

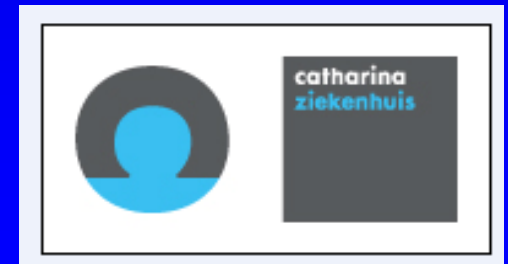
# *Imaging & Physiology Summit*

## **Pd/Pa at rest, iFR, resting gradient, and more: Why Can They Never Be As Good As Hyperemic Indexes**

*Seoul, Korea, december 7th, 2013  
main arena*



Nico H. J. Pijls, MD, PhD  
Catharina Hospital,  
Eindhoven, The Netherlands



## “FFR - light <sup>TM</sup>”

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 makes most sense and is the basis of Fractional Flow Reserve (**FFR**)*

# Why Are Resting Indices Insufficient ?

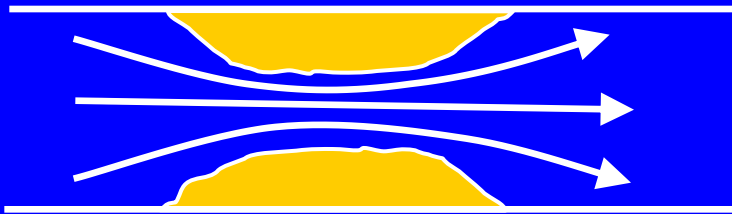
- Limited Clinical Significance
- *Limited Physiological Meaning*

***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

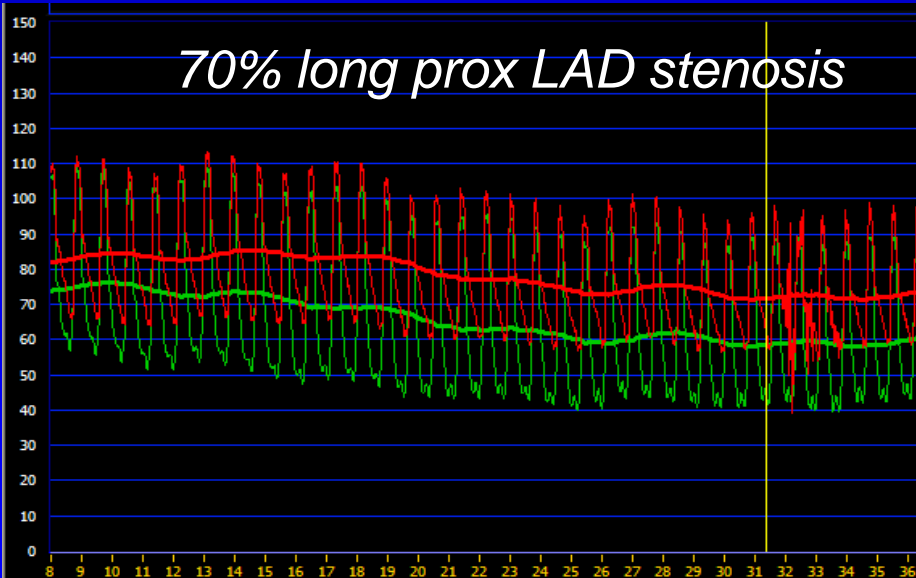
**s** = separation coefficient



Small gradient at rest

Large gradient at hyperemia

*70% long prox LAD stenosis*



iFR = 0.89 FFR = 0.85

*50% ostial left main stenosis*

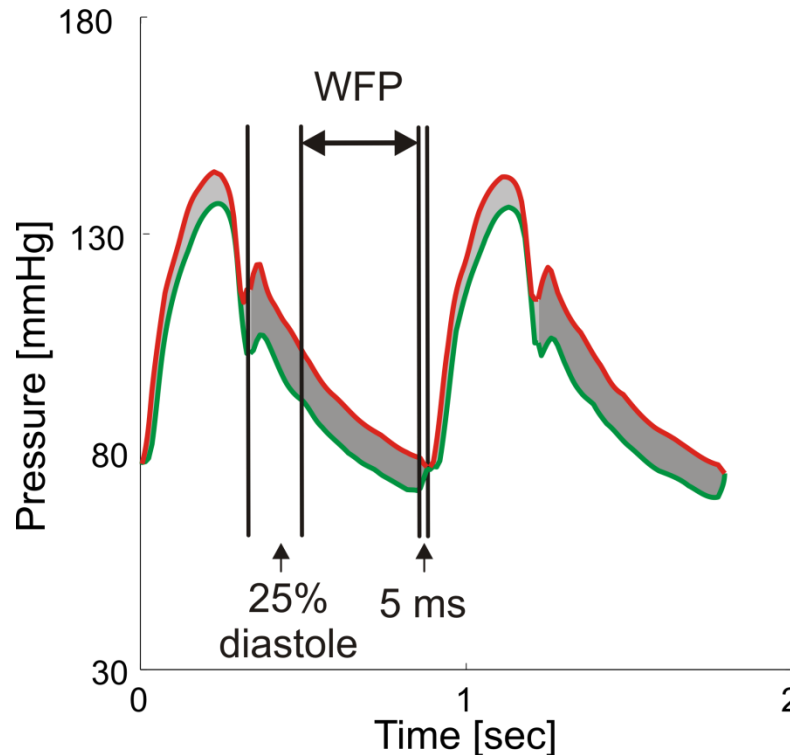


iFR = 0.94 FFR = 0.57

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



# REST

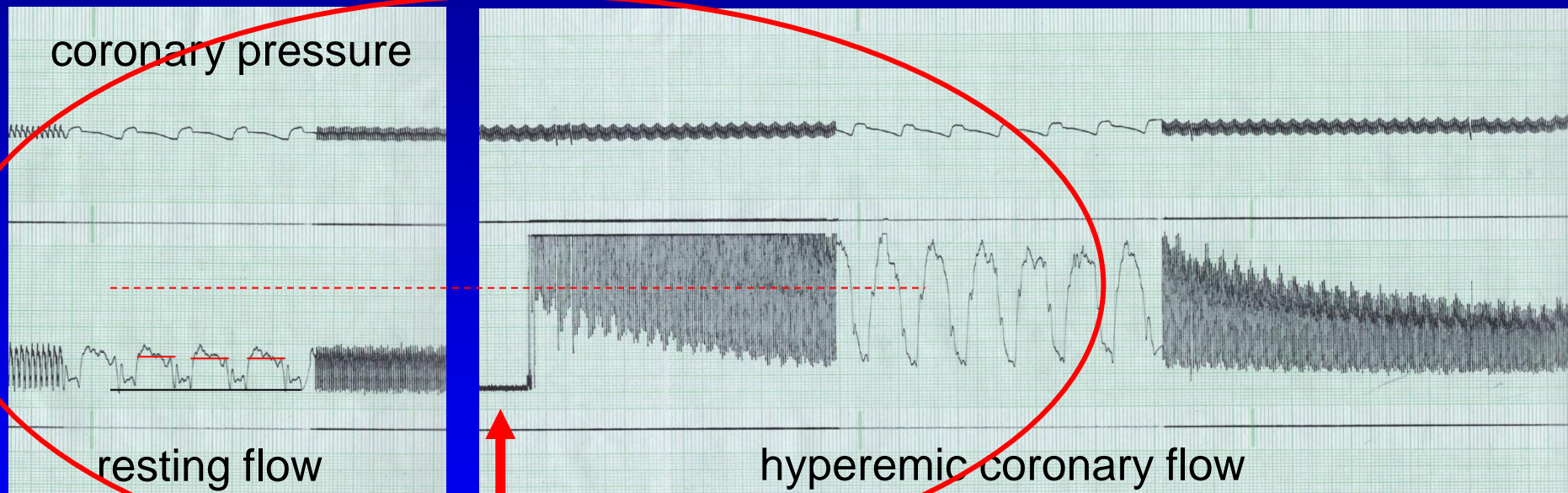


**iFR = Pd / Pa at rest during WFP (Sen et al, JACC 2012)**

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

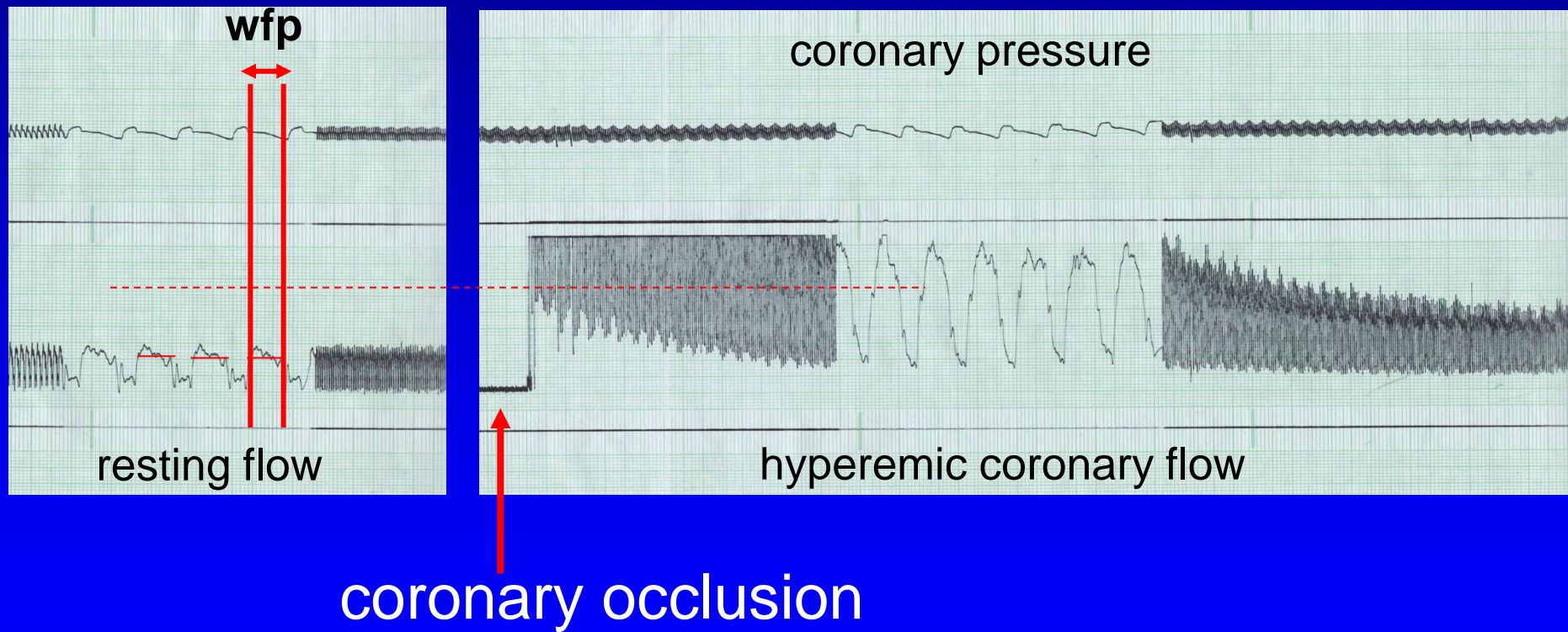
In the presence of constant coronary pressure

$$\longrightarrow R \sim 1 / \text{Flow}$$

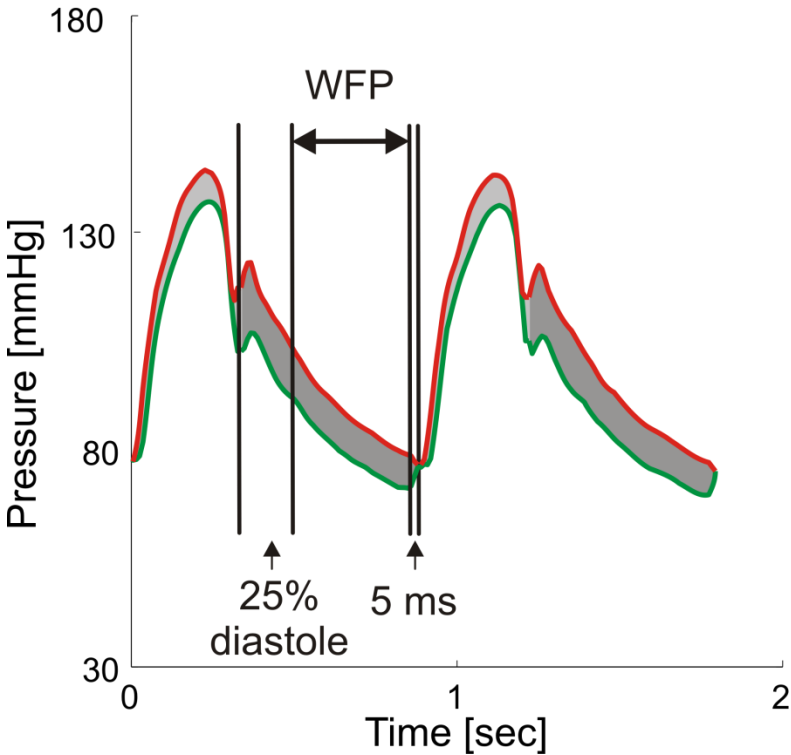


coronary occlusion

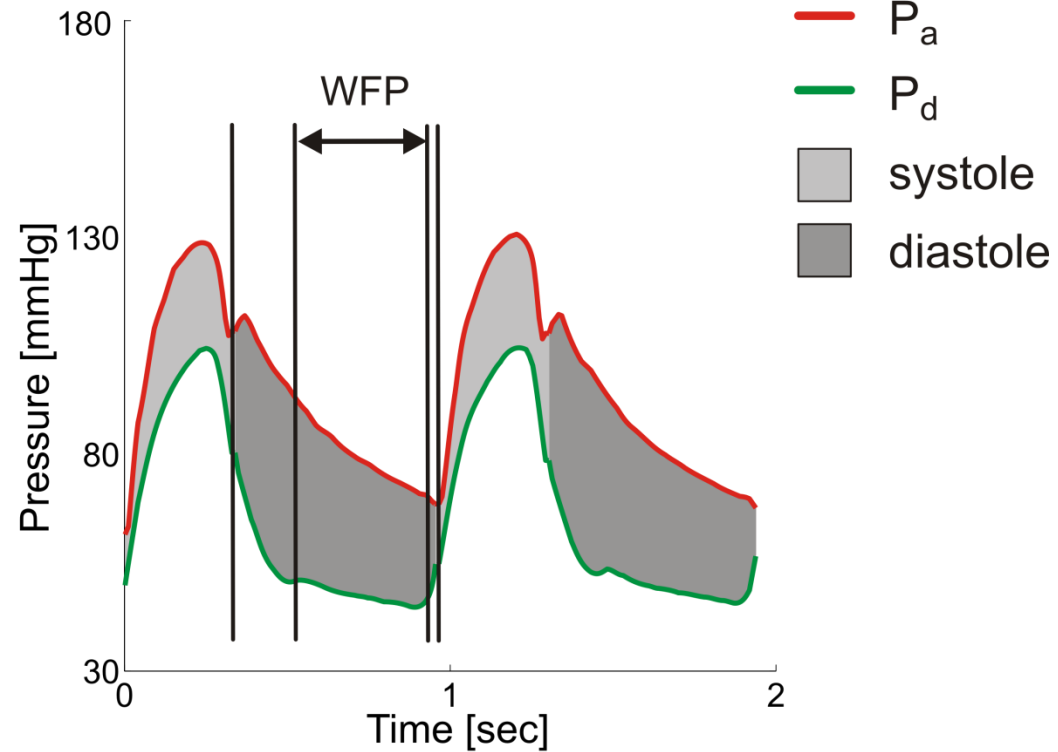
*minimal myocardial resistance during the so-called “wave-free period” is ~ 250 % higher than average myocardial resistance at maximum hyperemia in all dogs and swine*



REST



HYPEREMIA



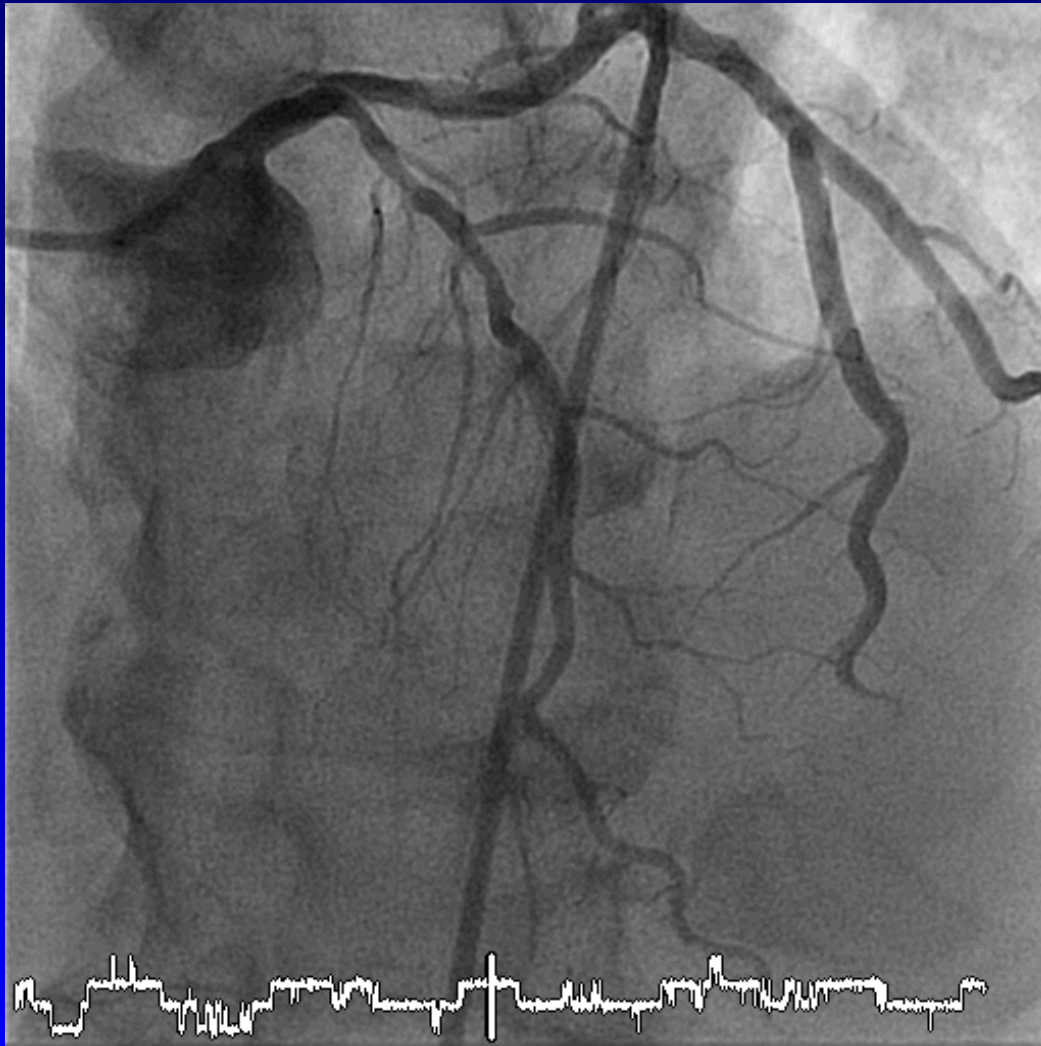
**$iFR = P_d / P_a$  during WFP  $\rightarrow$  strongly dependent on hyperemia**

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





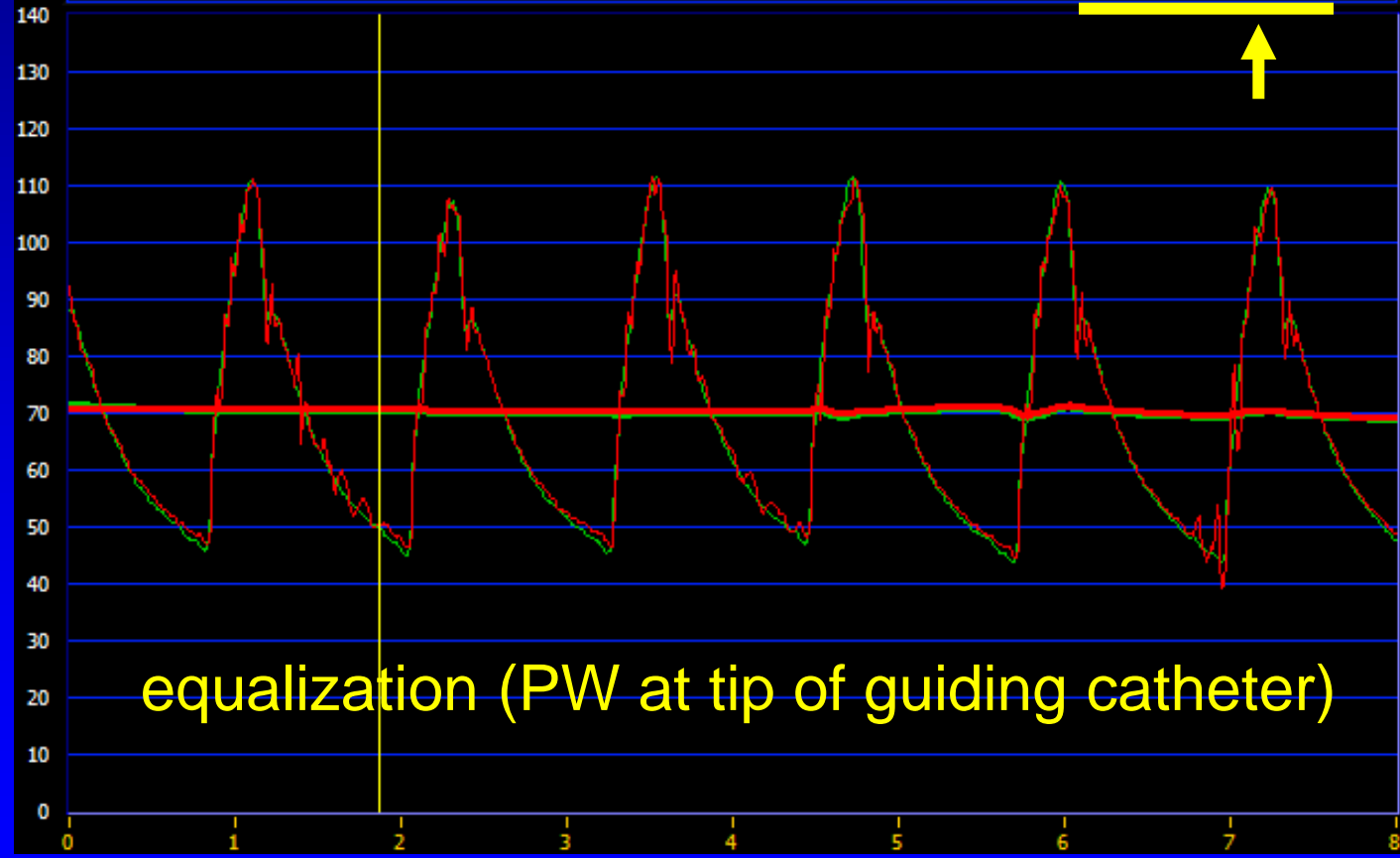
Mr M, born 26-03-1937,  
*long mild/moderate proximal LAD lesion*



FOLDER	PATIENT ID	DATE	TIME	VESSEL	PROCEDURE	ACTION	TYPE	SIZE
KIRKELS	JAJ Meijer	2012-10-01	13:58:18				FFR	49Kb
kastelijn	JAJ Meijer	2012-10-01	13:57:12				FFR	125Kb
jorritsma	JAJ Meijer	2012-10-01	13:54:55				FFR	10Kb
JAJ Meijer	JAJ Meijer	2012-10-01	13:54:24				FFR	12Kb
iFR352	JAJ Meijer	2012-10-01	13:53:09				FFR	9Kb

