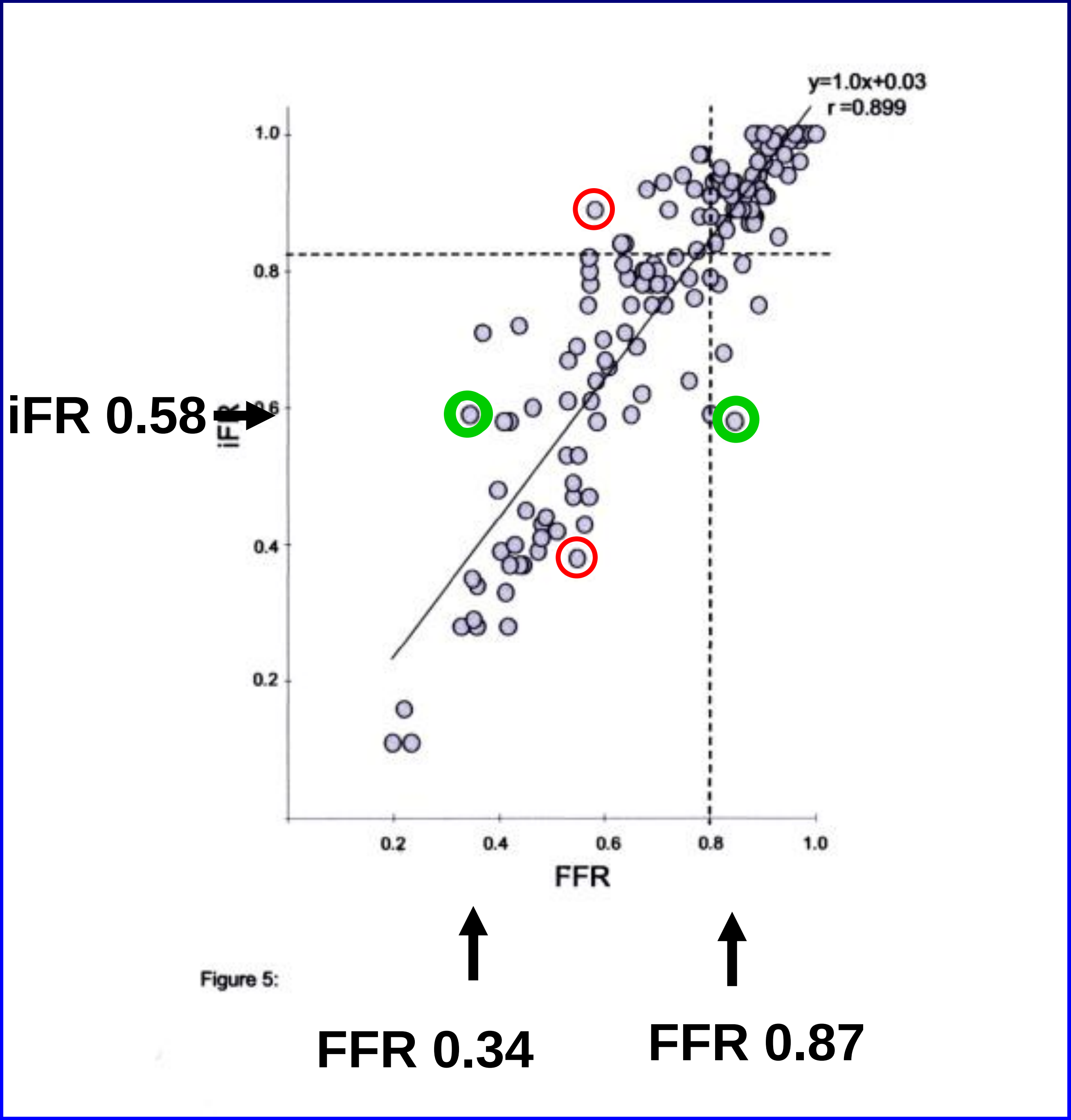


Figure 5:

ADVISE STUDY (N= 131)