PRINT EDIT RENAME EXPORT ERASE SETUP

JAJ Meijer 2012-10-01 13:53:09



**71**  
Pa mean  
**70**  
Pd mean  
**1,00**  
FFR

**1,9**  
CURSOR



RESET

long moderate proximal LAD lesion; equalization

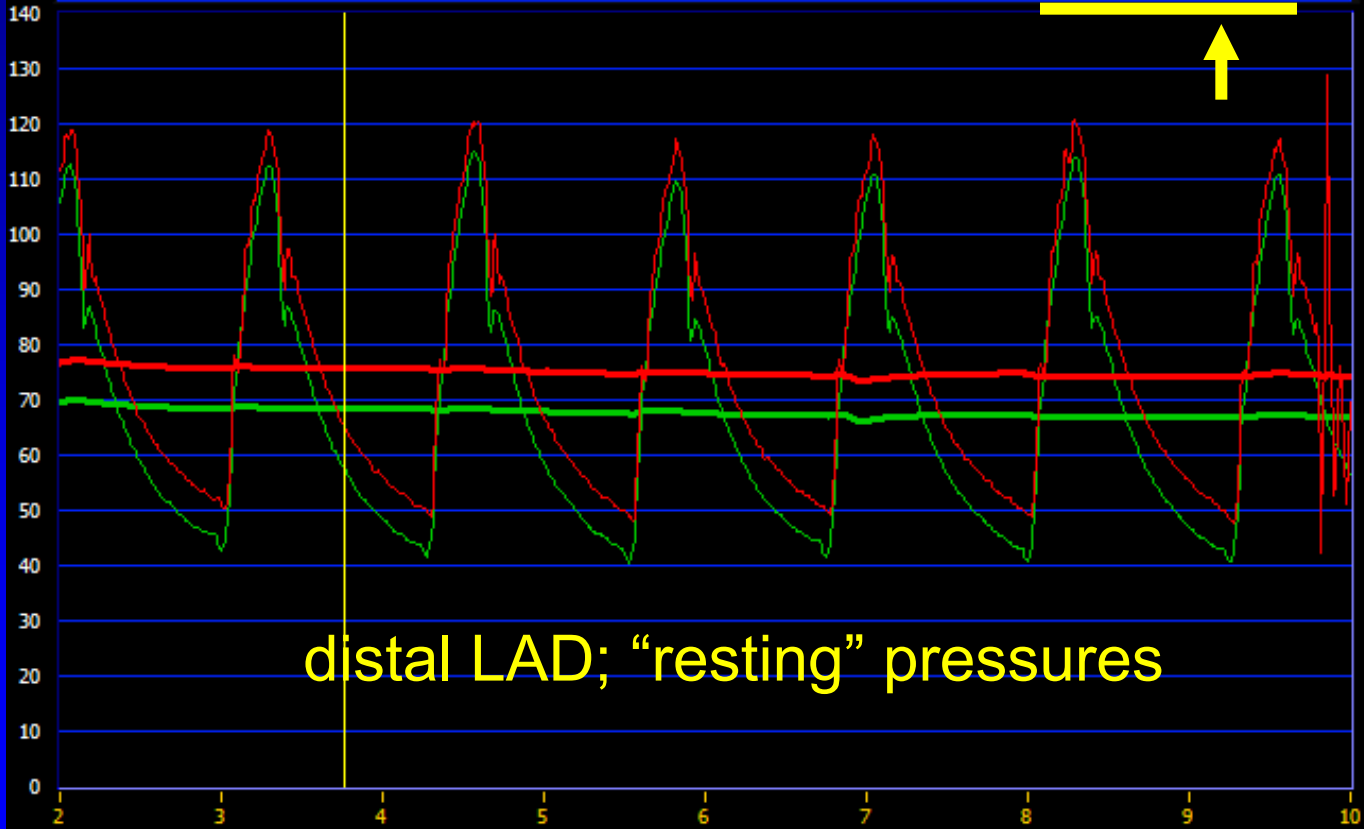


- ARCHIVE
- CUSTOM
- FOLDER
- KIRKELS
- kastelijn
- jorritsma
- JAJ Meijer
- iFR352

PATIENT ID	DATE	TIME	VESSEL	PROCEDURE	ACTION	TYPE	SIZE
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JAJ Meijer	2012-10-01	13:53:09				FFR	9Kb

- PRINT
- EDIT
- RENAME
- EXPORT
- ERASE
- SETUP

JAJ Meijer 2012-10-01 13:54:24



**76**  
Pa mean  
**69**  
Pd mean  
**0,91**

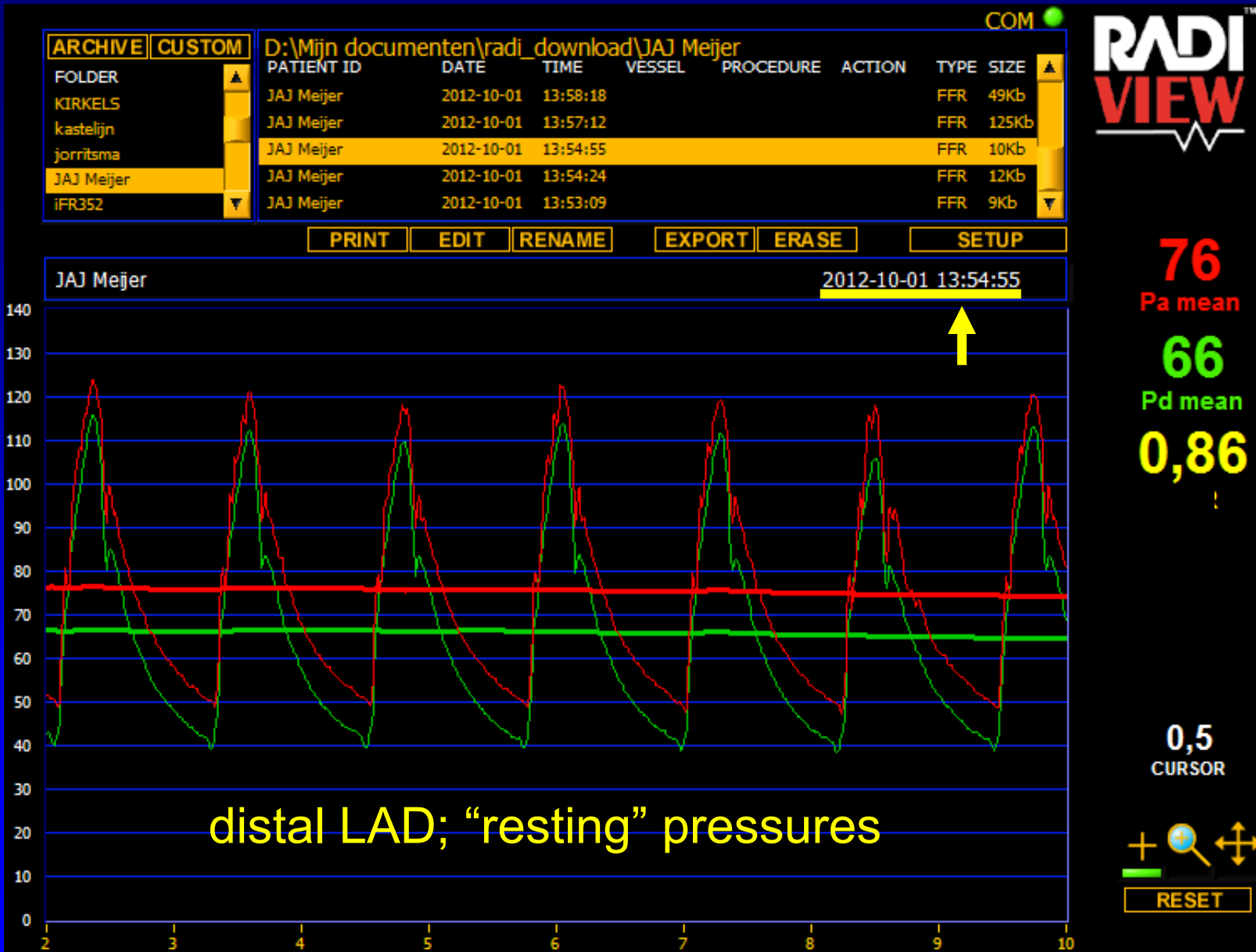
**3,8**  
CURSOR



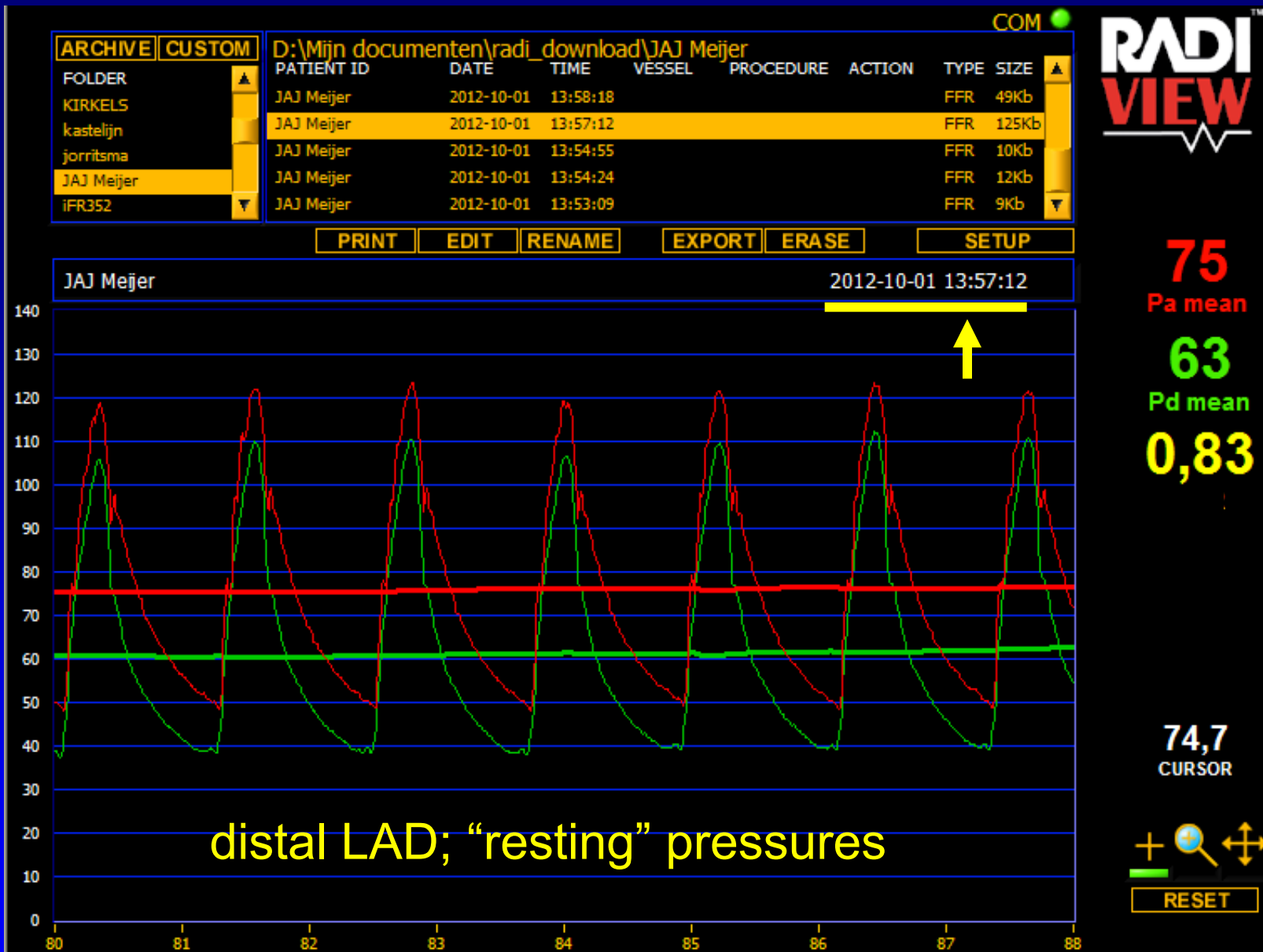
RESET

PW in distal LAD; patient "asleep" (relaxed)

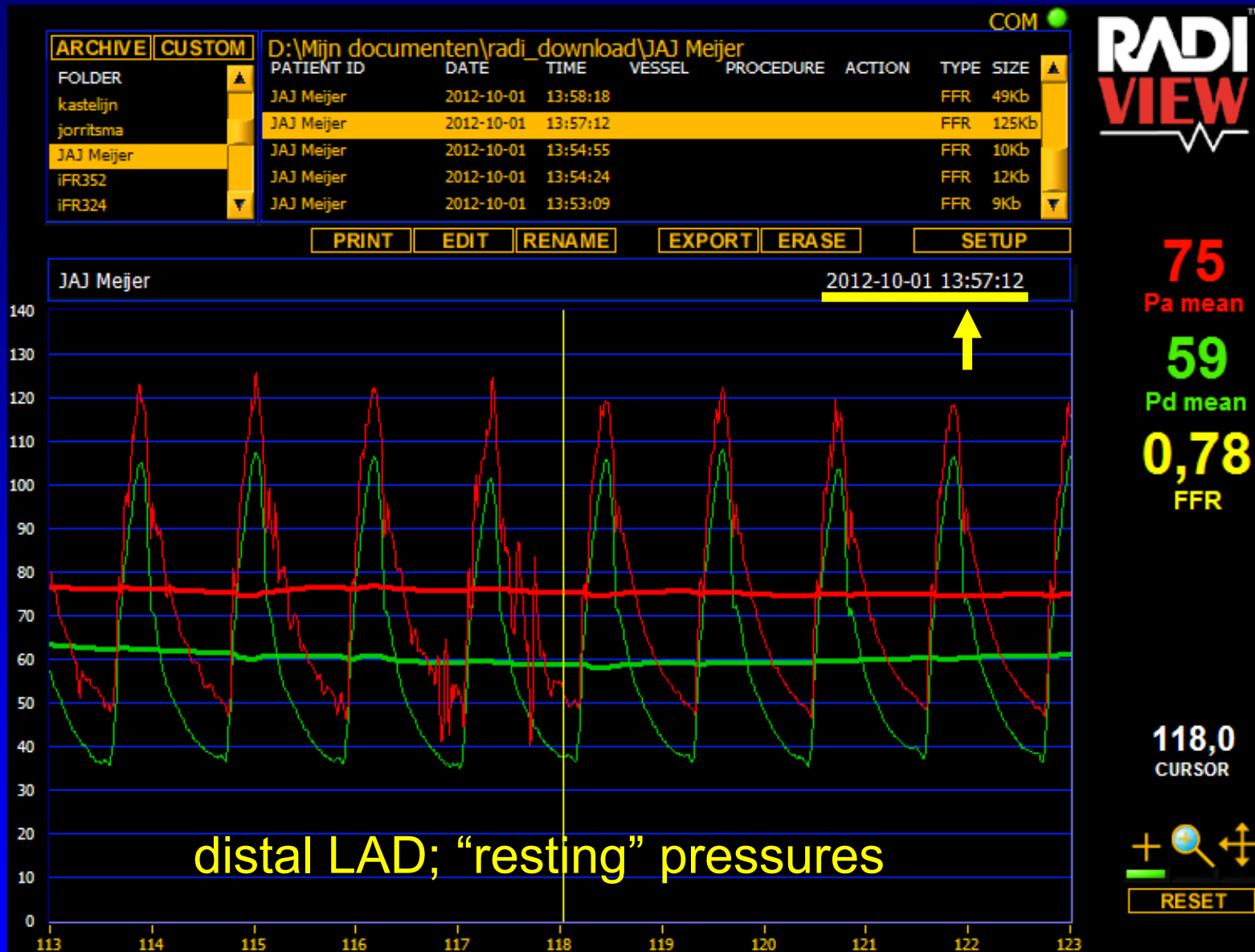




PW in distal LAD; patient "awake"



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



advancing the wire 2 cm and pulling it back again

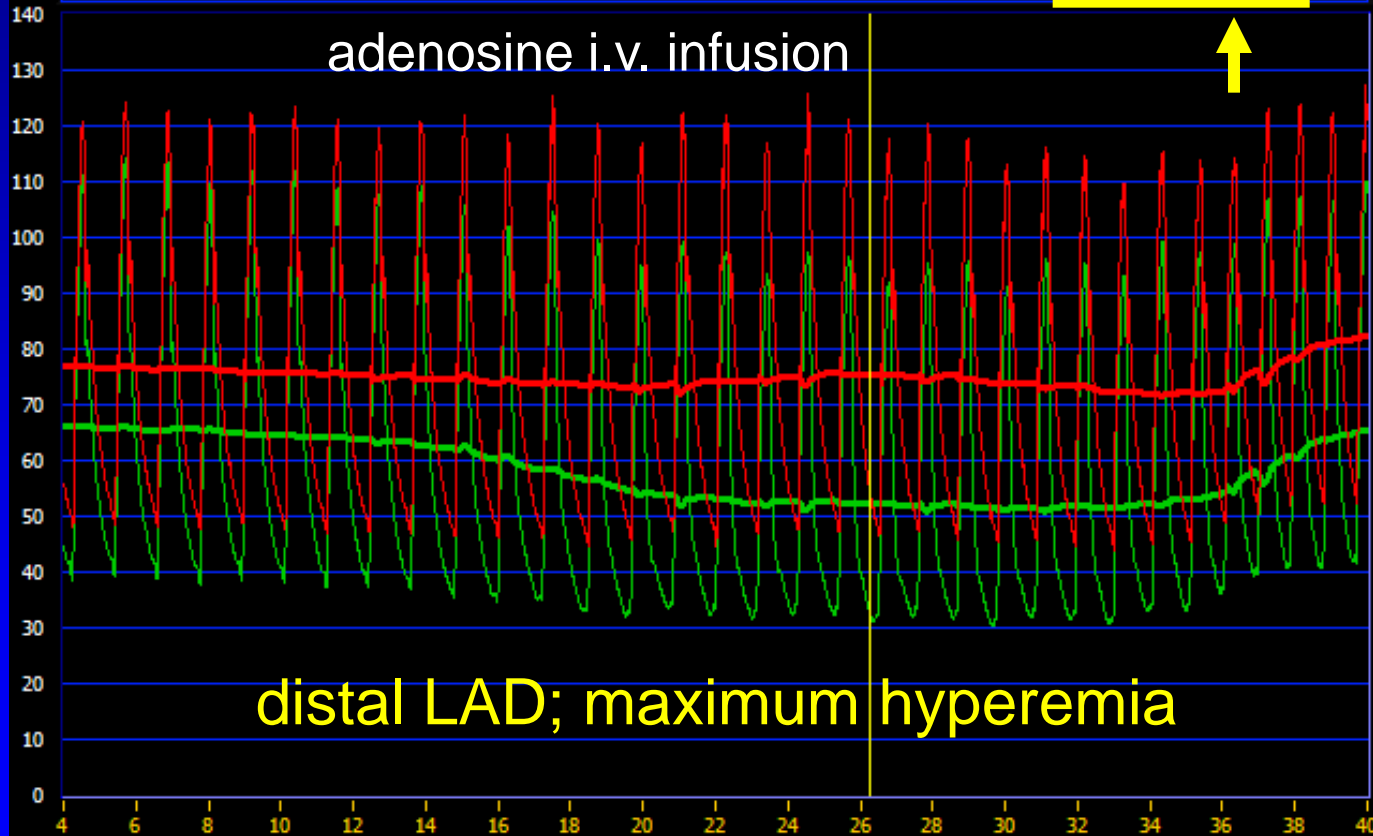
ARCHIVE CUSTOM

D:\Mijn documenten\radi\_download\JAJ Meijer

FOLDER	PATIENT ID	DATE	TIME	VESSEL	PROCEDURE	ACTION	TYPE	SIZE
KIRKELS	JAJ Meijer	2012-10-01	13:58:18				FFR	49Kb
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JAJ Meijer	JAJ Meijer	2012-10-01	13:54:24				FFR	12Kb
iFR352	JAJ Meijer	2012-10-01	13:53:09				FFR	9Kb

PRINT EDIT RENAME EXPORT ERASE SETUP

JAJ Meijer 2012-10-01 13:58:18



**75**  
Pa mean

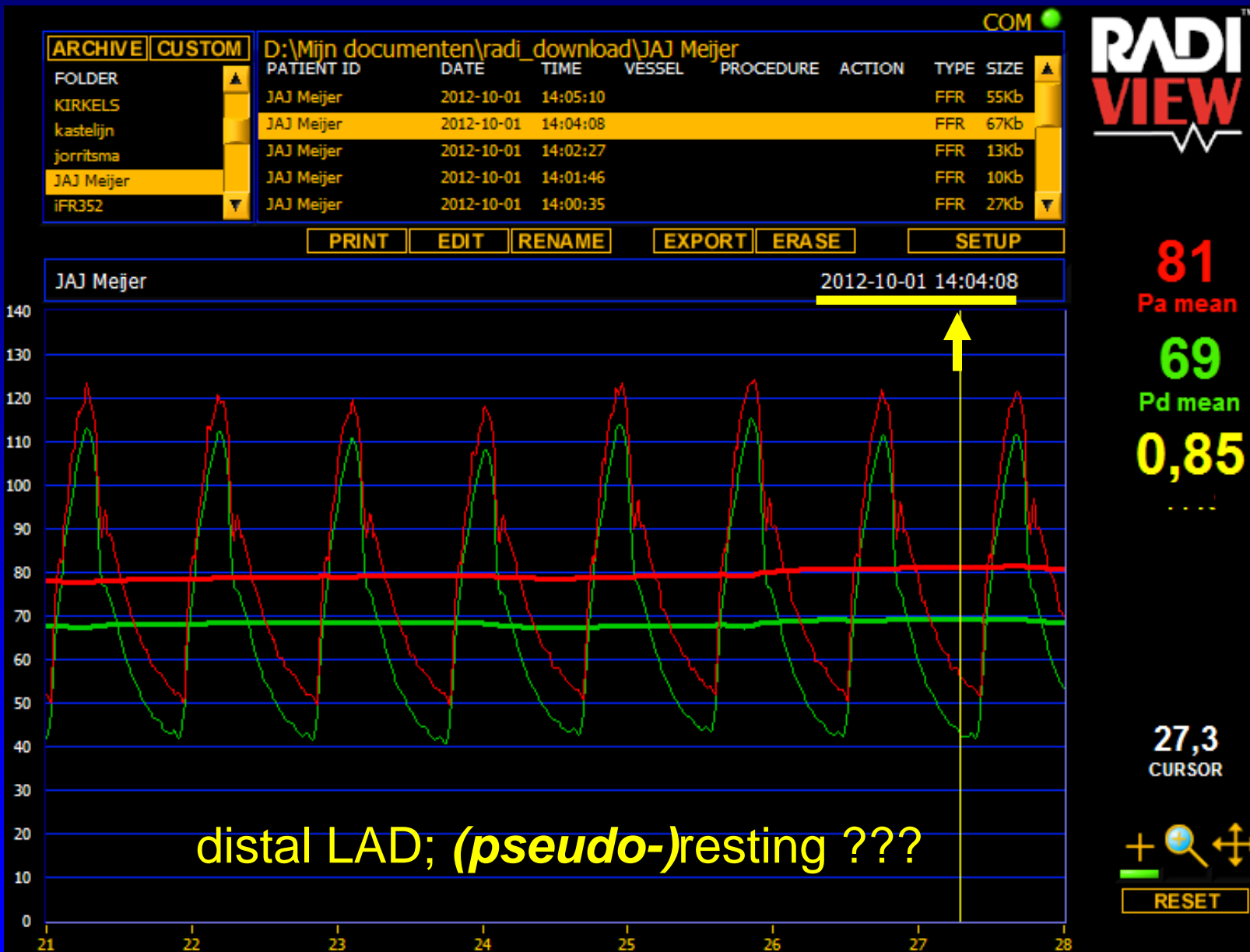
**52**  
Pd mean

**0,69**  
FFR

**26,3**  
CURSOR

+ [magnifying glass] [crosshair]  
RESET

Measurement of FFR



After waiting for 5 minutes, not touching anything



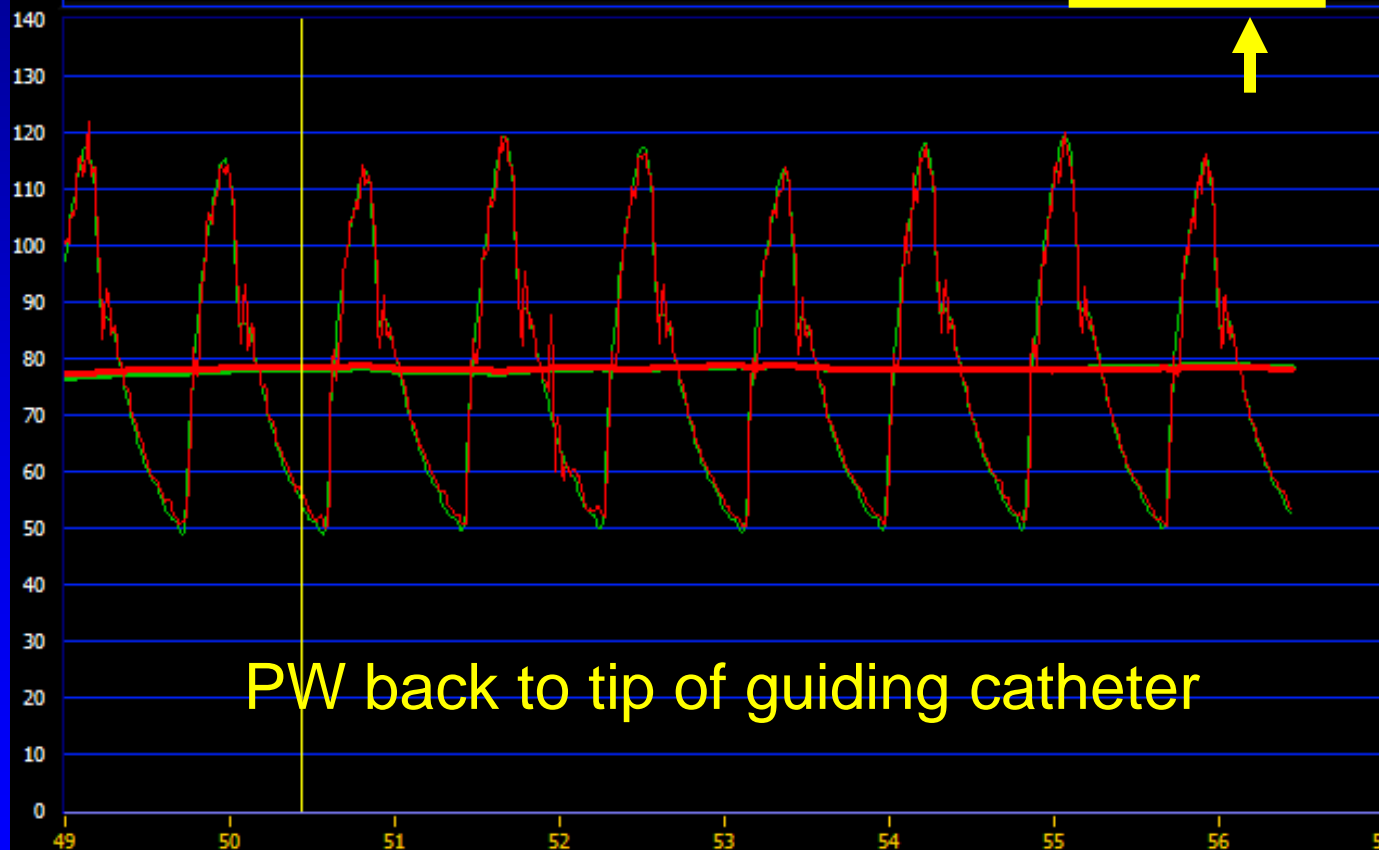
ARCHIVE CUSTOM

D:\Mijn documenten\radi\_download\JAJ Meijer

FOLDER	PATIENT ID	DATE	TIME	VESSEL	PROCEDURE	ACTION	TYPE	SIZE
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kastelijm	JAJ Meijer	2012-10-01	14:04:08				FFR	67Kb
jorritsma	JAJ Meijer	2012-10-01	14:02:27				FFR	13Kb
JAJ Meijer	JAJ Meijer	2012-10-01	14:01:46				FFR	10Kb
iFR352	JAJ Meijer	2012-10-01	14:00:35				FFR	27Kb

PRINT EDIT RENAME EXPORT ERASE SETUP

JAJ Meijer 2012-10-01 14:05:10



78  
Pa mean  
78  
Pd mean  
0,99

50,4  
CURSOR



RESET

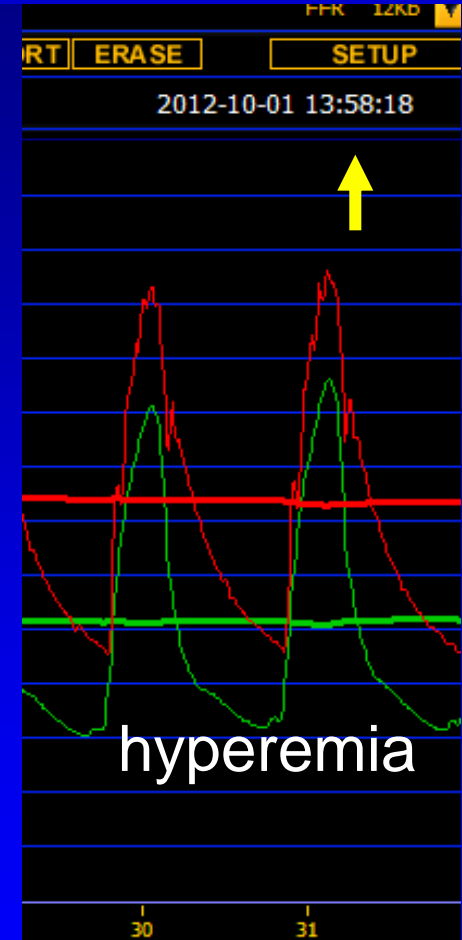
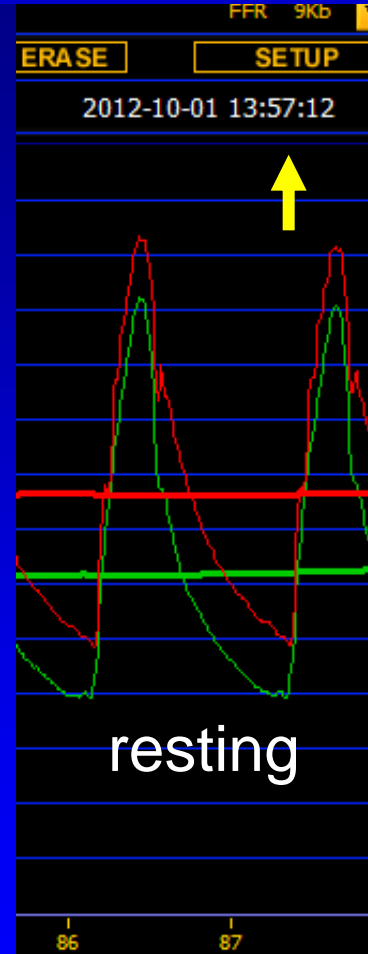
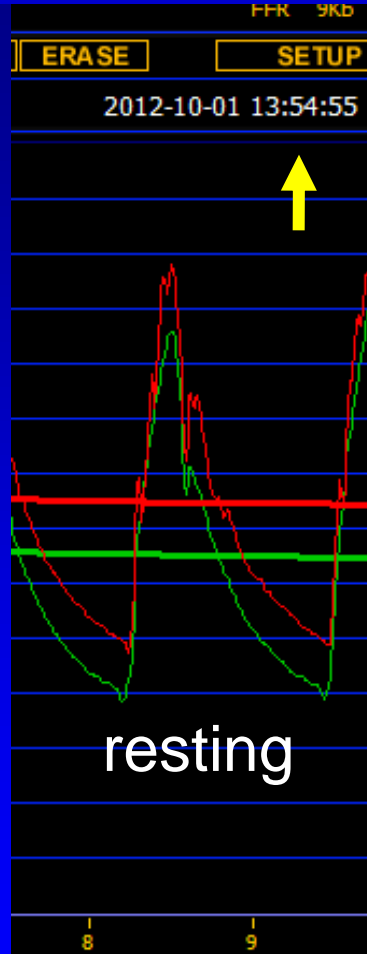
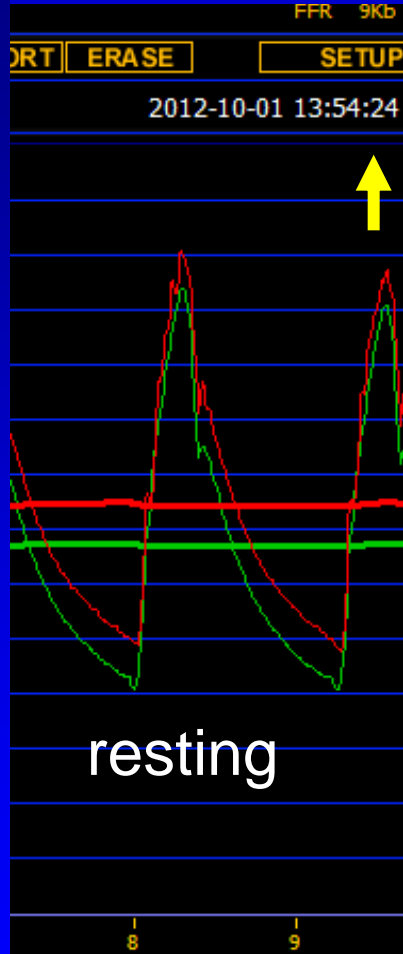
verification of equal pressures and absence of drift

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)***

***0.93 (Indolfi)***

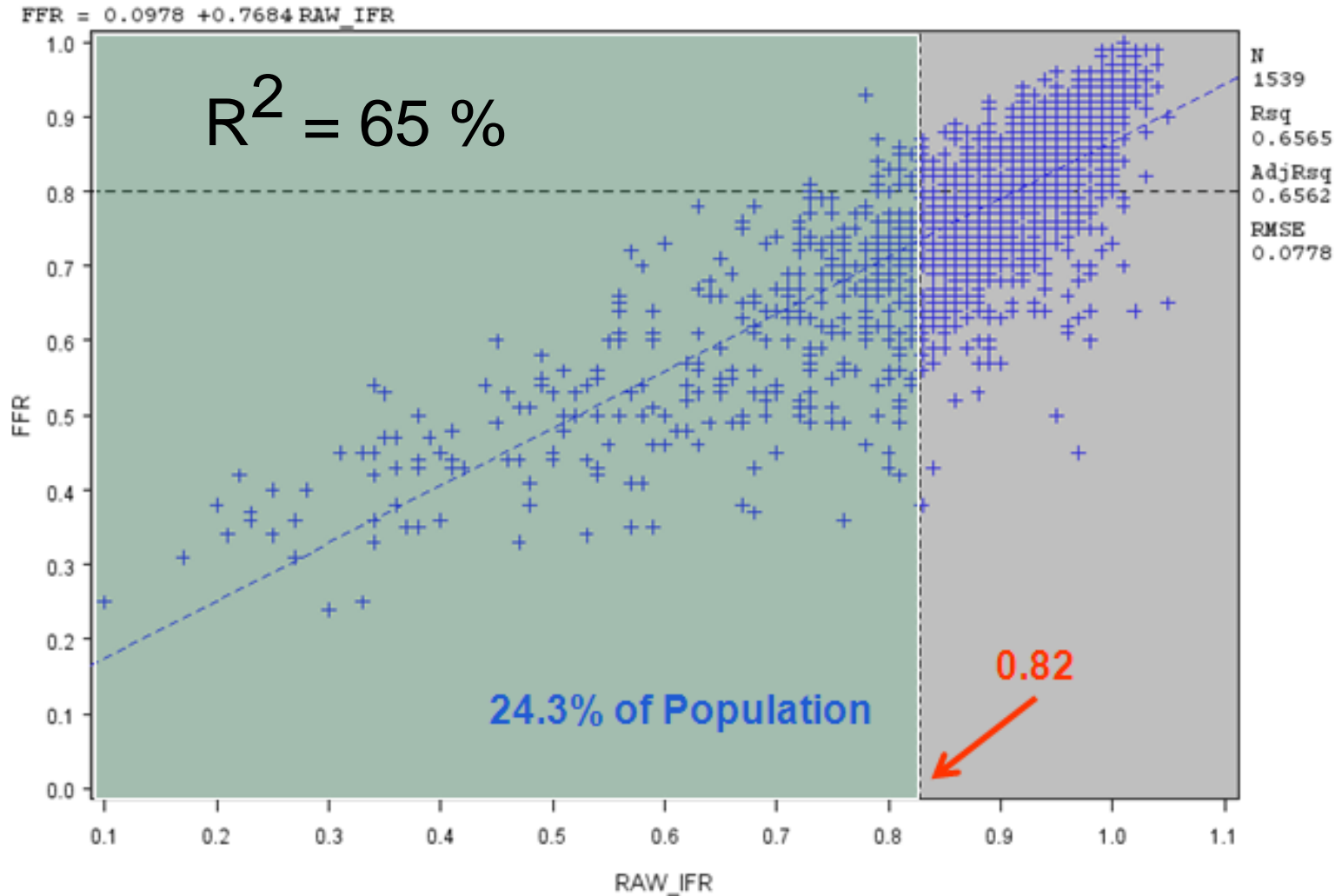
***Similar for all indexes which rely upon resting value of flow***

## Data Contribution

	<u>Patients</u>	<u>Lesions</u>
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
<b>Total</b>	<b>1802</b>	<b>1850</b>

# Correlation FFR and iFR

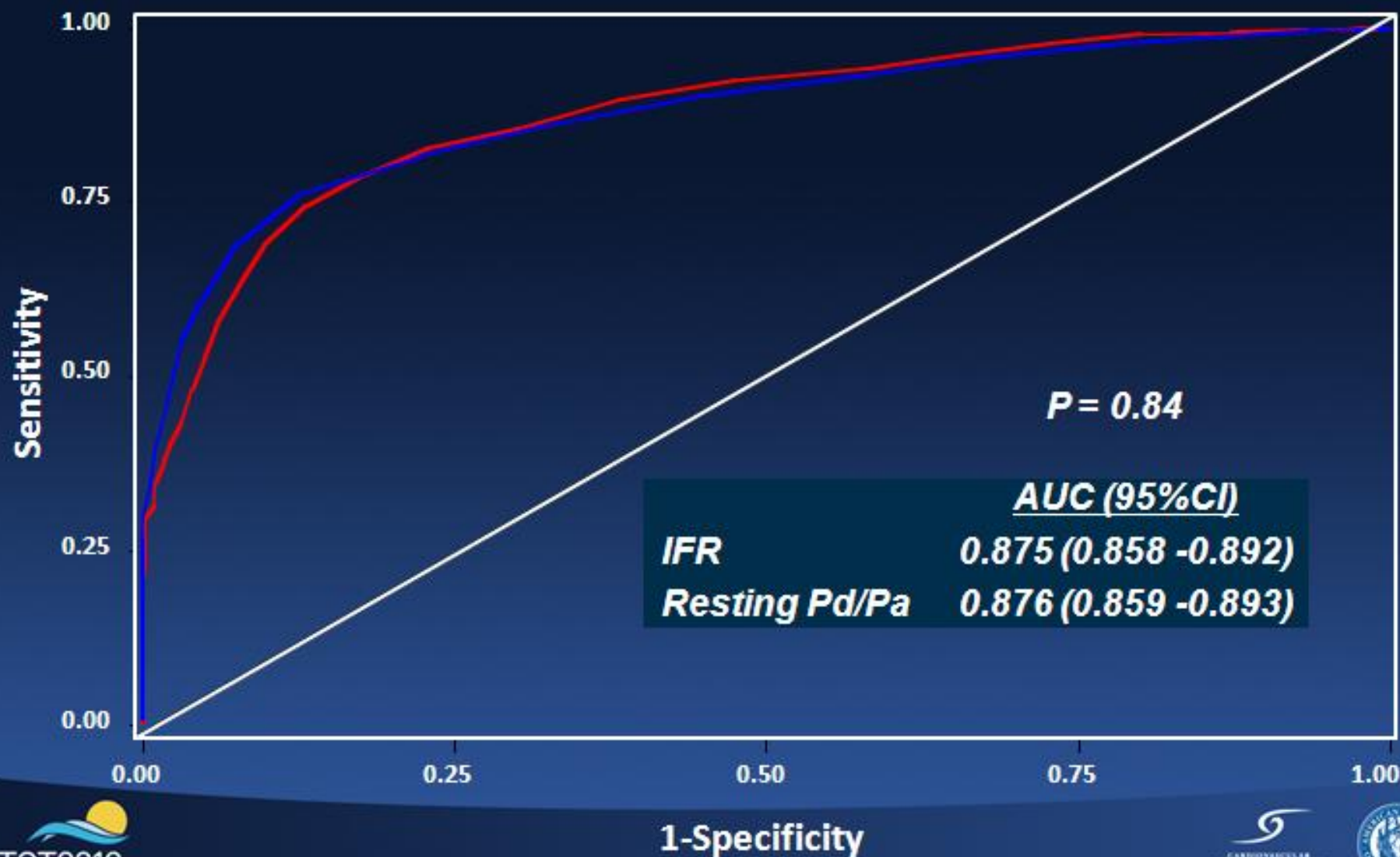
## iFR vs. FFR with 95% Cutoffs



# ROC Curve iFR and Pd/Pa Based on FFR 0.80

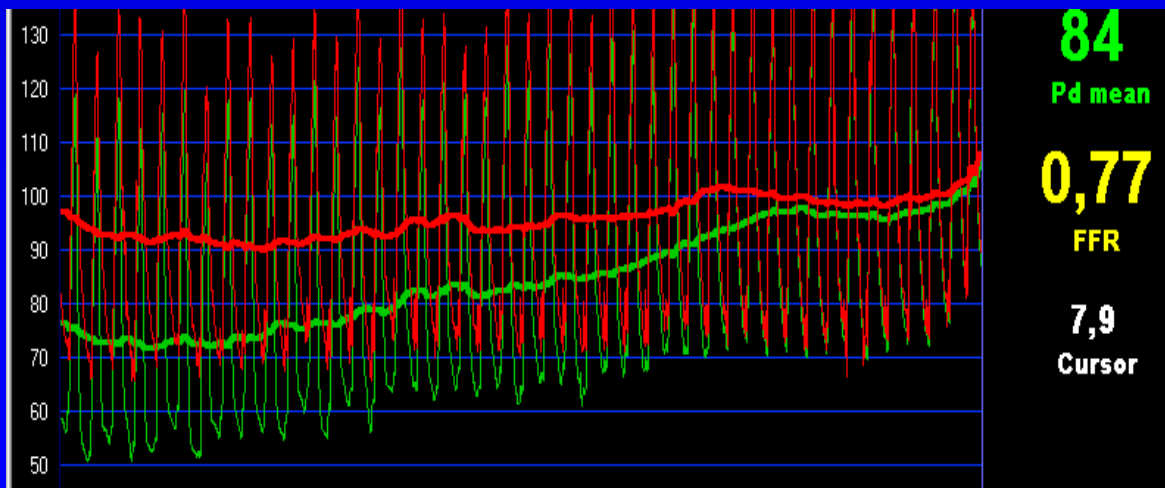
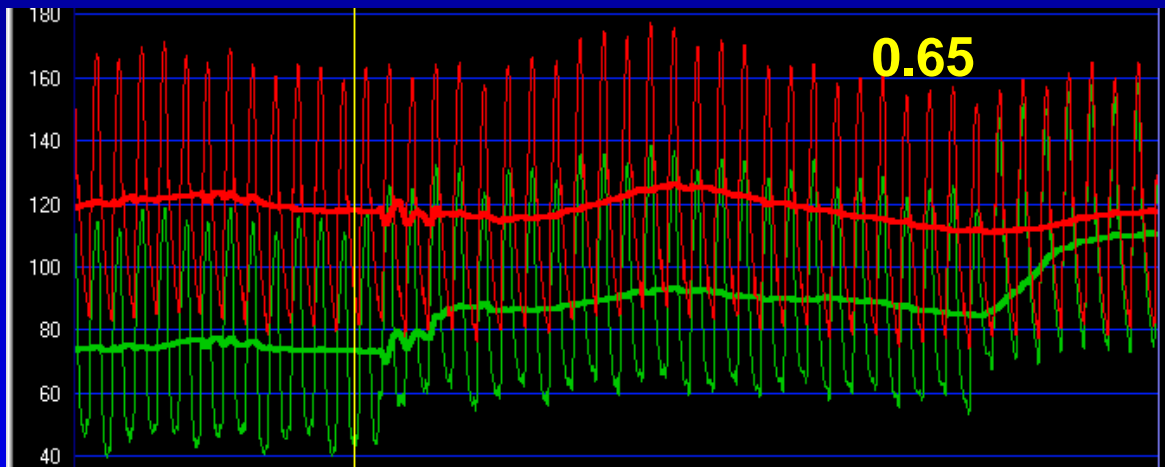
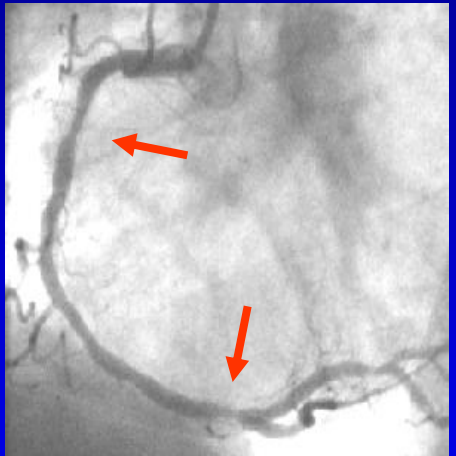
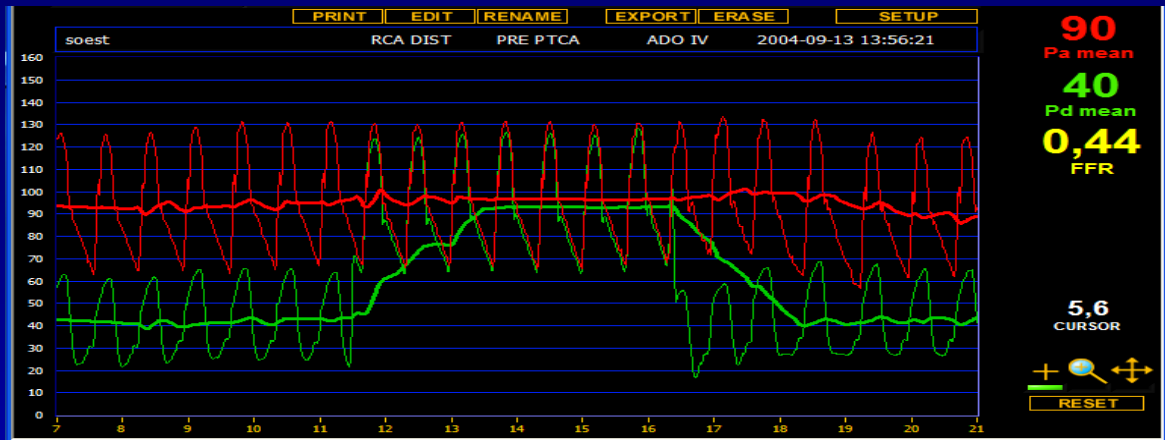
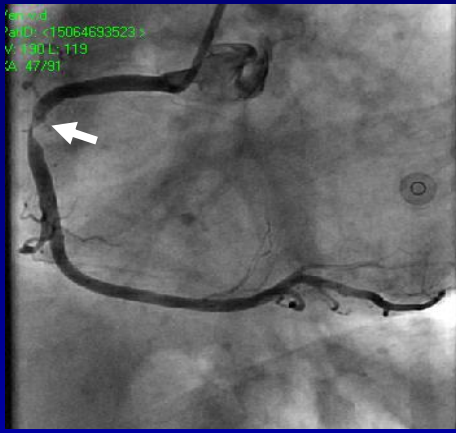
— IFR

— Resting Pd/Pa

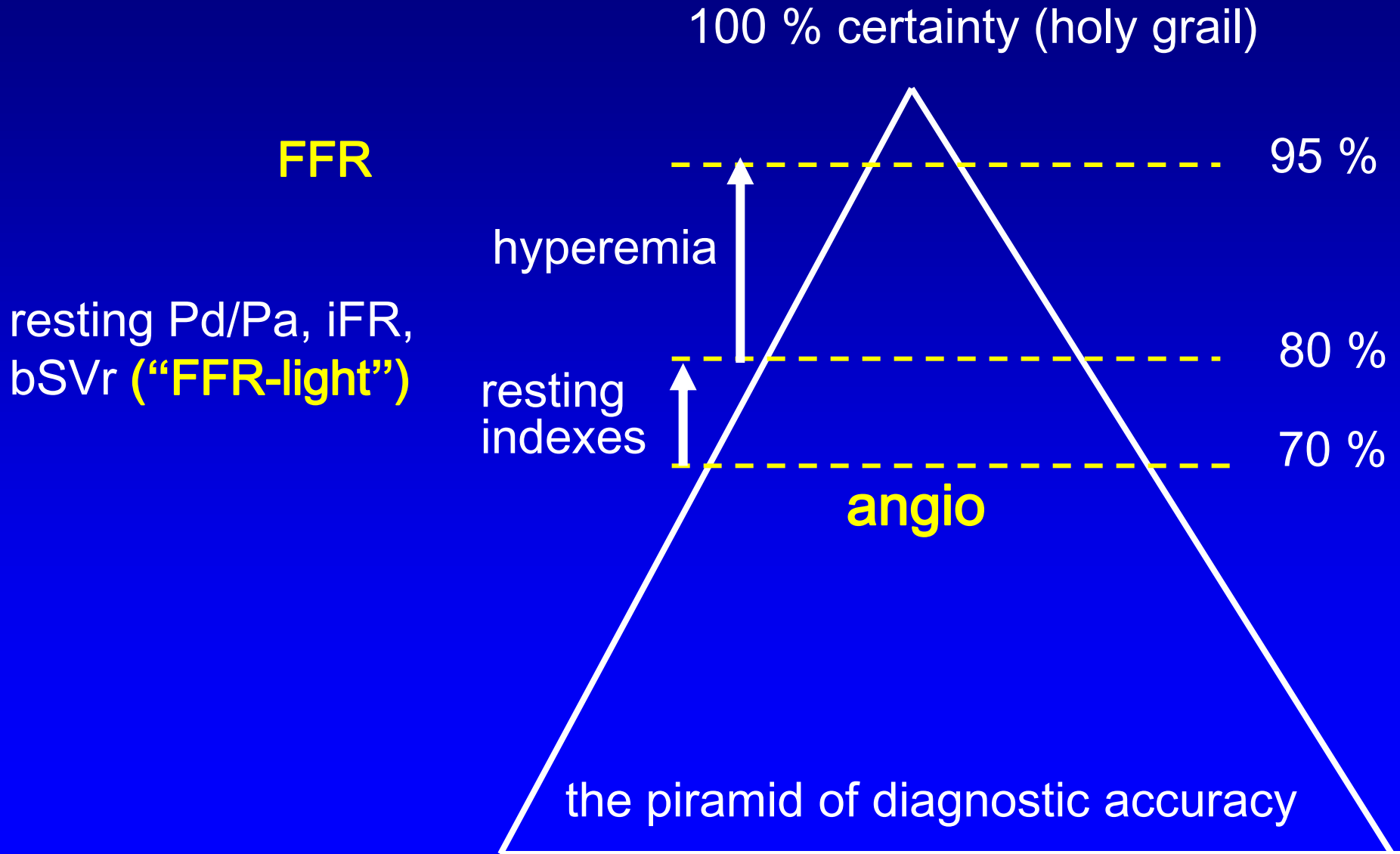


## necessity of hyperemia

- If Pd/Pa at rest (or comparable indices) is  $\leq 0.80$  , as a matter of fact FFR will also be  $\leq 0.80$  and hyperemia in itself is not strictly mandatory to decide upon inducible ischemia
- But without hyperemia and FFR , 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 losing a lot of valuable information