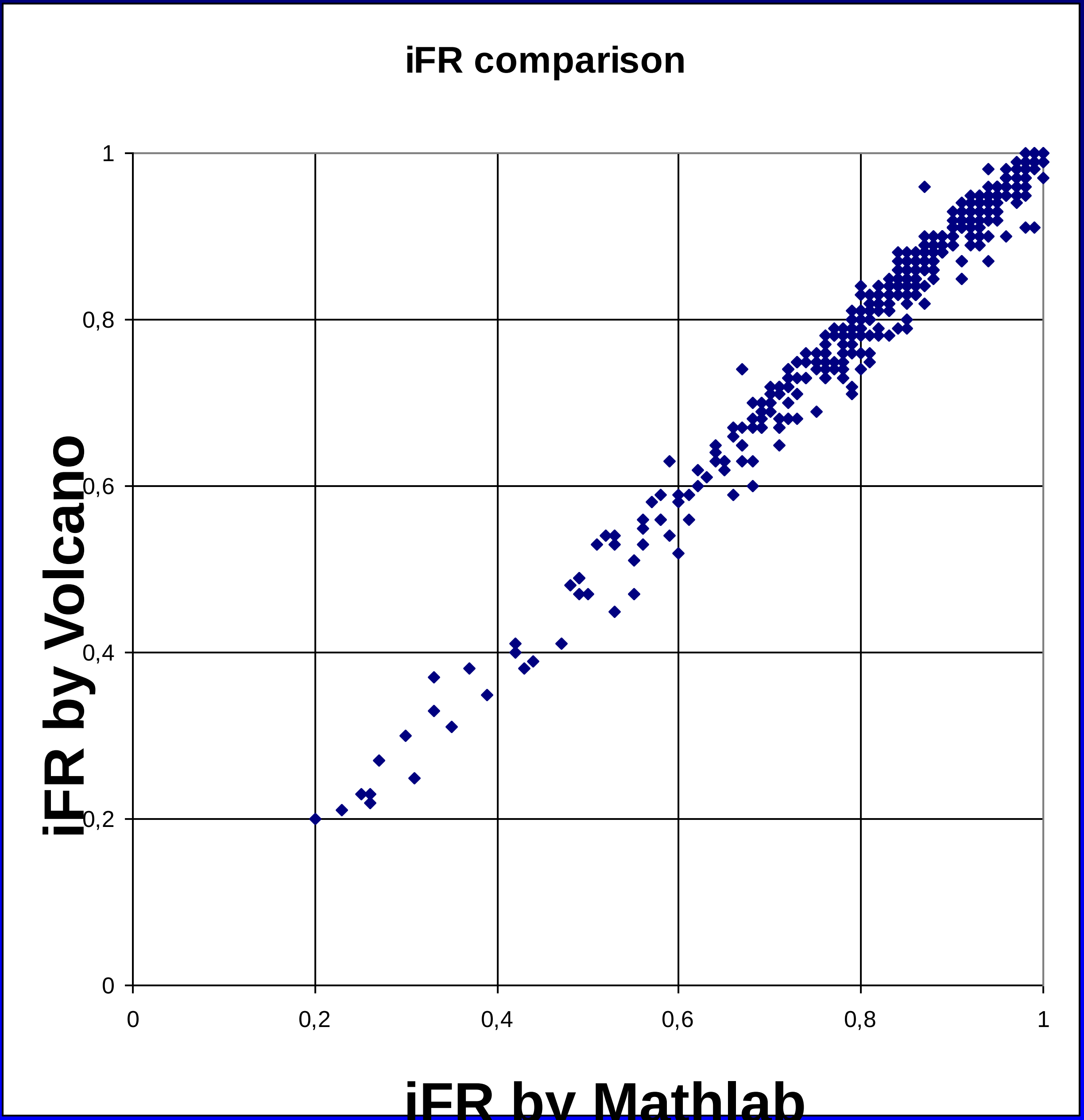
From:
Sen, Davies, et al
JACC 2011



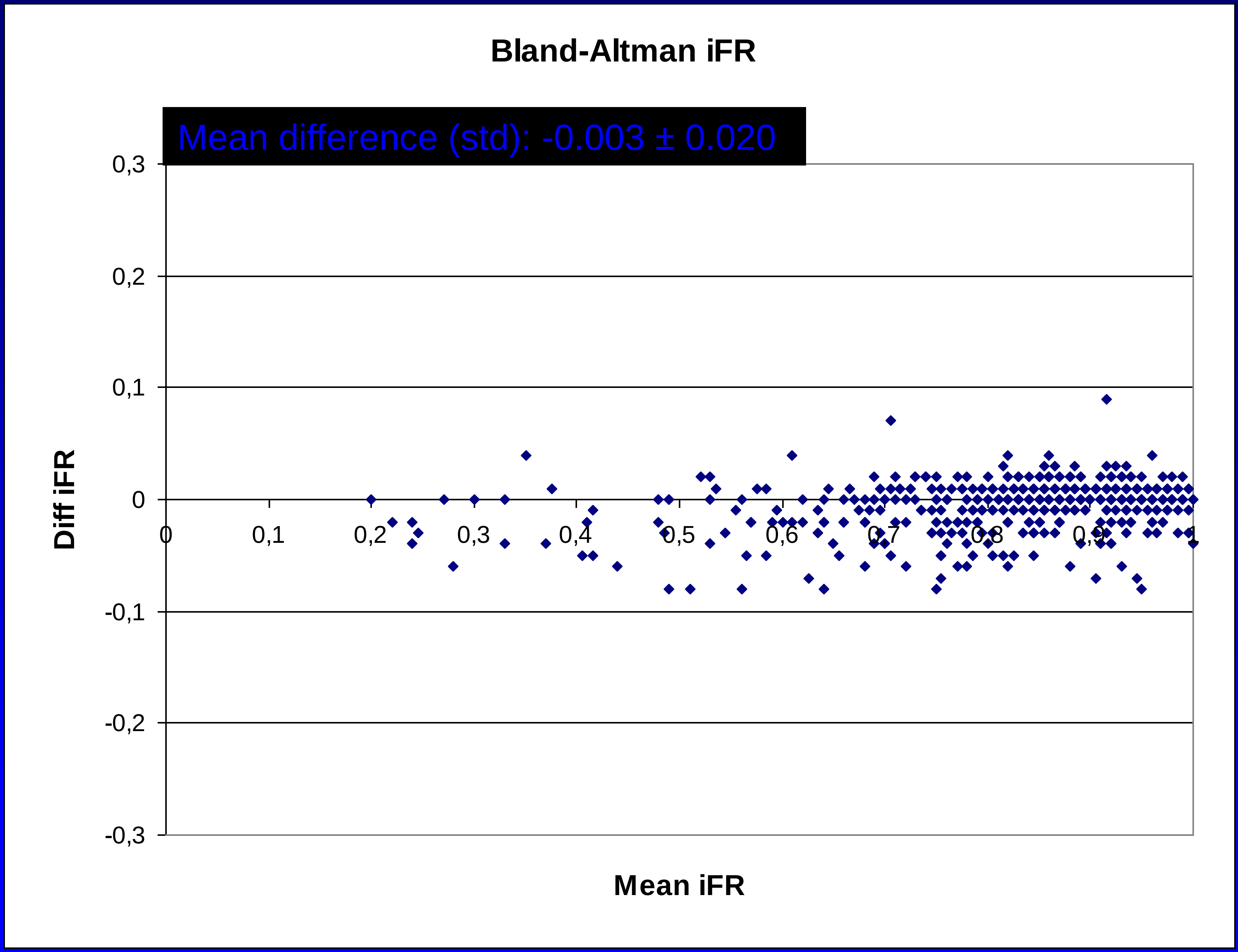
ADVISE STUDY (N= 131)

From:
Sen, Davies, et al
JACC 2011

N=685



Berry et al
JACC 2013;


Bland-Altman iFR
Mean difference (std): -0.003 ± 0.020
0,3
0,2
0,1
0
-0,1
-0,2
-0,3
Diff iFR
0
0,1
0,2
0,3
0,4
0,5
0,6
0,7
0,8
0,9
1
Mean iFR