# Correct Classification of Ischemic Stenosis

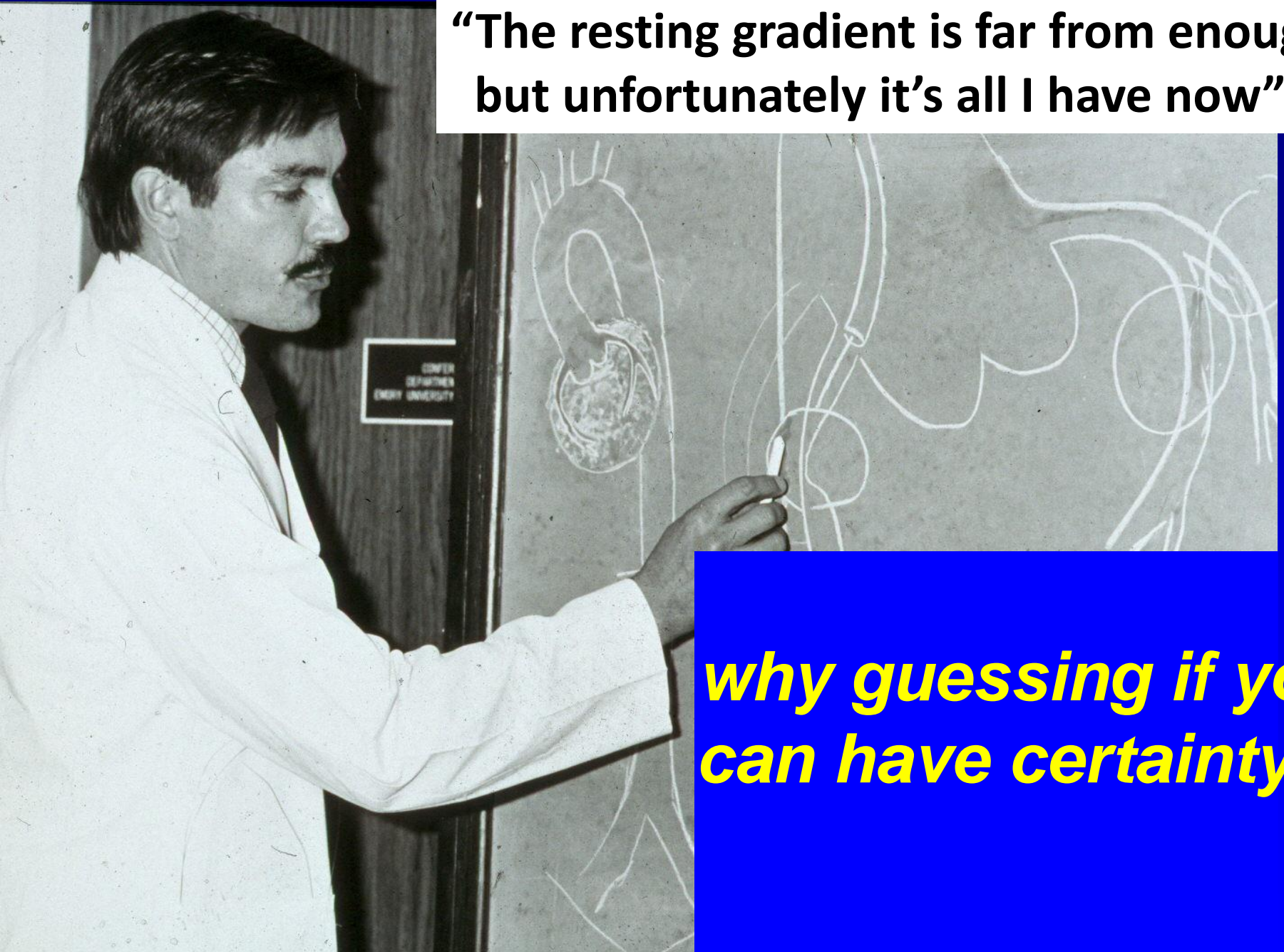


# CONCLUSIONS

- 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  $\Delta P$ , 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%  
**(wrong decision in 1 out of every 5 patients !)**

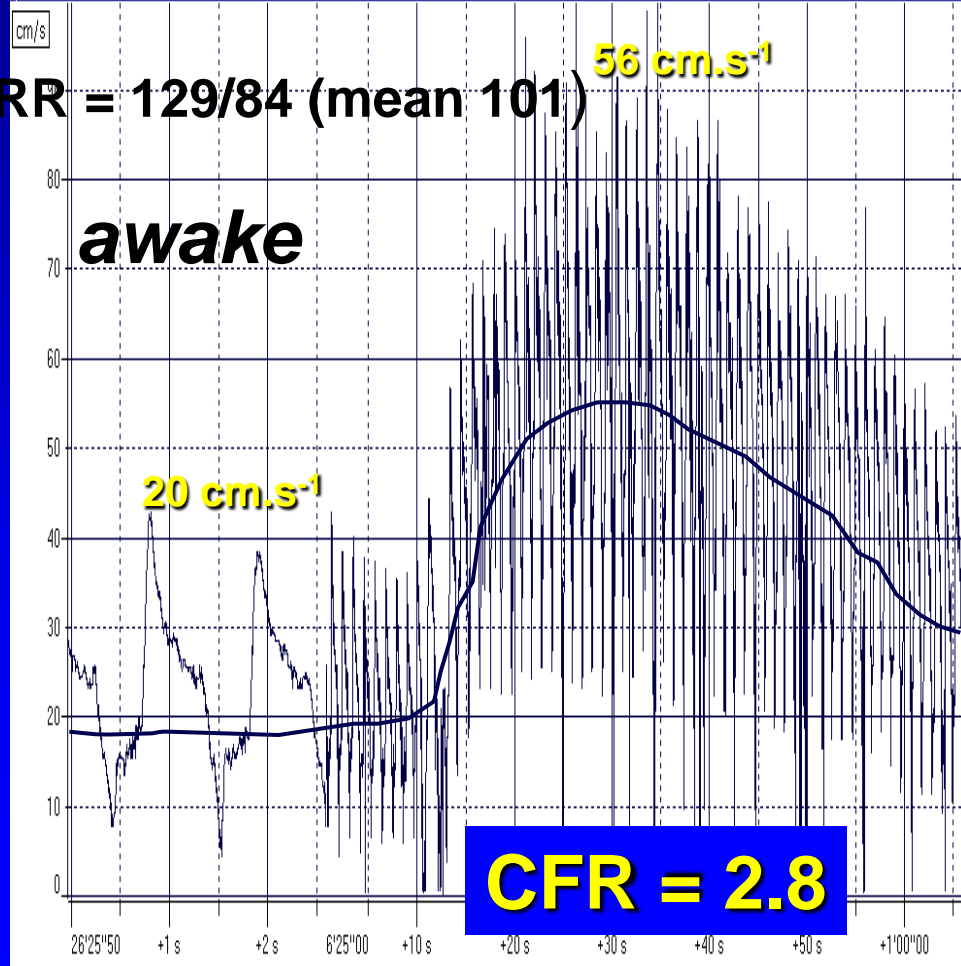
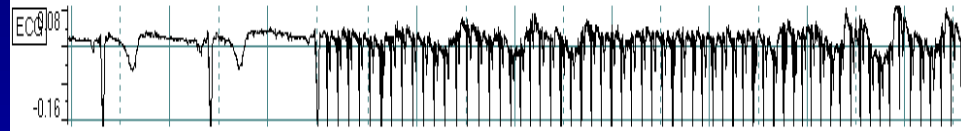
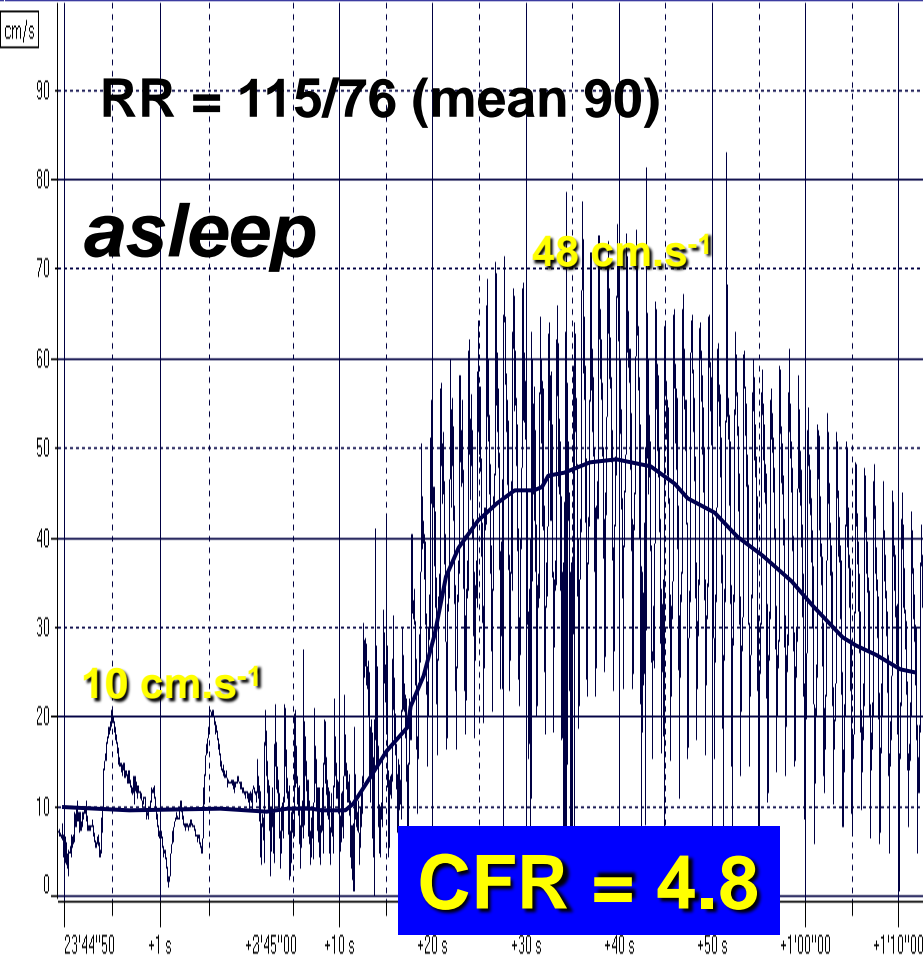
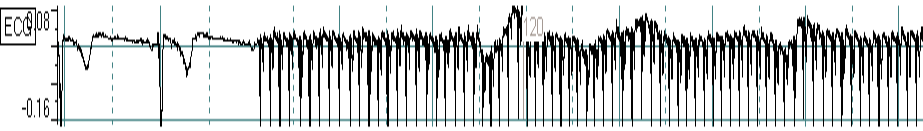


**“The resting gradient is far from enough  
but unfortunately it’s all I have now”.**



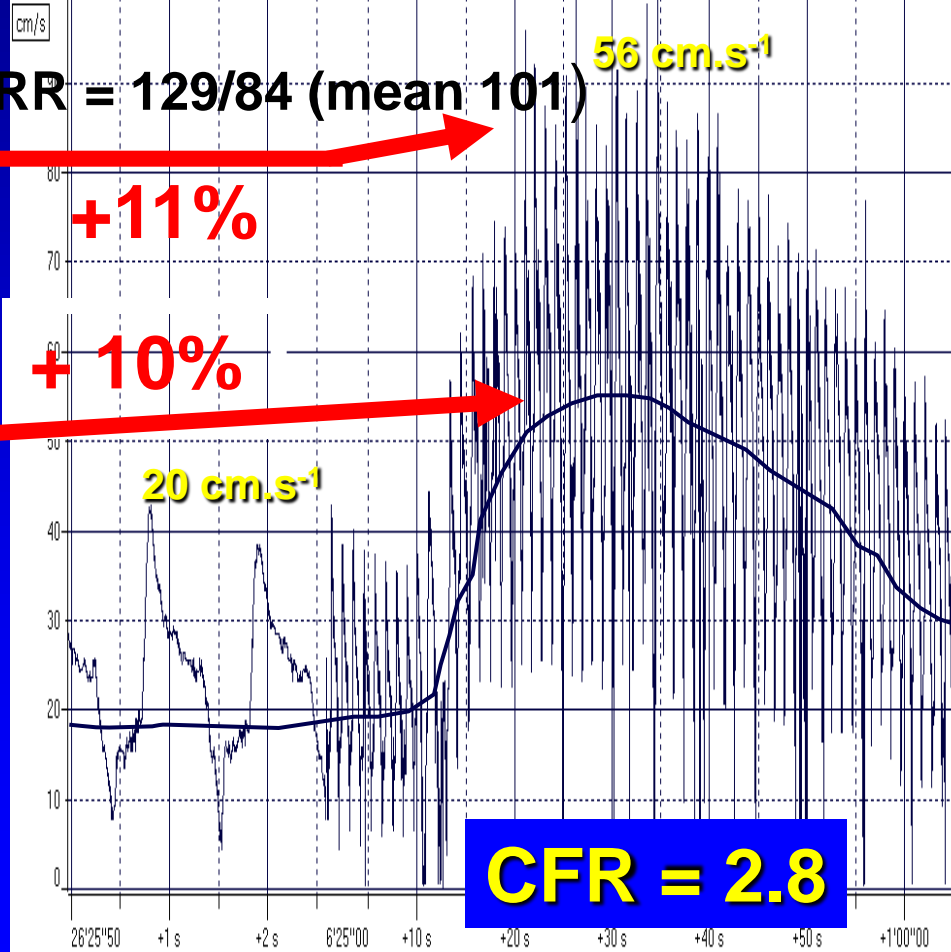
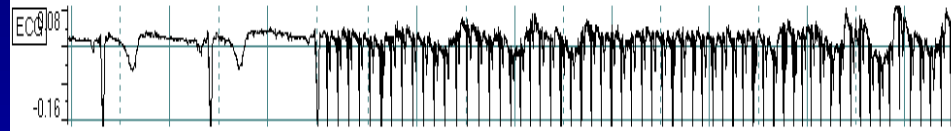
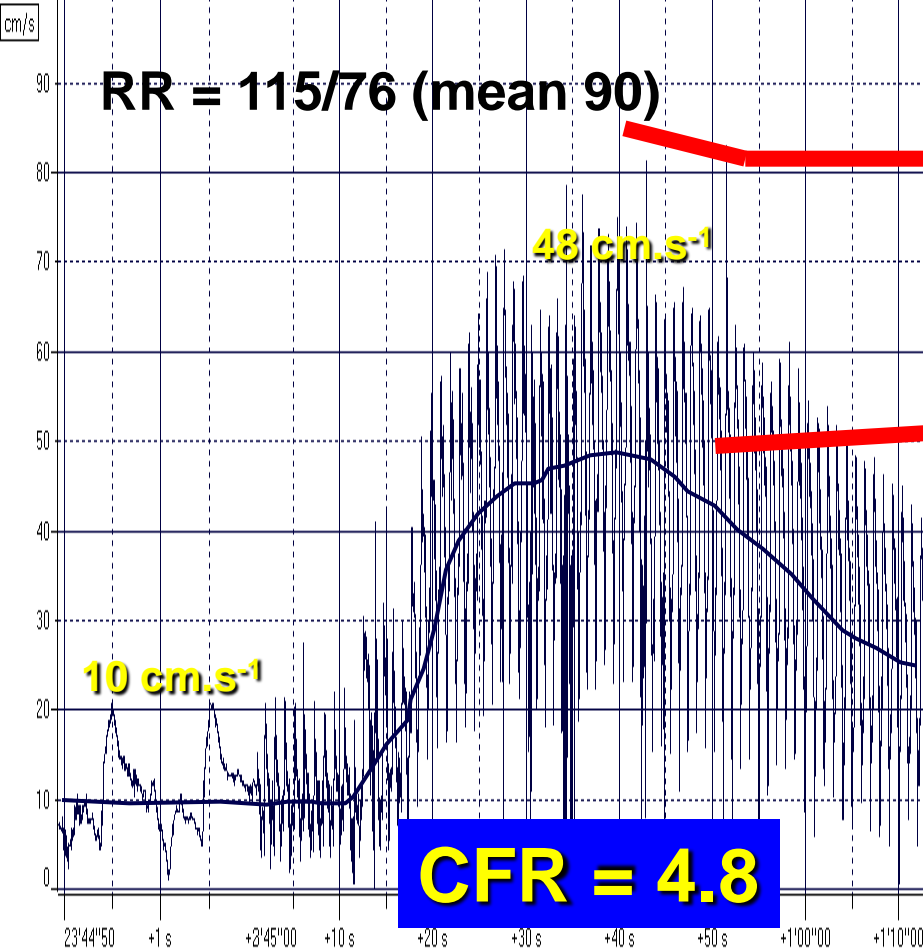
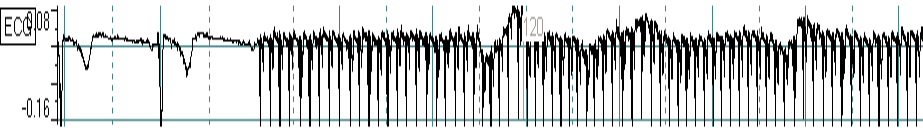
***why guessing if you  
can have certainty ?***

# Resting flow in the cath lab is an illusion: Influence of the "Resting Flow" on CFR



# Resting flow in the cath lab is an illusion:

## FFR IS NOT AFFECTED !

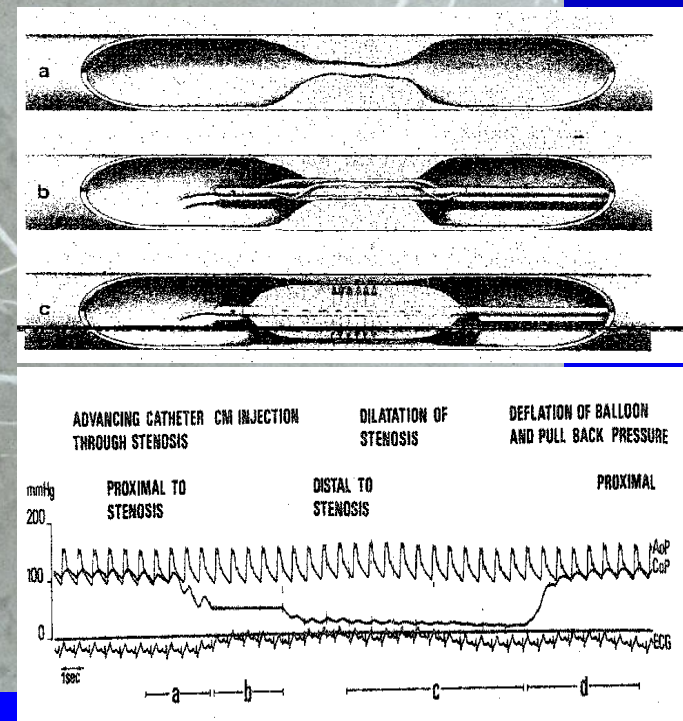
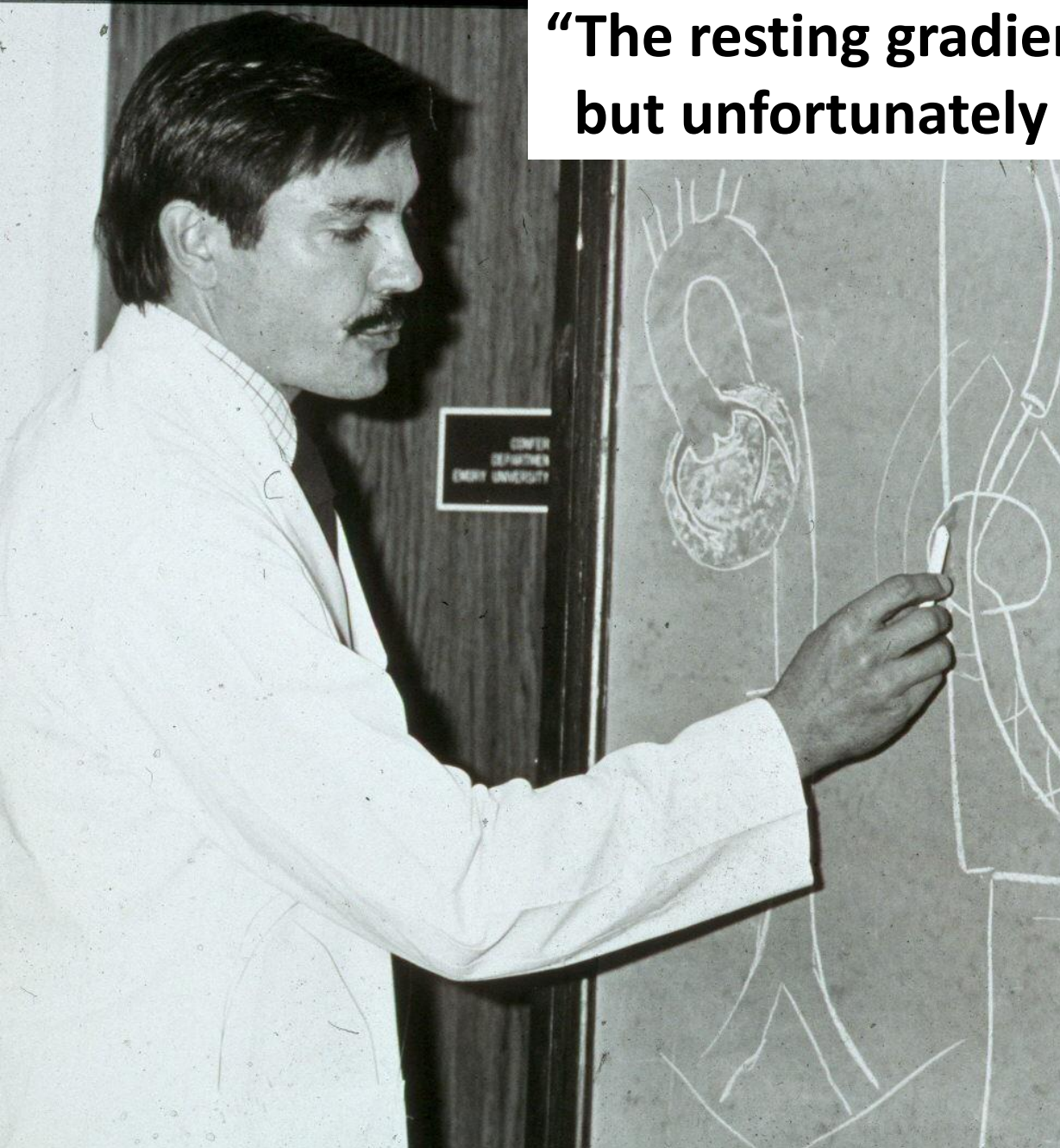


+11%

+10%



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



Neem als basis

TCT 2012 (soortgelijke voordracht)

Budapest (soortgelijke voordracht)

Latere data:

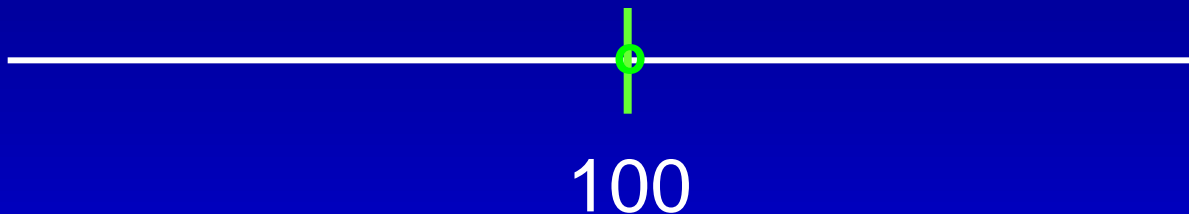
Dia's met reproductie

Inaccuracy van 80% en van 70% tov die 80%  
(lijn met intervallen)

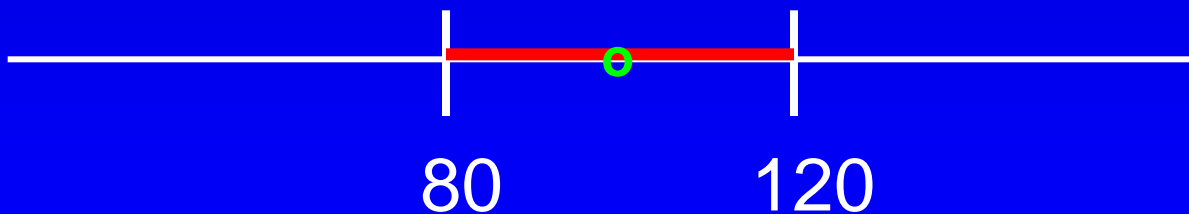
Ook Nils Johnson

## Hocus-pocus with statistics (1)

true value = 100

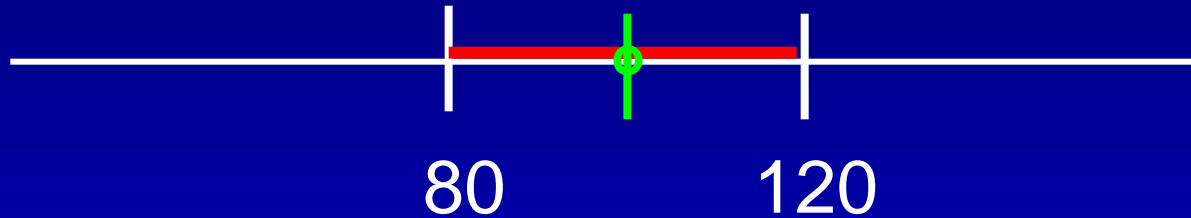


measuring methodology #1 : accuracy = 80 %

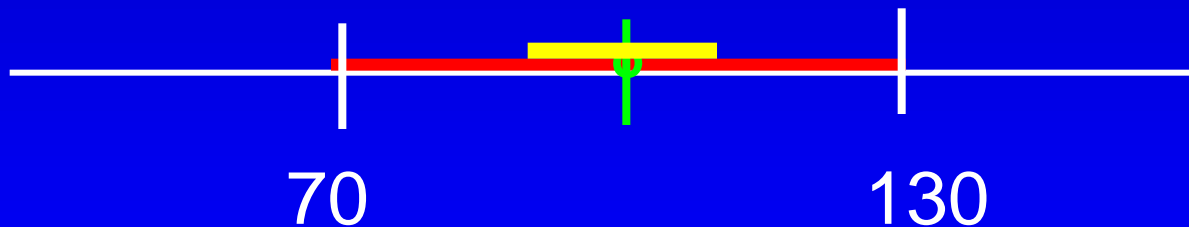


measured value between 80 and 120

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 ?

—————→  $(0.8 \times 0.9) = 0.72$  (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  $\text{GFR} < 60 \text{ ml/min} \rightarrow$  prehydration
- Accuracy of GFR measurement is  $\leq 3 \text{ ml/min}$   
*(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” ???*

## Hocus-pocus with statistics (3)

About reproducibility and “wrong decisions”

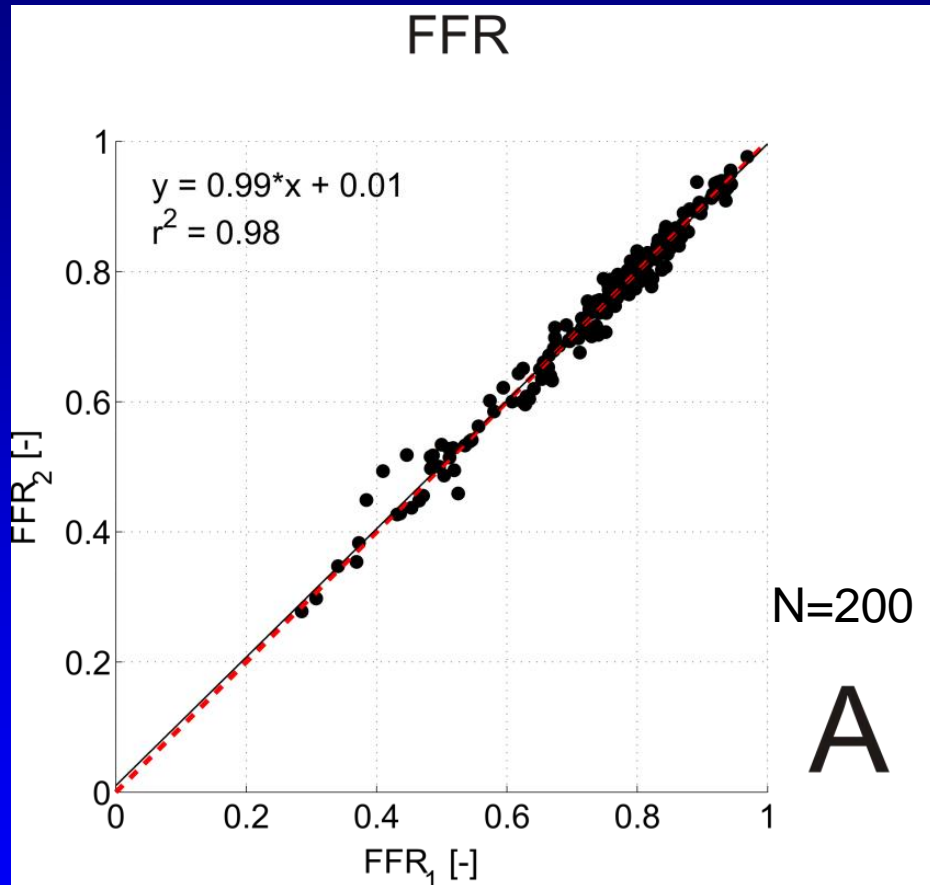
*What is fundamentally wrong in this reasoning?*

→ *confusing a-priori and a-posteriori knowledge*

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

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

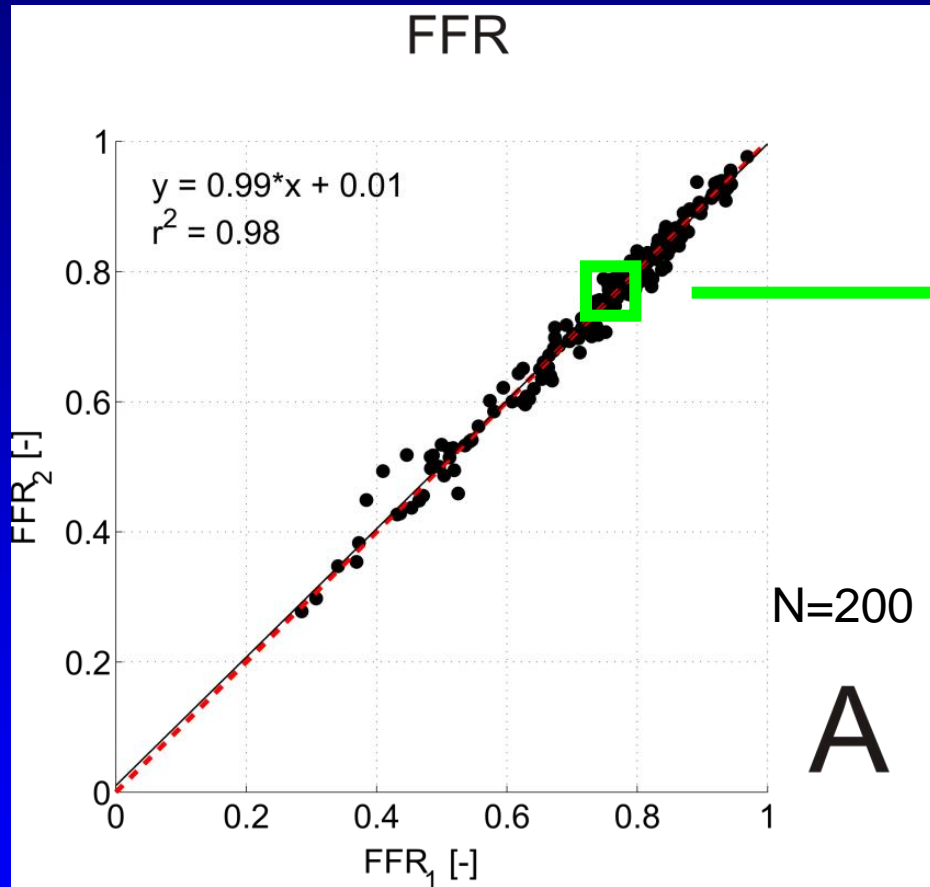
# Reproducibility of FFR



*VERIFY study, Berry et al, JACC 2013 ( published february 2013)*

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

# Reproducibility of FFR

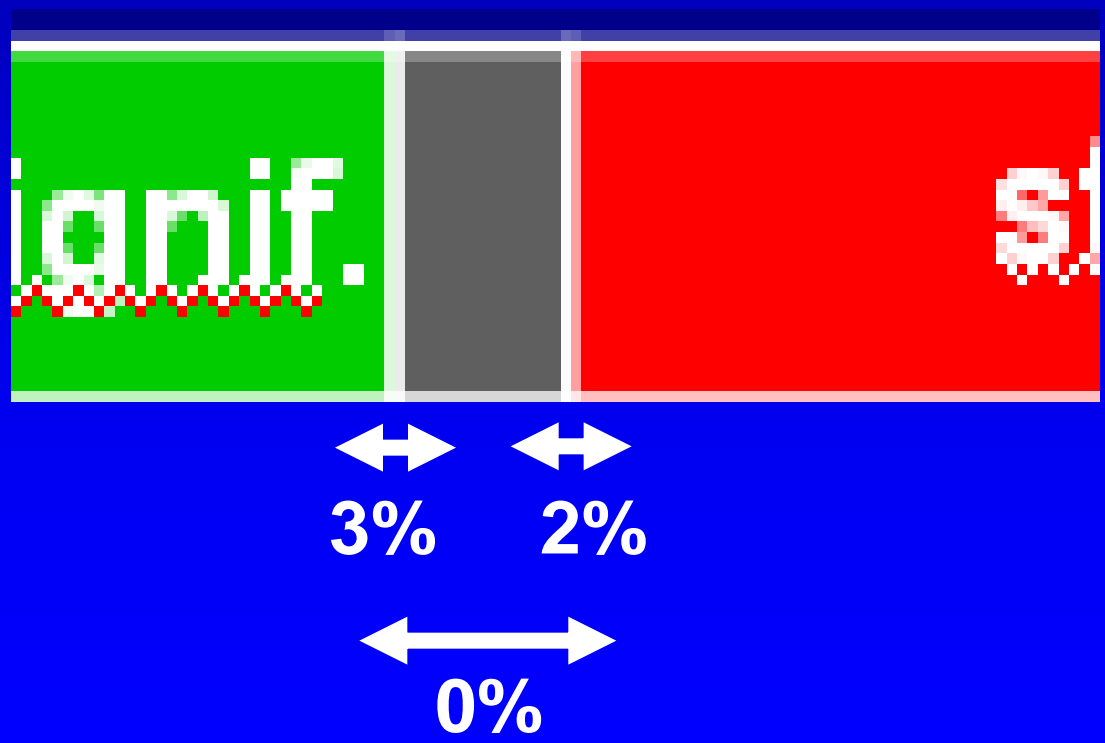


gray zone  
0.76-0.80

*VERIFY study, Berry et al, JACC 2013 ( published february 2013)*

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

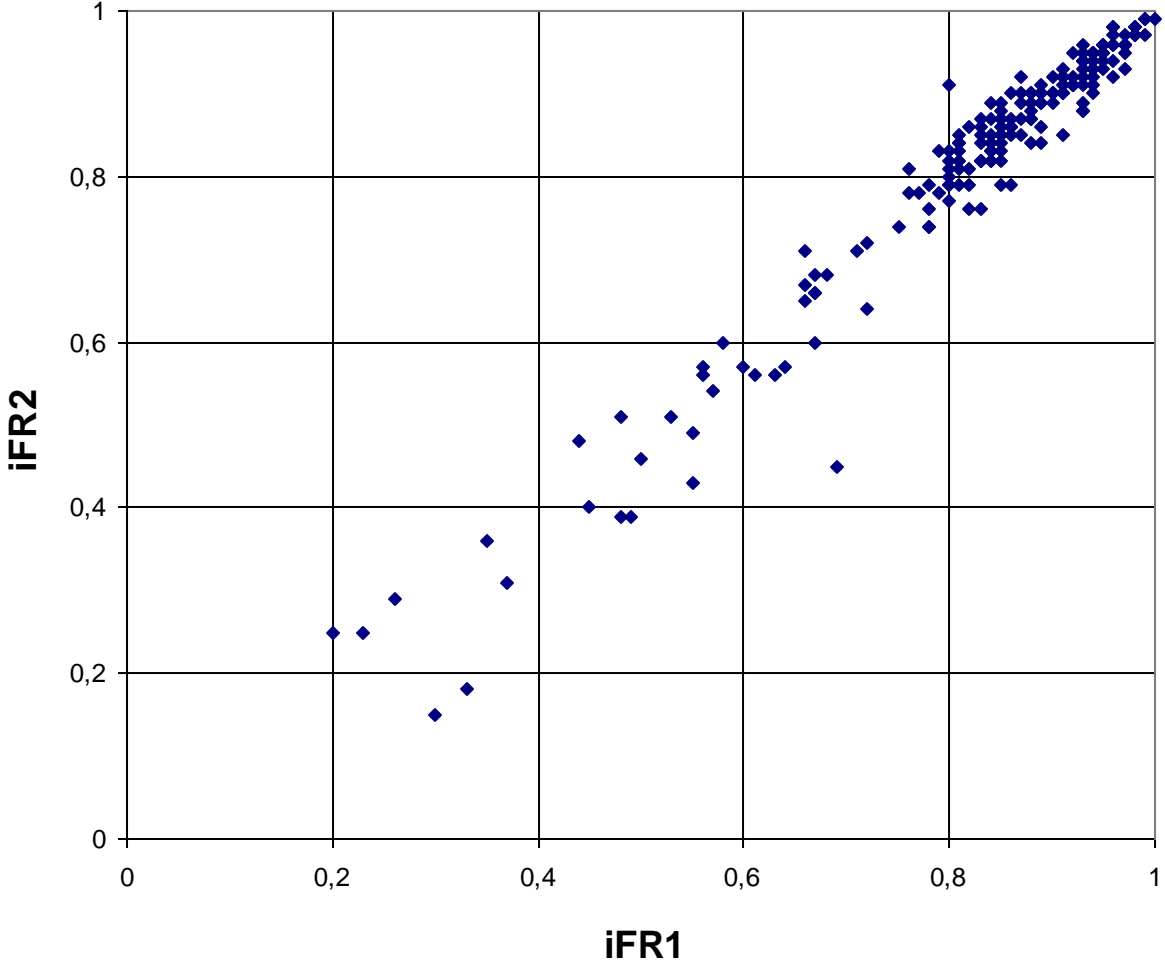
**At 1200 consecutive in-duplo measurements of FFR, there was NOT ANY cross-over across the gray zone**