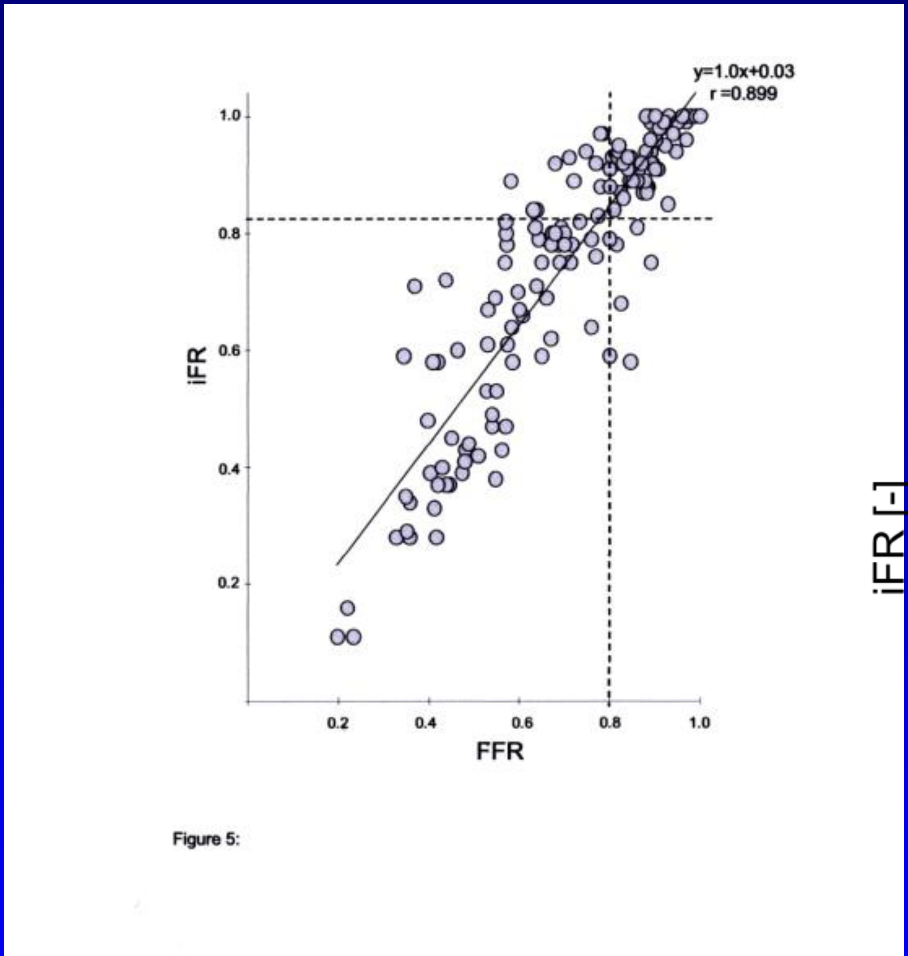
Overall Precision

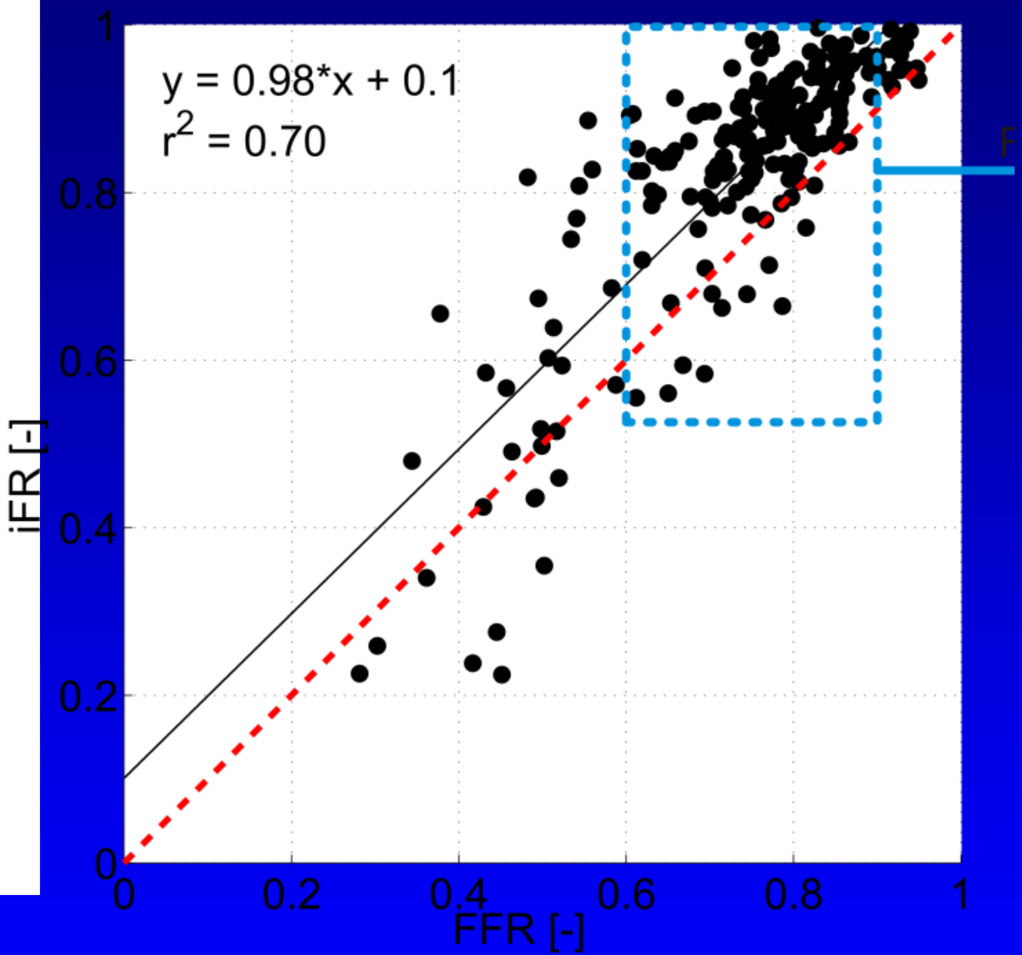
Proportion of Patients with 90% Precision

	PPV	NPV	Total
iFR	44.2%	12.9%	57.1%
Pd/Pa	43.1%	--	43.1%

Proportion of Patients with 95% Precision

	PPV	NPV	Total
iFR	24.3%	--	24.3%
Pd/Pa	33.4%	--	33.4%





FFR 0.55