# Reproducibility iFR using matlab

Data from Verify Study

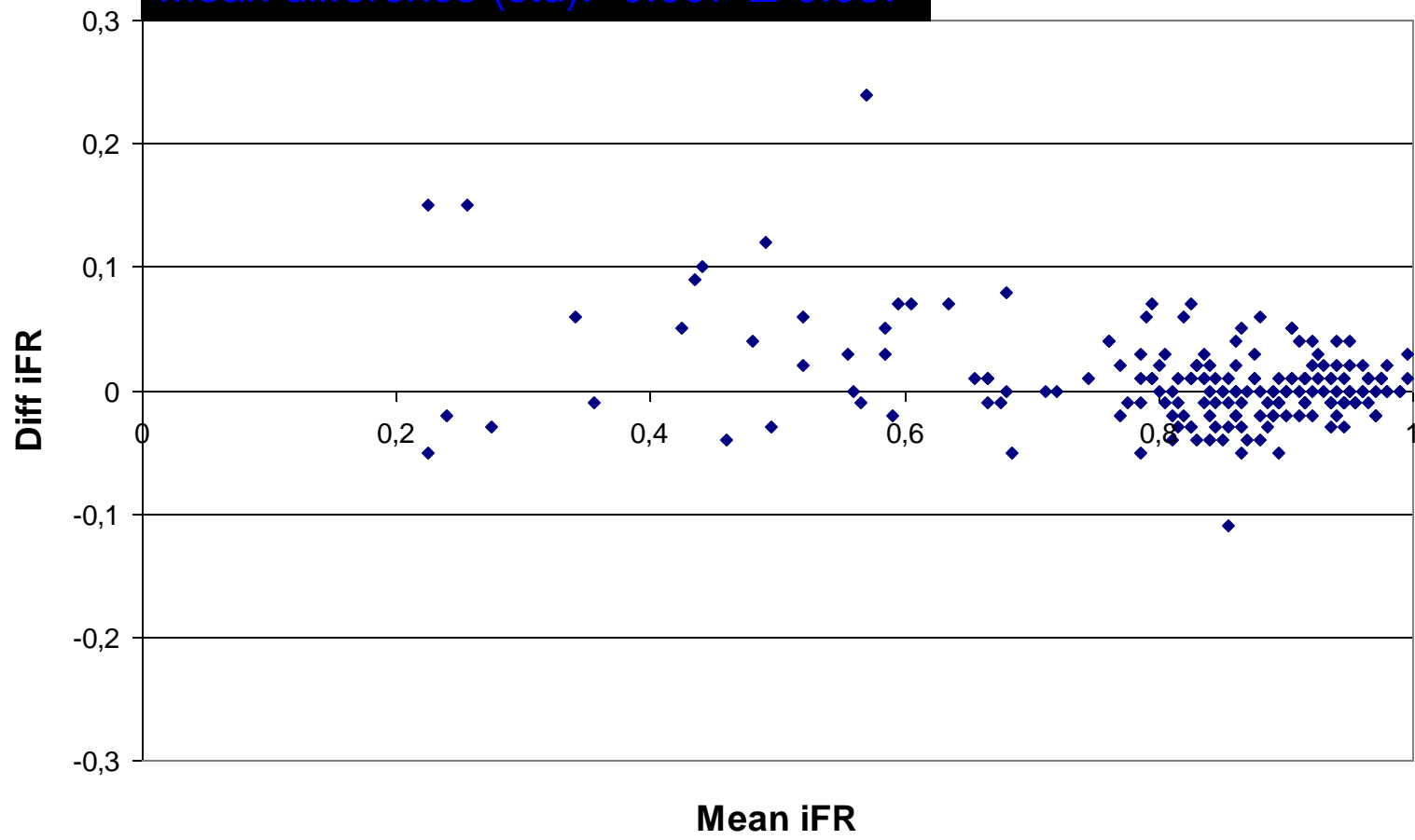
# Reproducibility iFR





### Bland-Altman Reproducibility iFR

Mean difference (std):  $-0.007 \pm 0.037$



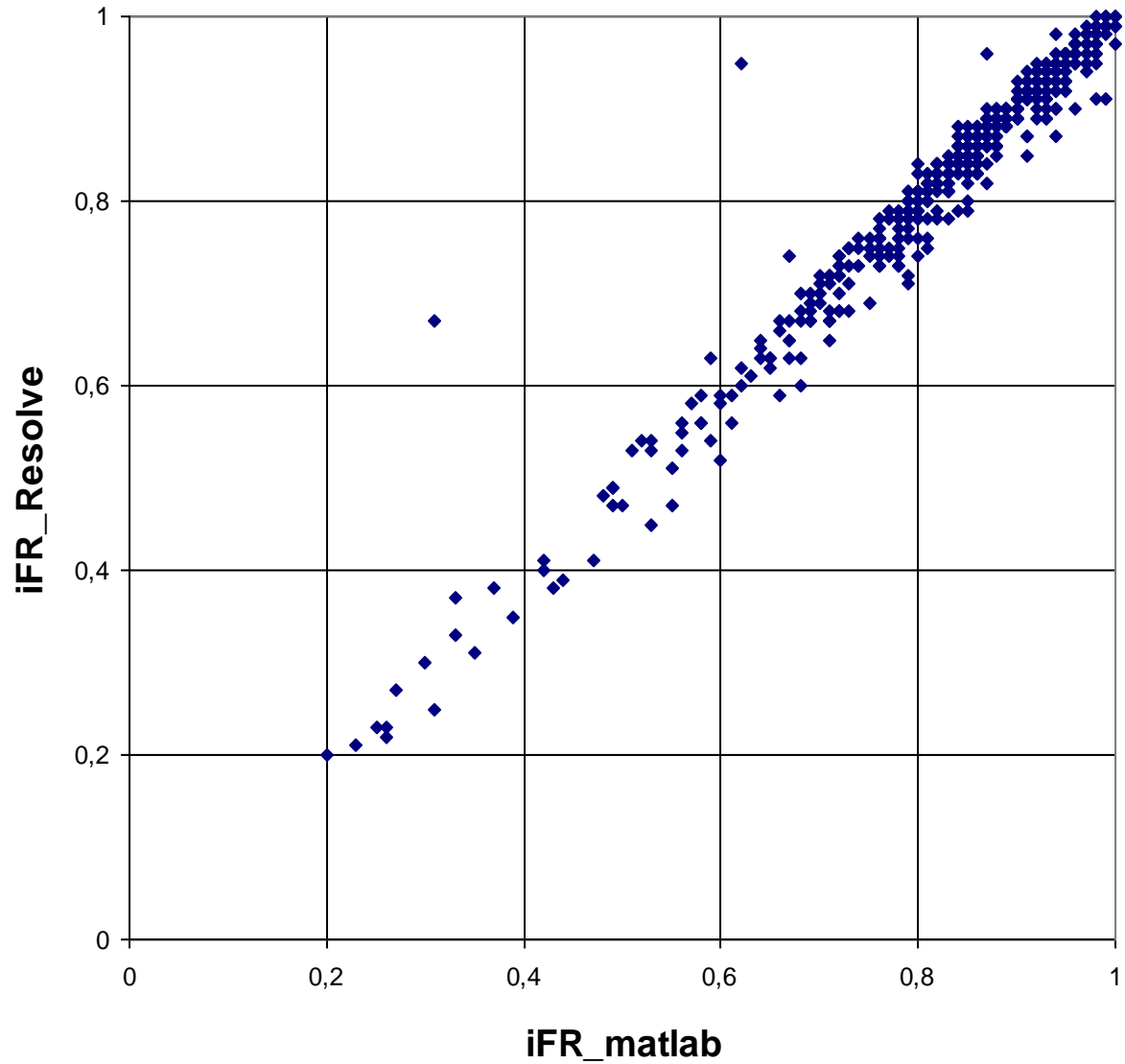
# Measurements compared

## $iFR_{\text{matlab}}$ vs $iFR_{\text{volcano}}$

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

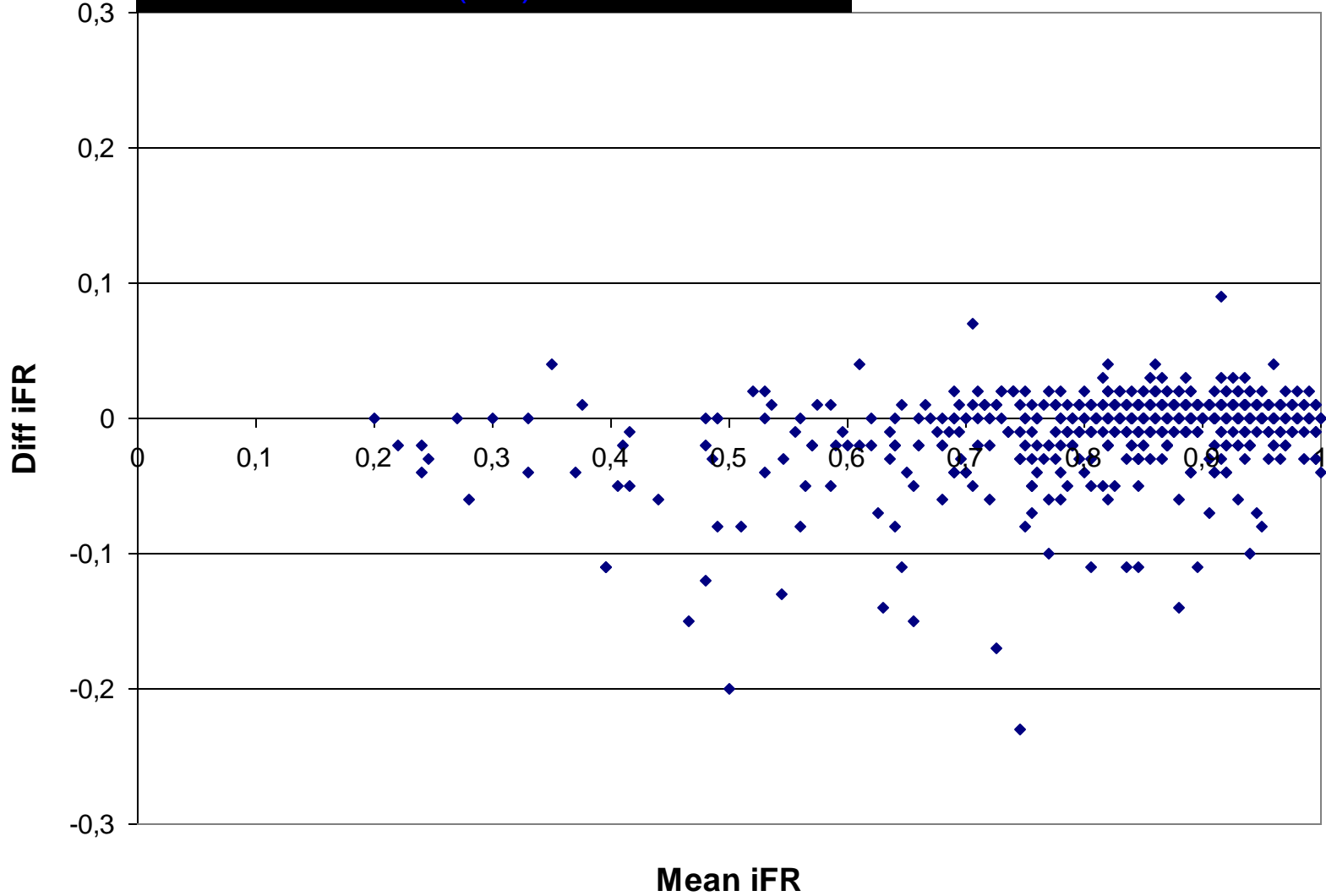
All 705 measurements

# iFR comparison



### Bland-Altman iFR

Mean difference (std):  $-0.005 \pm 0.034$



# Measurements compared

## $iFR_{\text{matlab}}$ vs $iFR_{\text{volcano}}$

Difference of 18 measurements  $\leq 0.1$

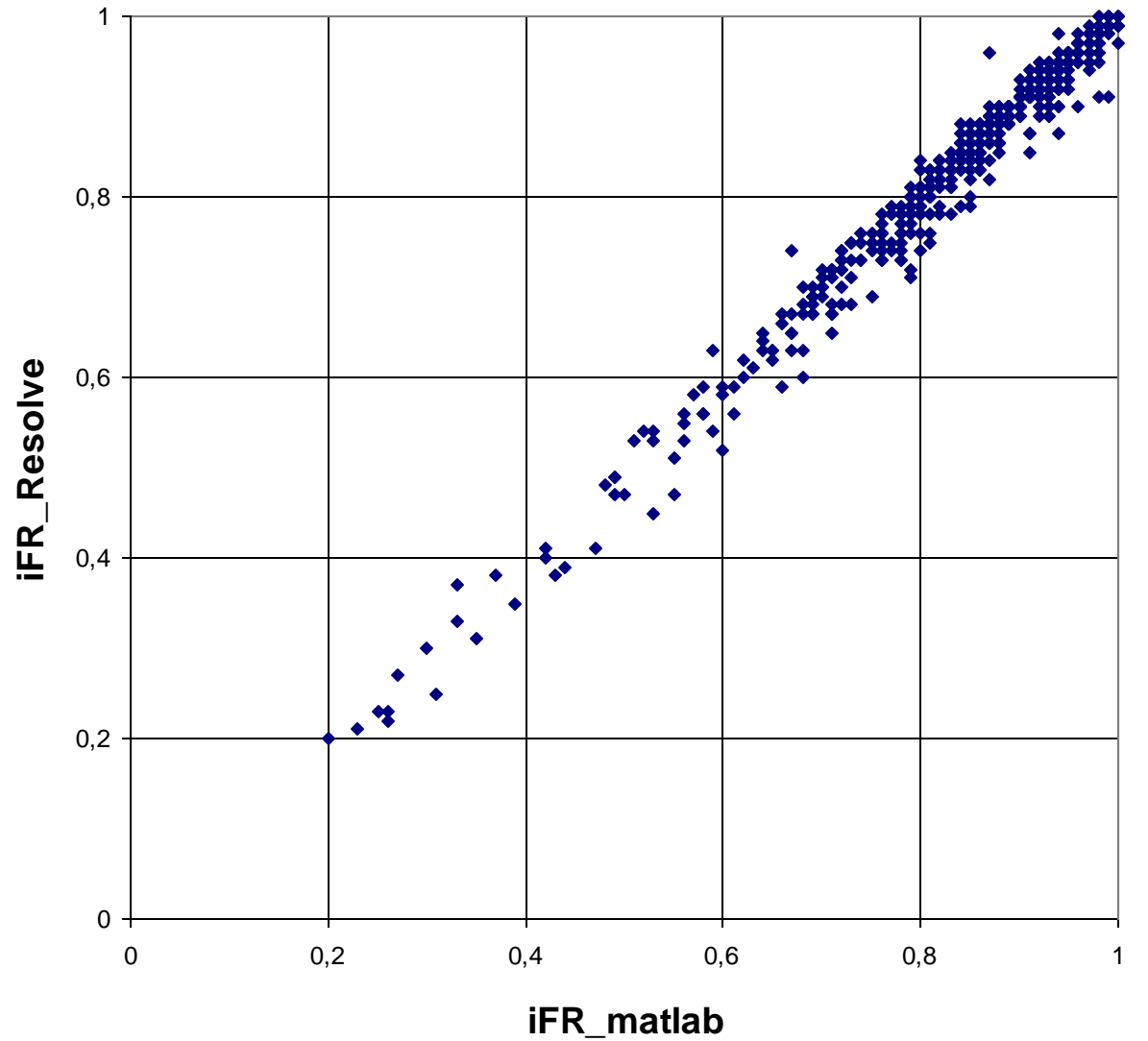
$$(iFR_{\text{volcano}} < iFR_{\text{matlab}})$$

Difference of 2 measurements  $\geq 0.1$

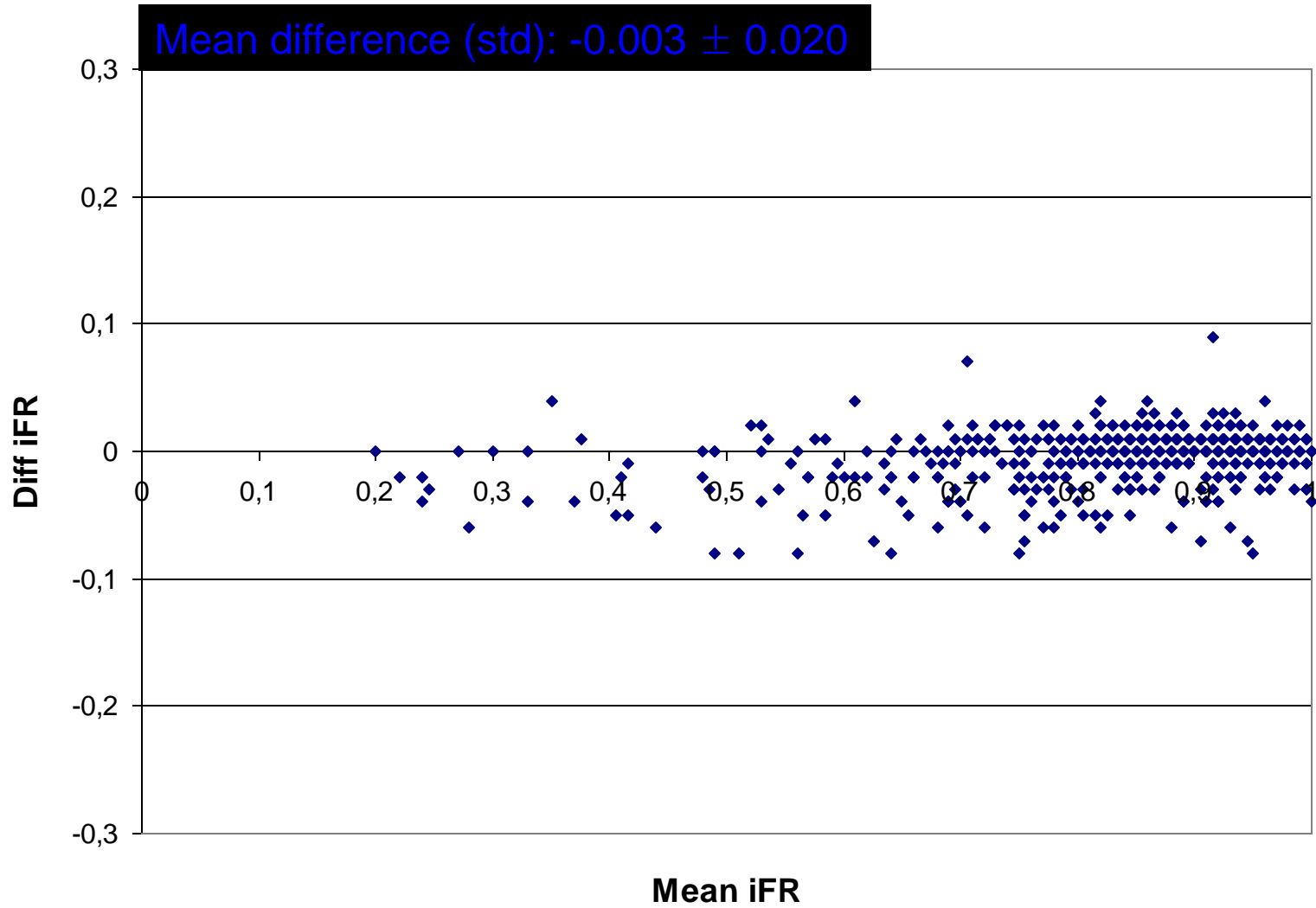
$$(iFR_{\text{volcano}} > iFR_{\text{matlab}})$$

Remain 685 measurements

# iFR comparison

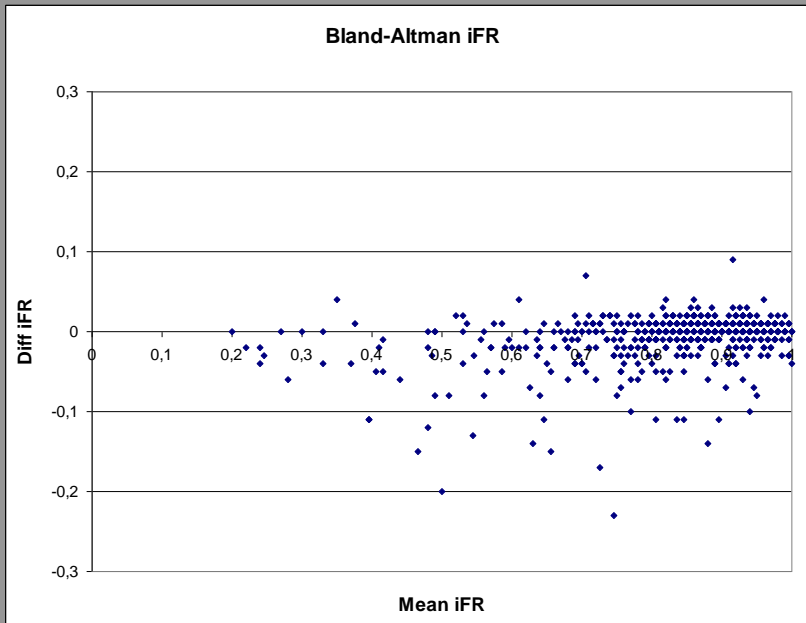


# Bland-Altman iFR



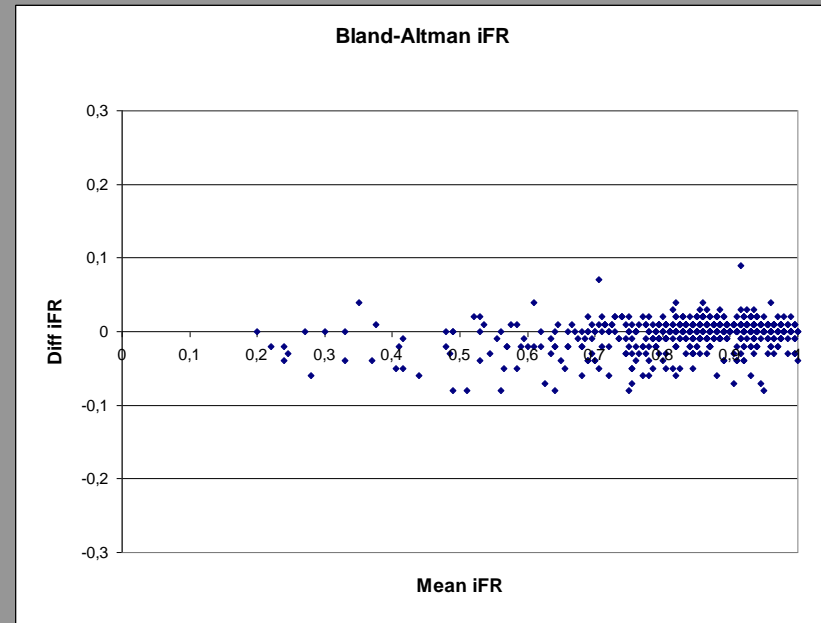
# Summary

705 measurements



Mean difference (std):  $-0.005 \pm 0.034$

685 measurements



Mean difference (std):  $-0.003 \pm 0.020$

Reproducibility; difference between two iFR measurements (Verify)

Mean difference (std):  $-0.007 \pm 0.037$



Cut-off

=

0.83

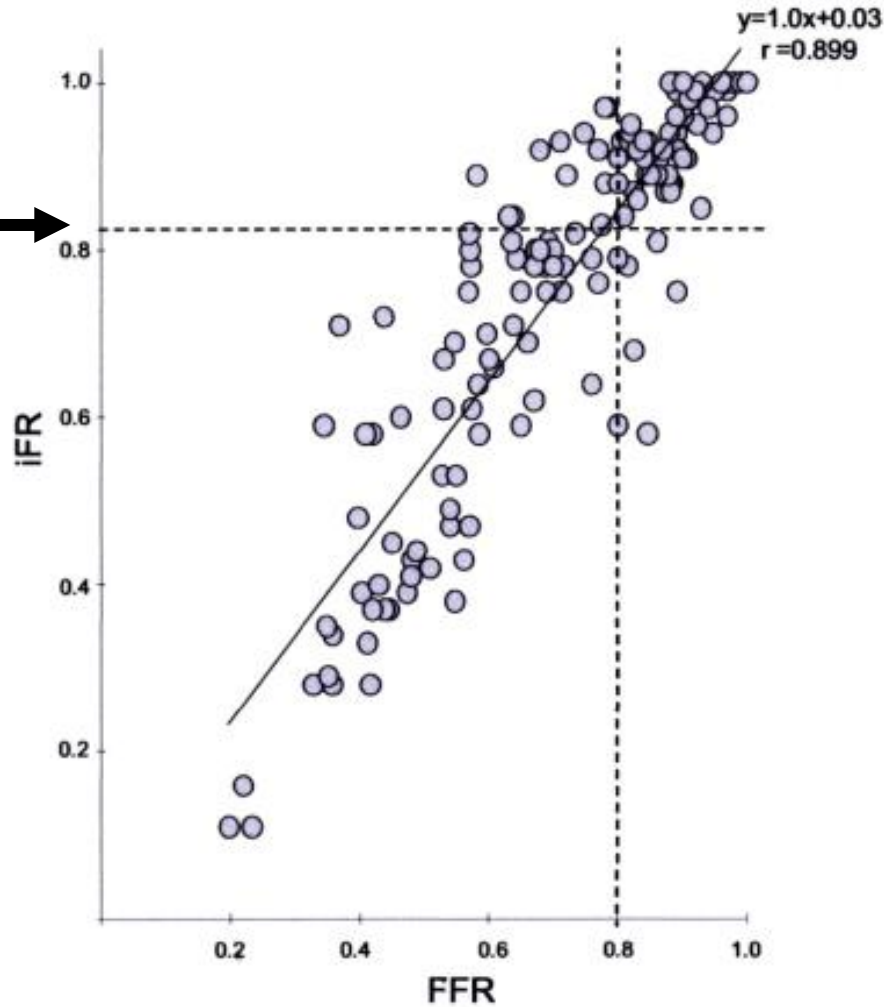


Figure 5:

**ADVISE  
STUDY  
(N= 131)**

From:  
Sen, Davies, et al  
JACC 2011

# ADVISE STUDY (N= 131)

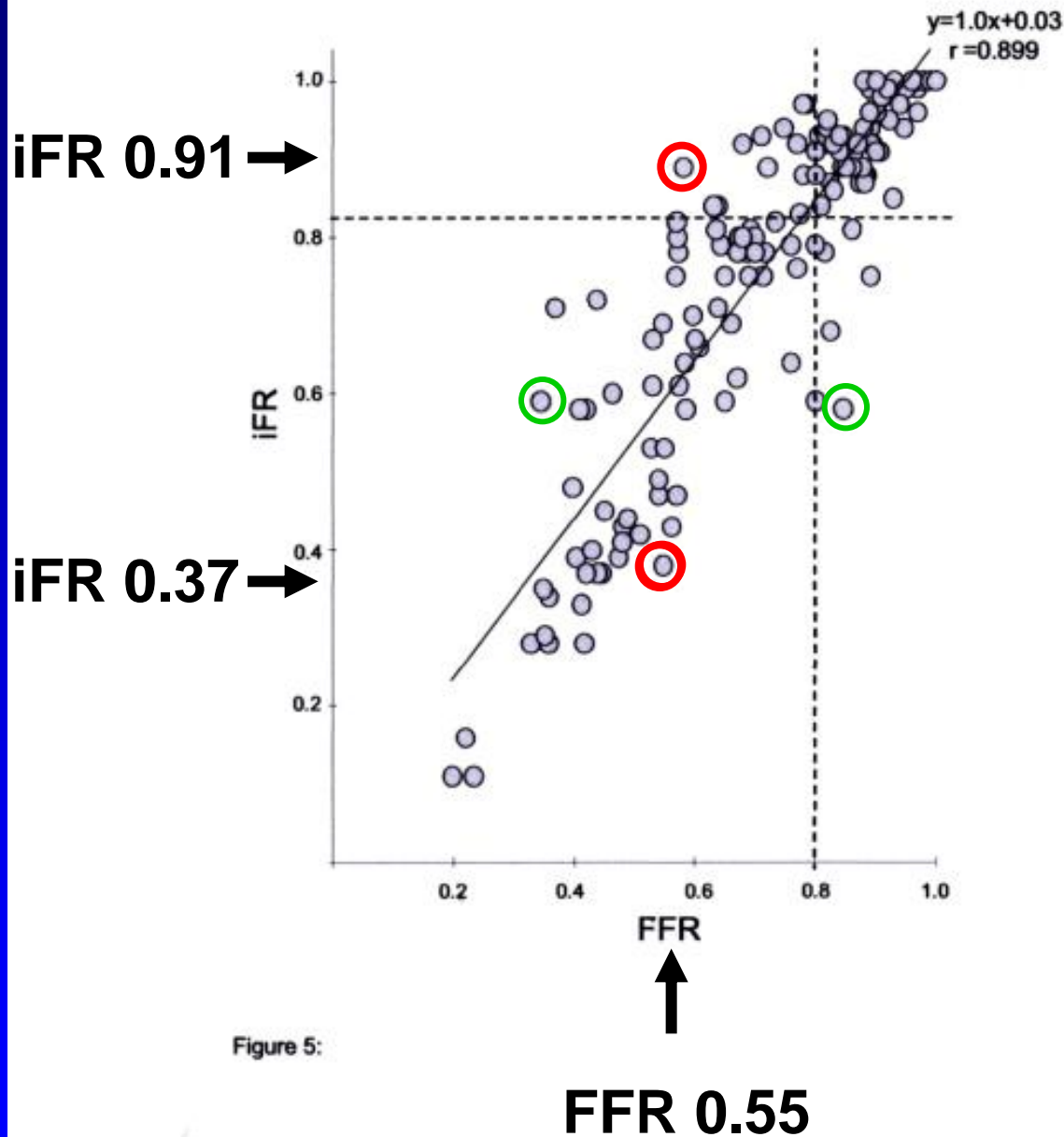


Figure 5:

From:  
Sen, Davies, et al  
JACC 2011

# ADVISE STUDY (N= 131)

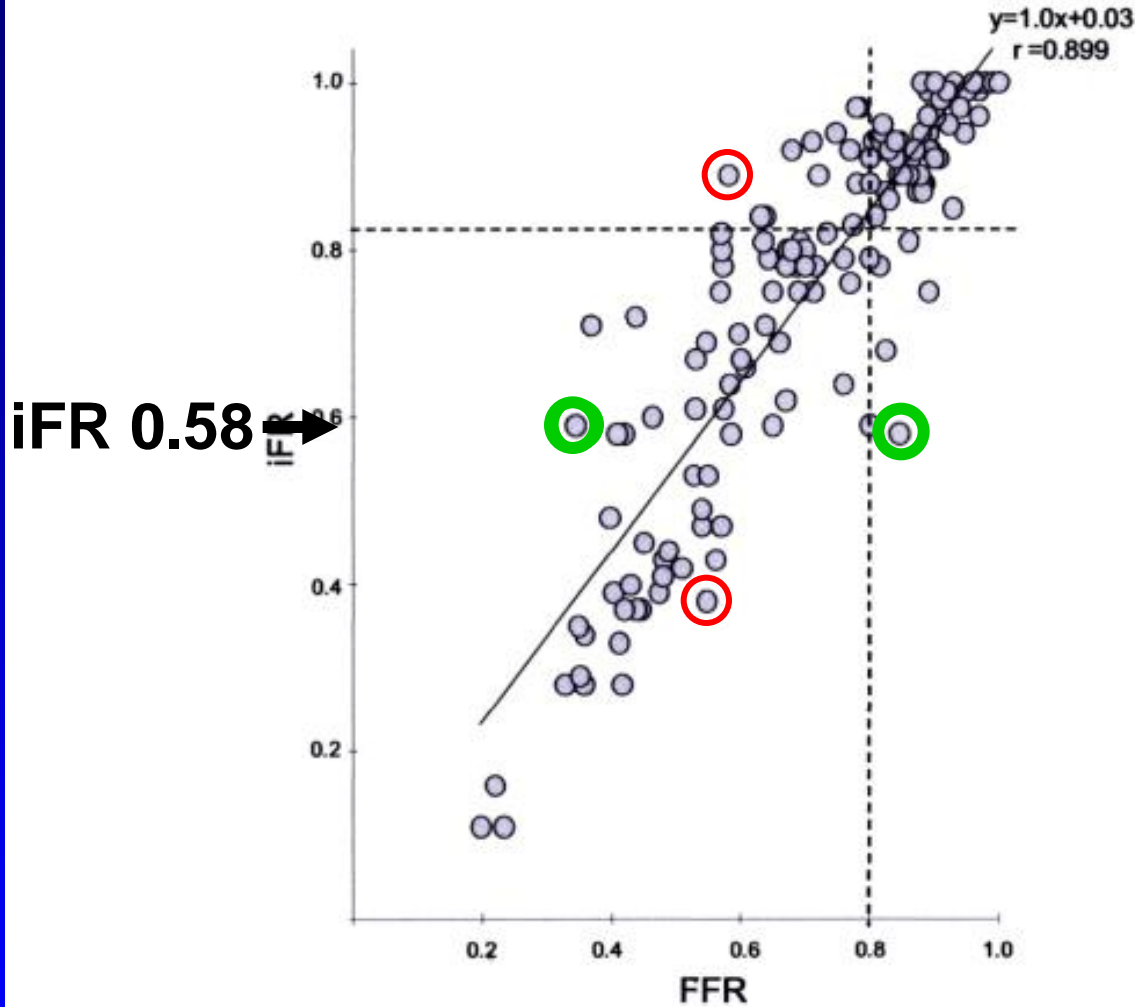


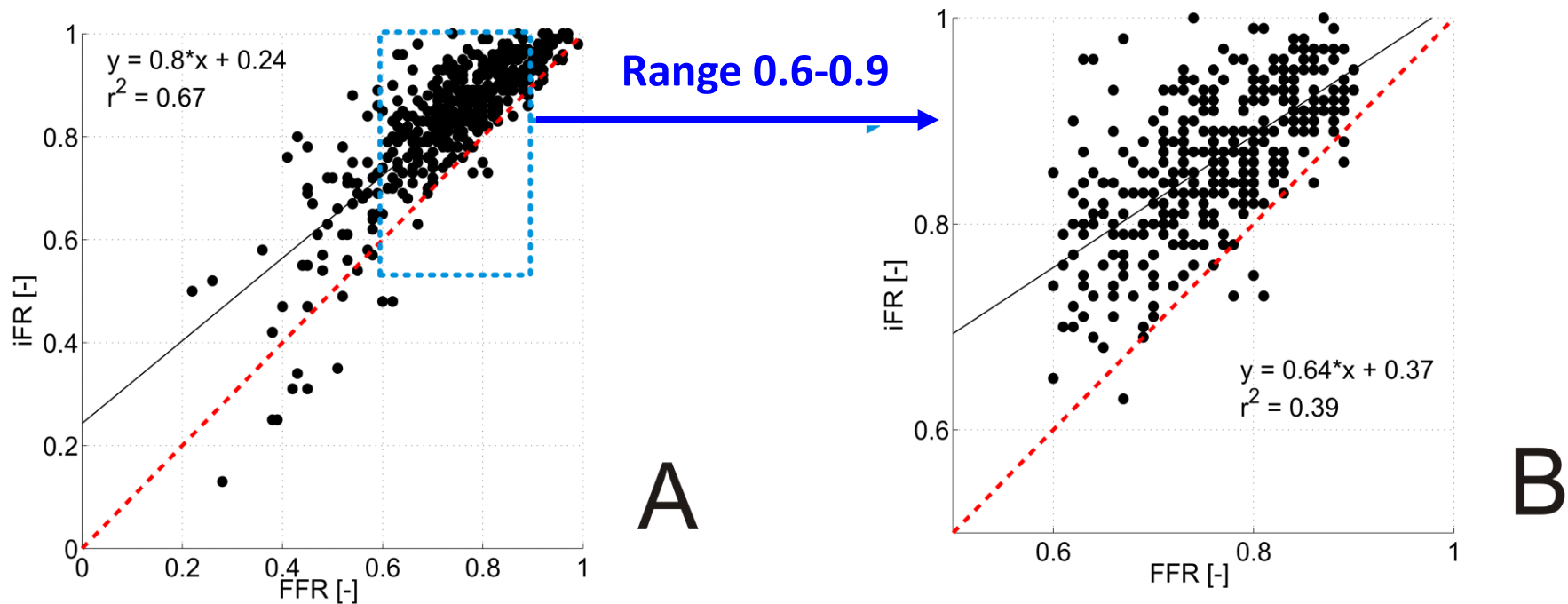
Figure 5:

↑  
**FFR 0.34**

↑  
**FFR 0.87**

From:  
Sen, Davies, et al  
JACC 2011

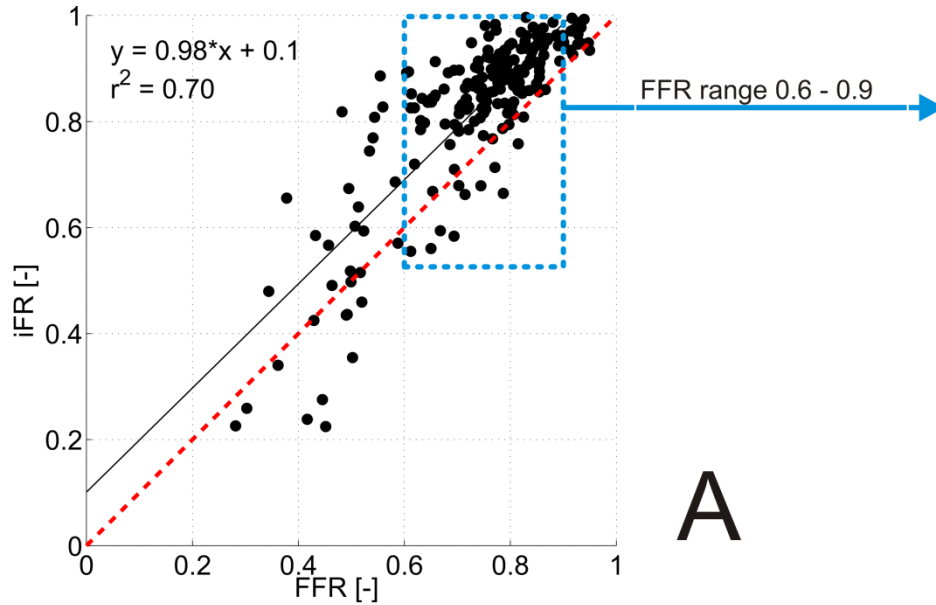
# Retrospective analysis IFR versus FFR in retrospective analysis in 500 patients in Aalst and Eindhoven



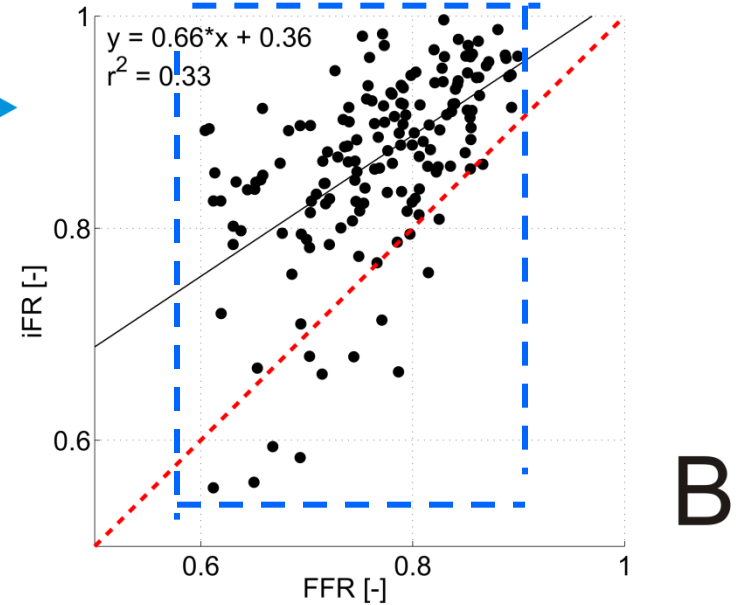
all data:  $R^2 = 0.67$   
diagn accuracy = 66 %

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

# Correlation between iFR and FFR ( N=206)



A



B

diagn accuracy = 67 %

**diagn accuracy = 58 %**

*(diagnostic accuracy of flipping a coin = 50 %)*

# ADVISE STUDY (N= 131)

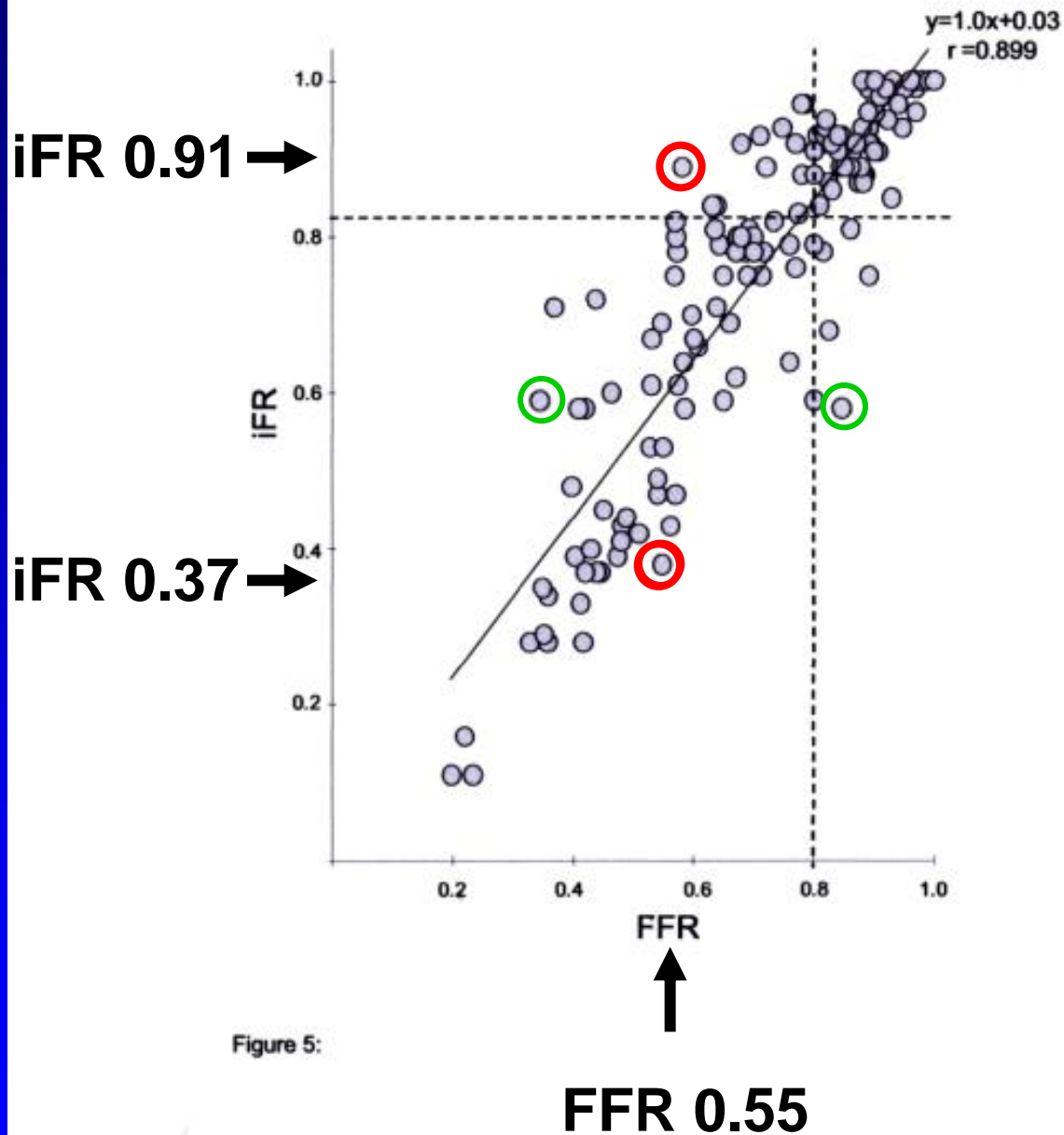


Figure 5:

From:  
Sen, Davies, et al  
JACC 2011

# ADVISE STUDY (N= 131)

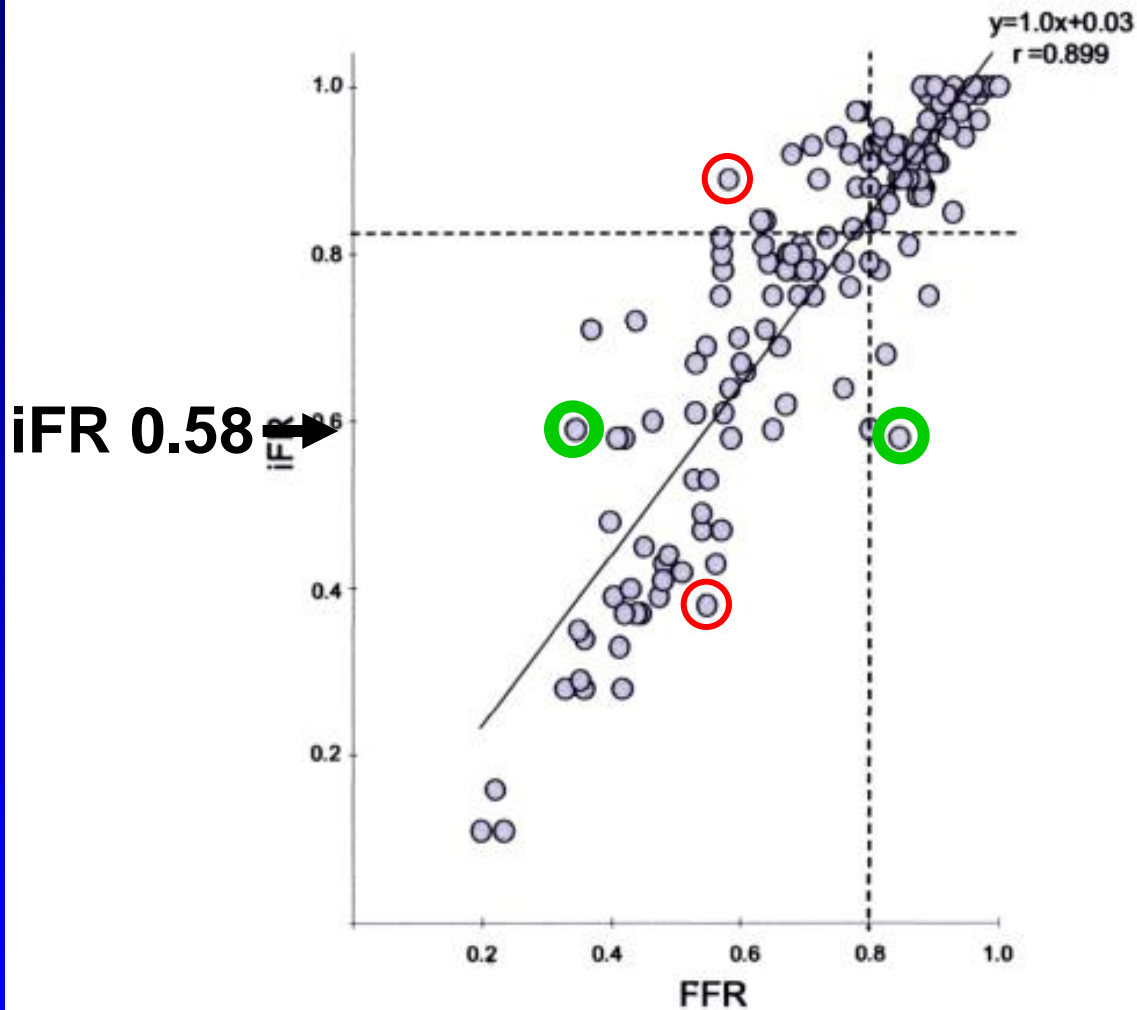


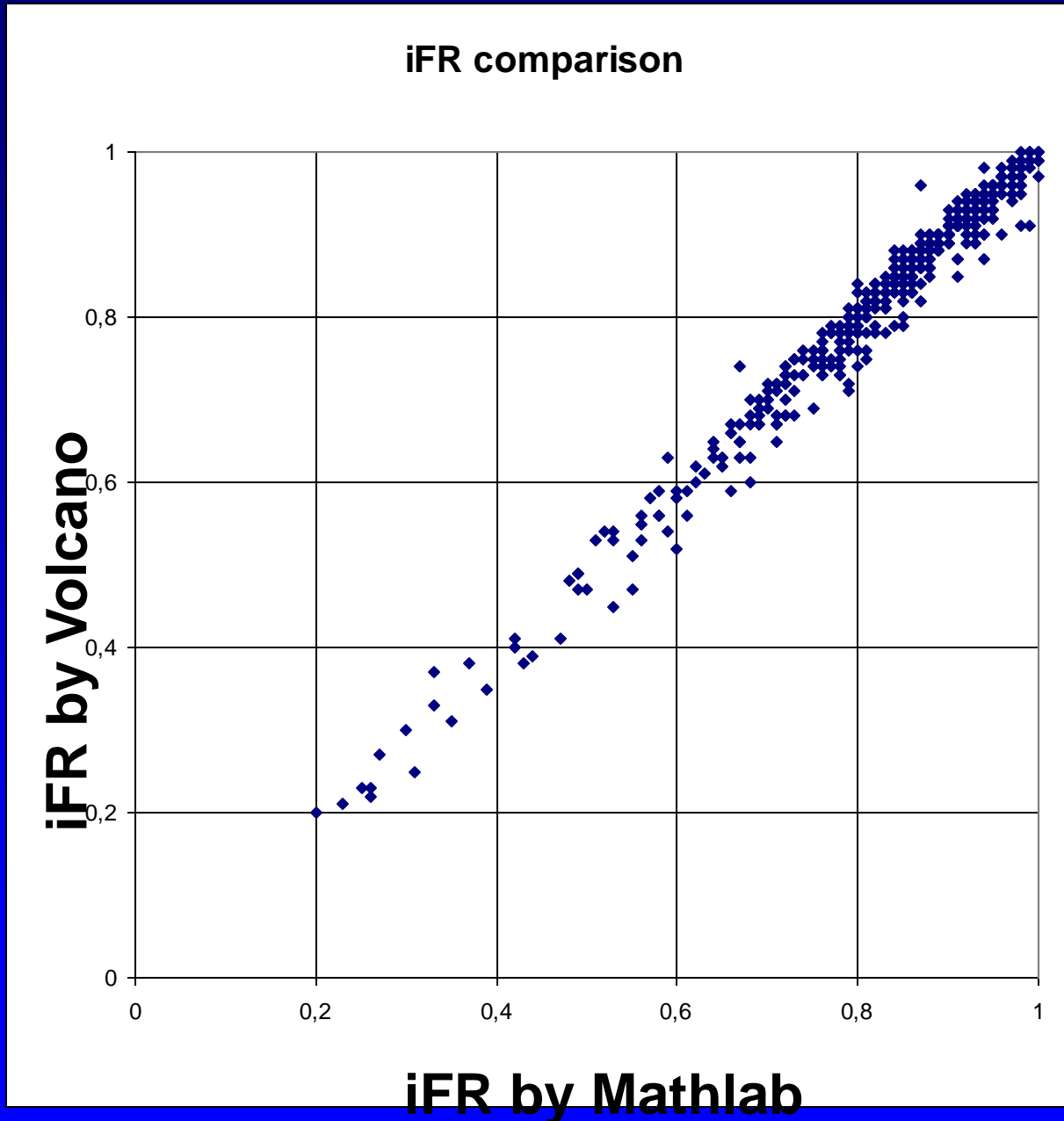
Figure 5:

↑  
**FFR 0.34**

↑  
**FFR 0.87**

From:  
Sen, Davies, et al  
JACC 2011

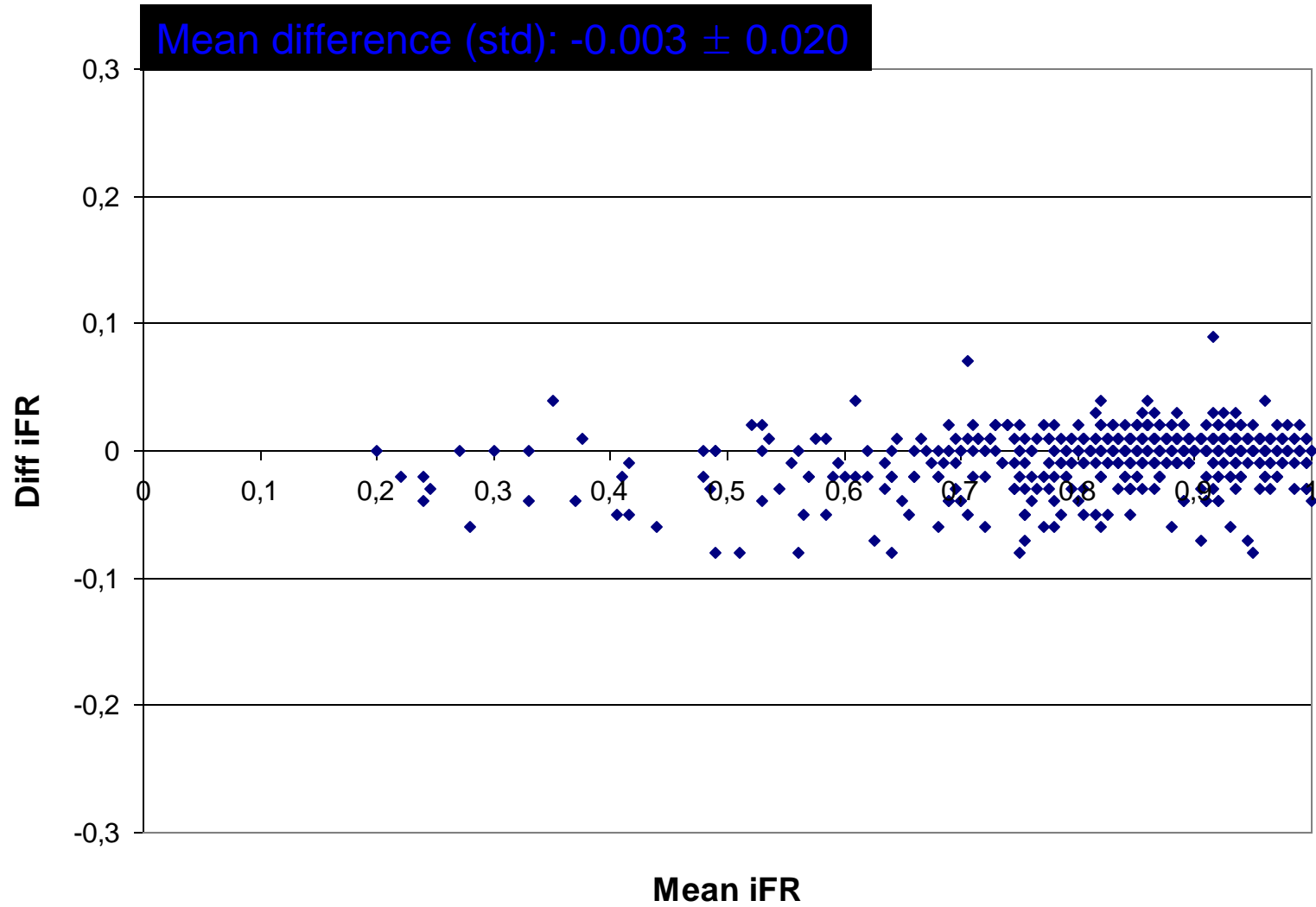
N=685



Berry et al  
JACC 2013;



# Bland-Altman iFR



# Overall Precision

## *Proportion of Patients with 90% Precision*

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

## *Proportion of Patients with 95% Precision*

	<b>PPV</b>	<b>NPV</b>	<b>Total</b>
<b>iFR</b>	24.3%	--	24.3%
<b>Pd/Pa</b>	33.4%	--	33.4%

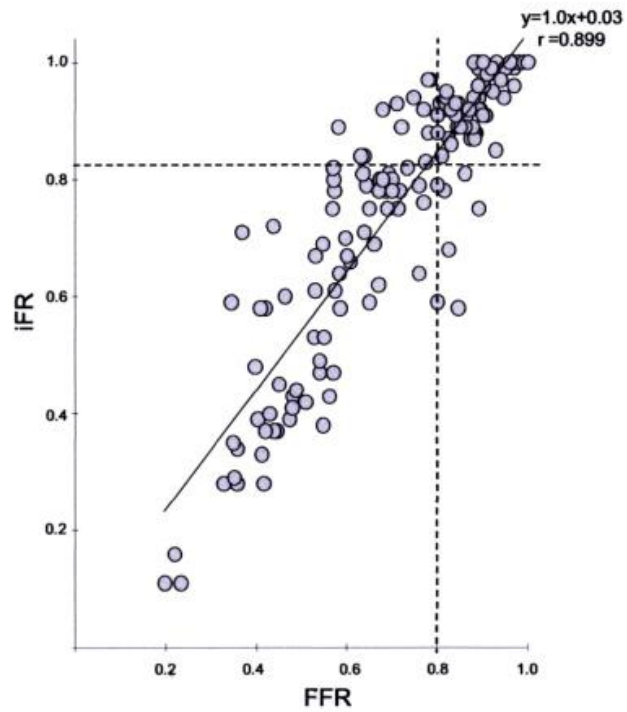
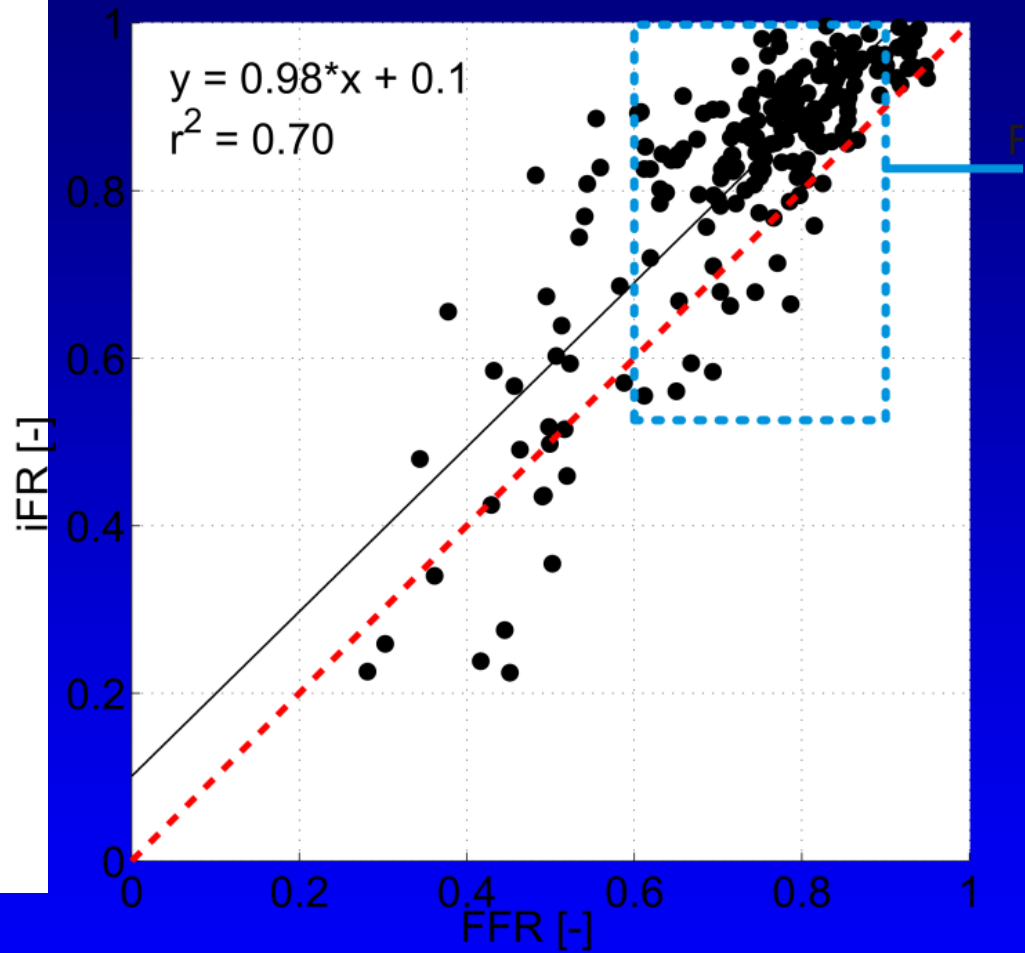


Figure 5:



FFR 0.55

# Volumetric coronary blood flow

*Q<sub>phasic</sub>*

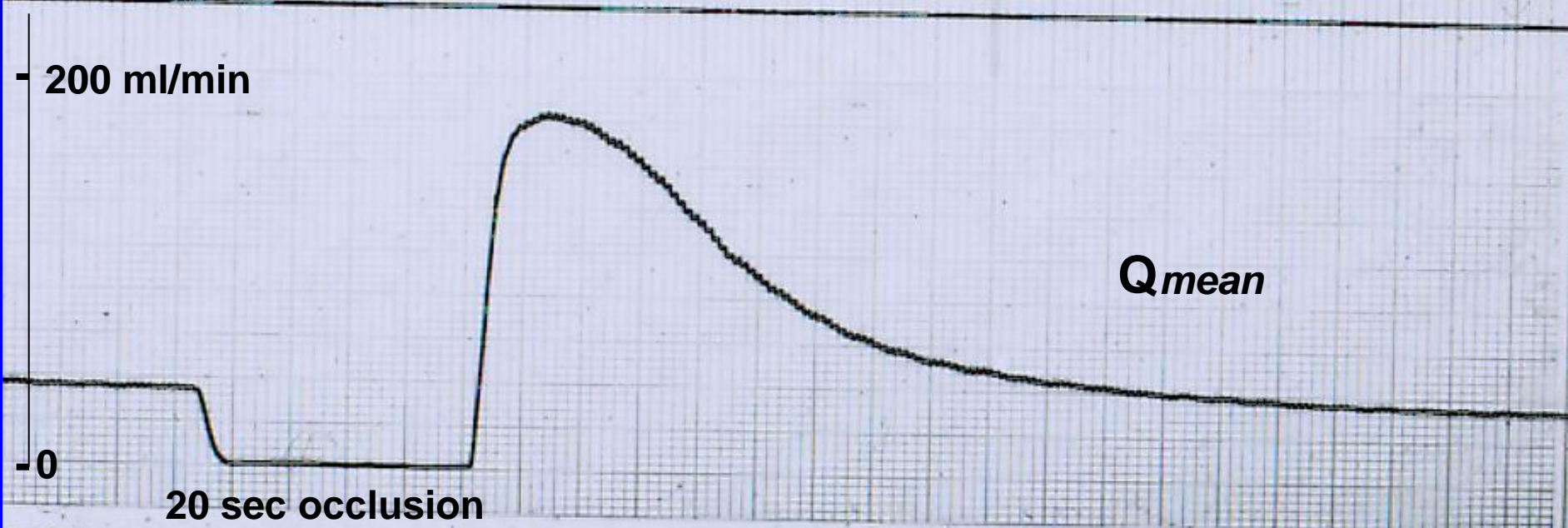


- 200 ml/min

- 0

20 sec occlusion

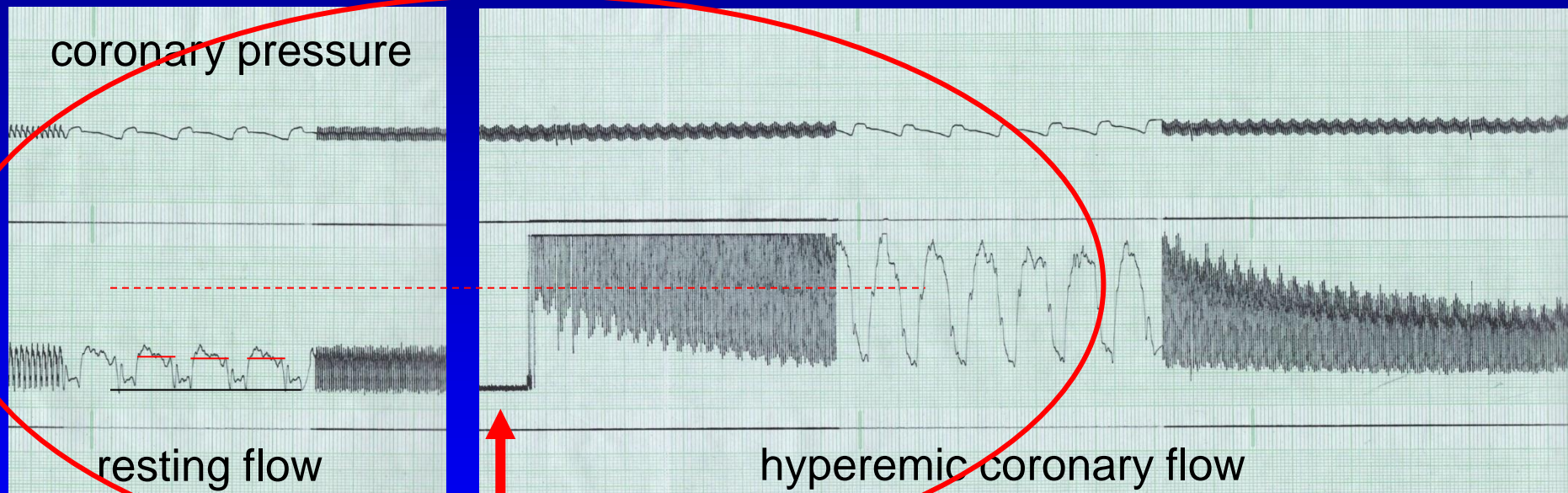
*Q<sub>mean</sub>*



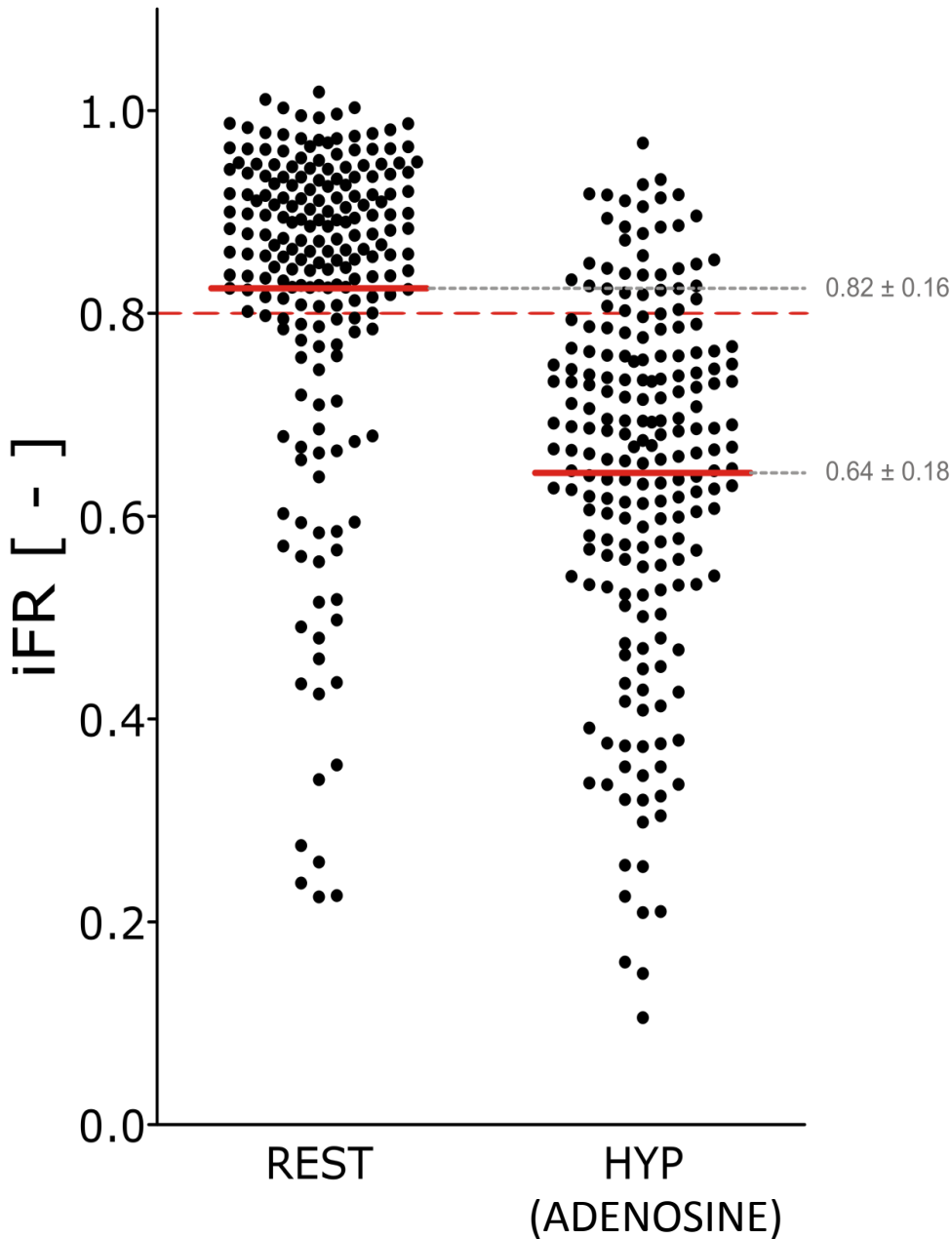


In the presence of constant coronary pressure

$$\longrightarrow R \sim 1 / \text{Flow}$$



coronary occlusion



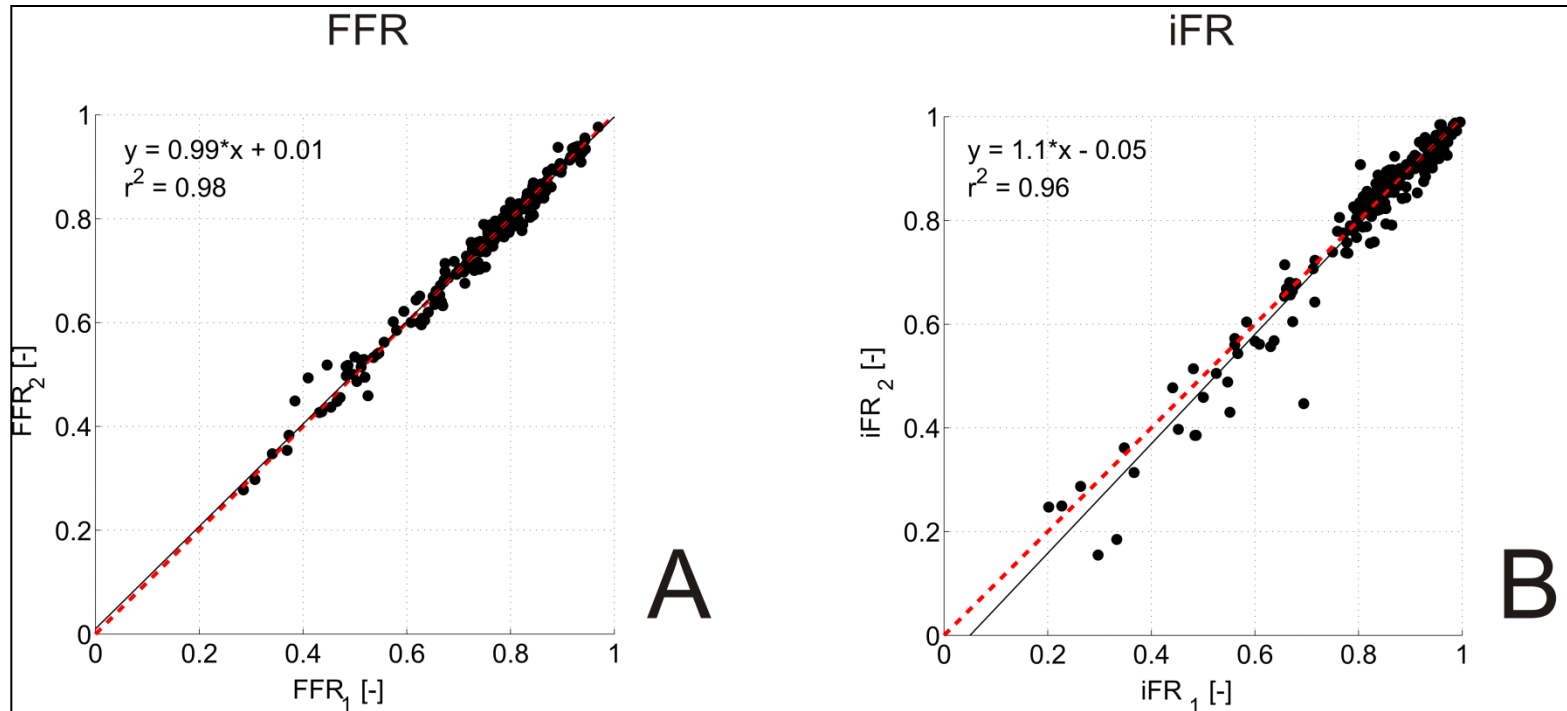
profound influence of hyperemia on iFR:

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

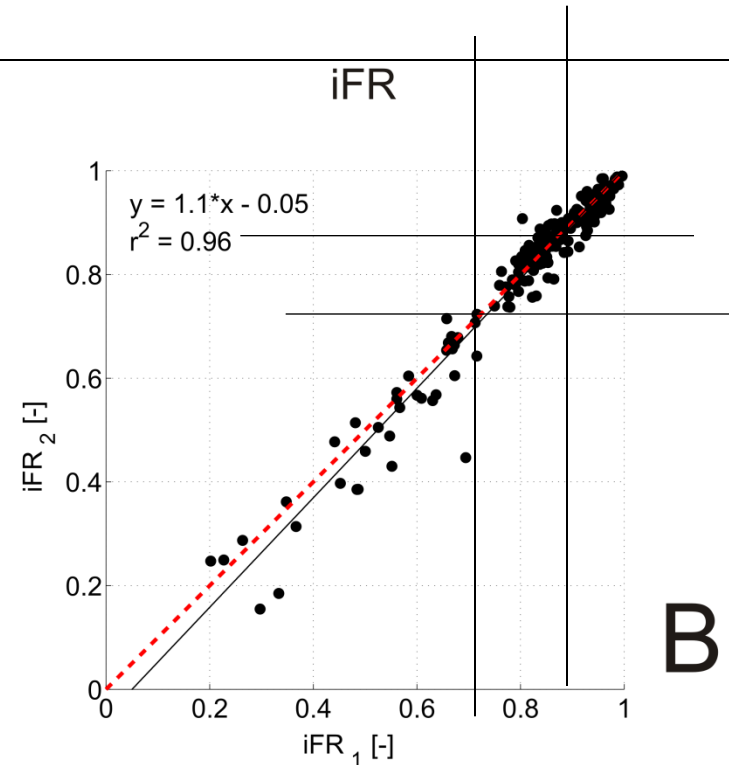
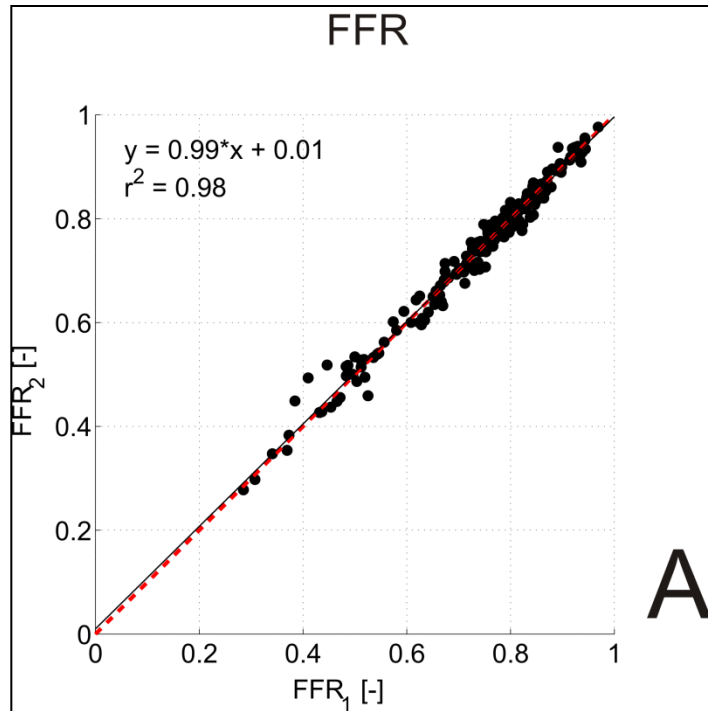
estimated decrease of resistance during “wave-free period”

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

# Reproducibility of FFR and iFR



# Reproducibility of FFR and iFR





Cut-off

=

0.83

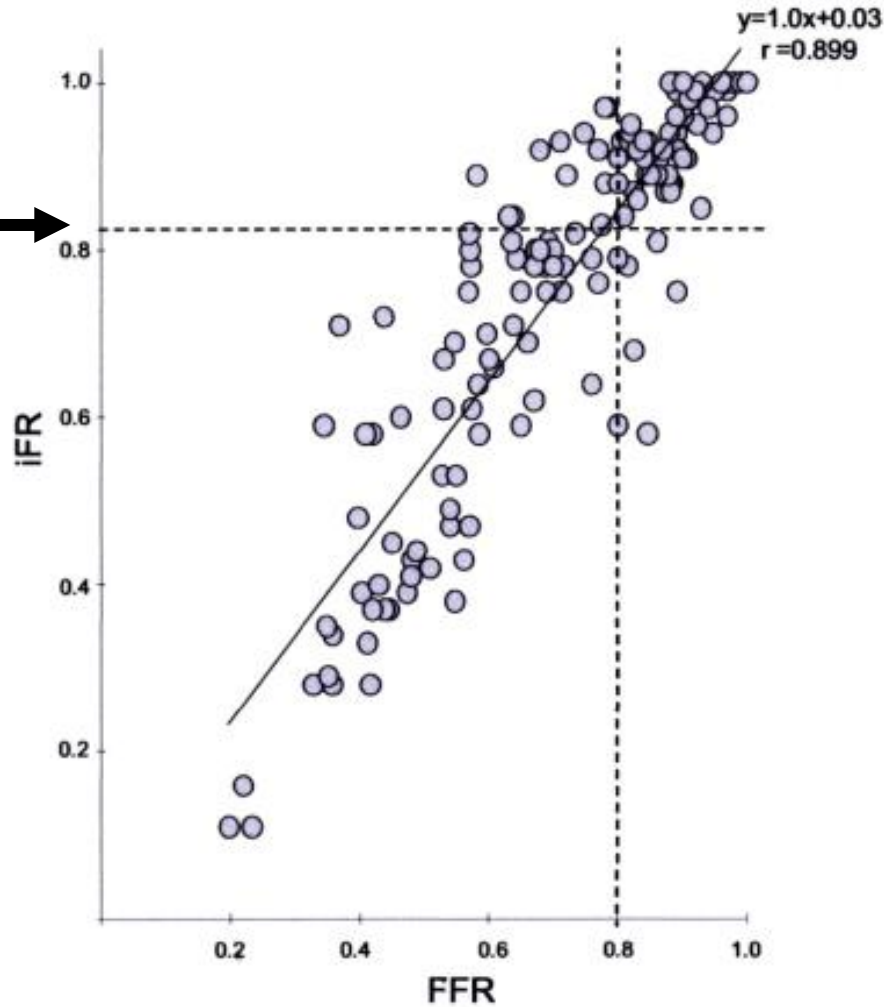


Figure 5:

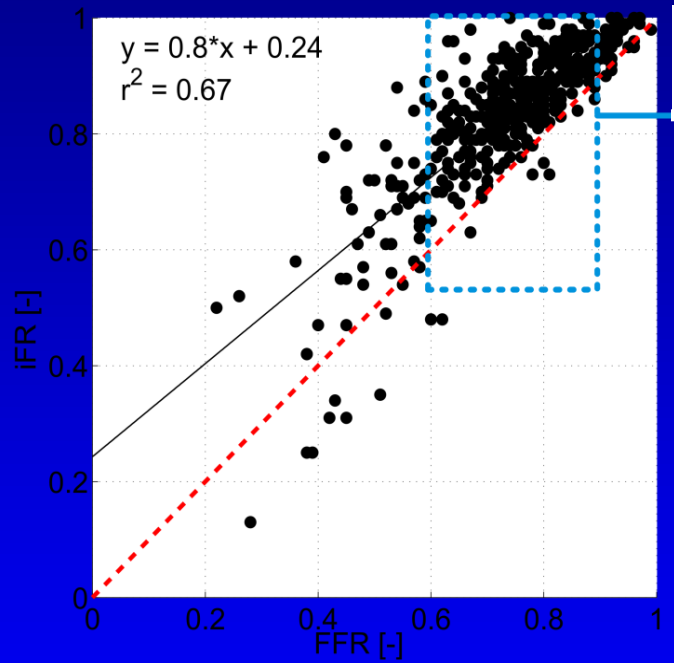
**ADVISE  
STUDY  
(N= 131)**

From:  
Sen, Davies, et al  
JACC 2011

## Retrospective analysis

### IFR versus FFR in 500 patients

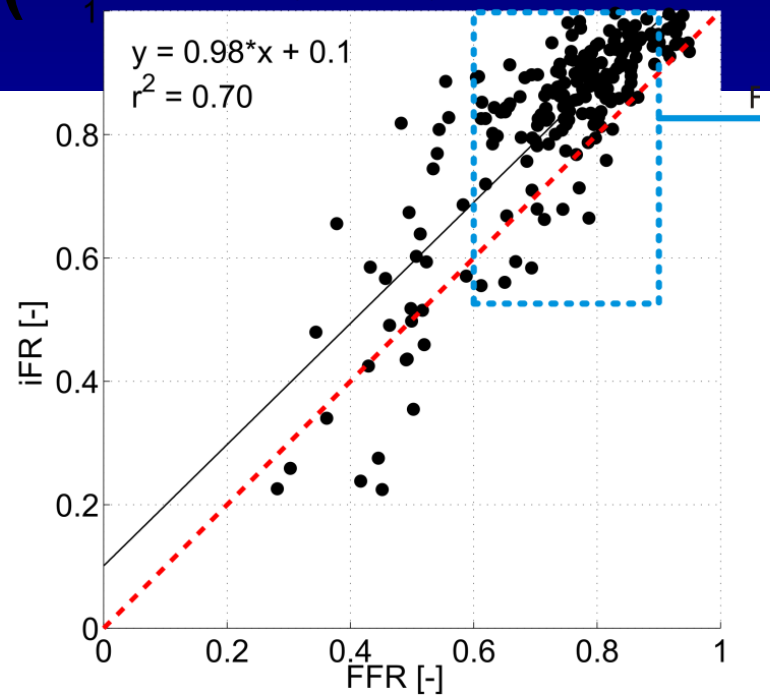
( VERIFY study, Berry et al, JACC 2013)



## Prospective analysis

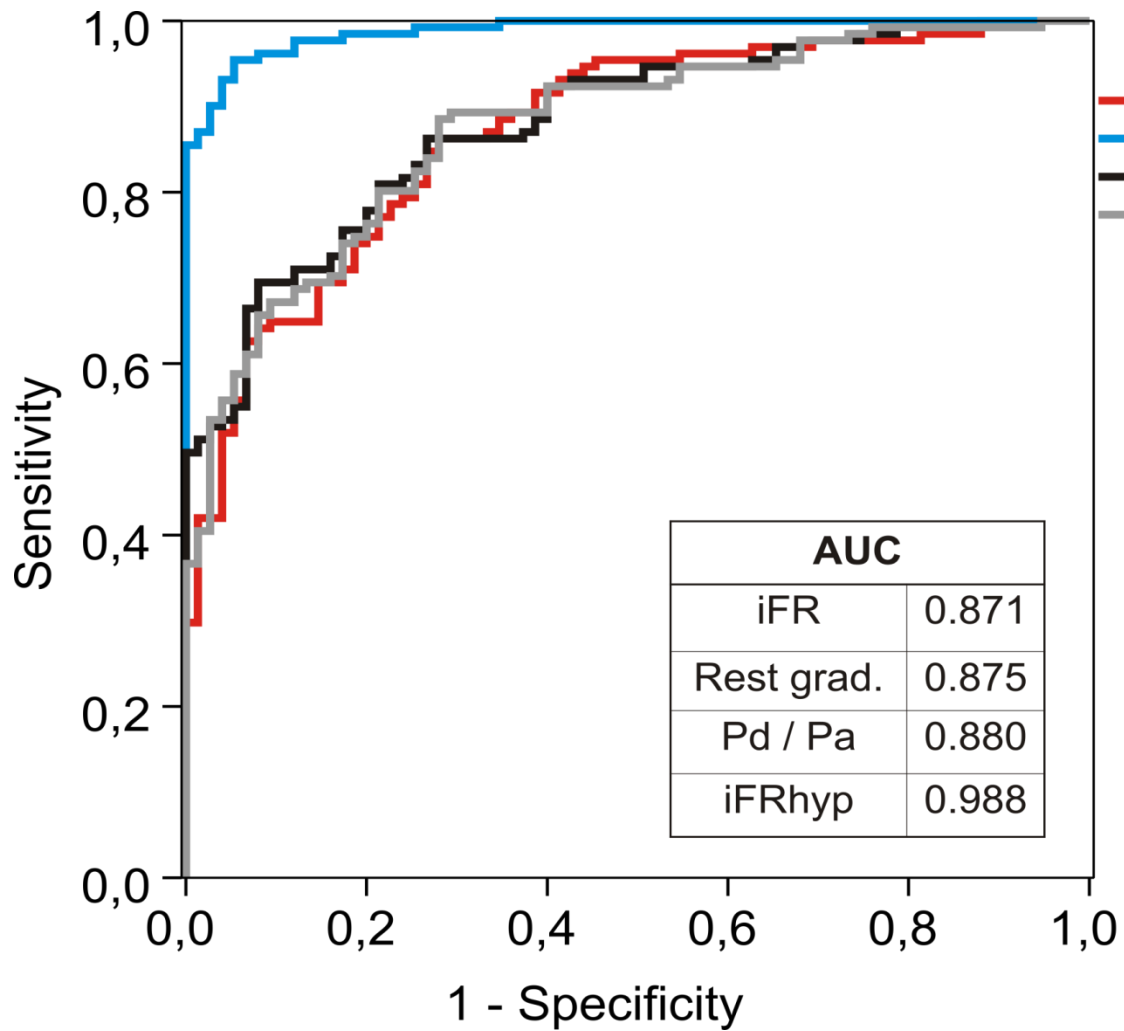
### IFR versus FFR in 205 patients

( VERIFY study, Berry et al, JACC 2013)



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

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



— iFR  
— iFRhyp  
— PdPa  
— Rest gradient

~  $FFR_{diast}$   
*defined by Abe,*  
*Circulation 2000*  
*threshold 0.76*

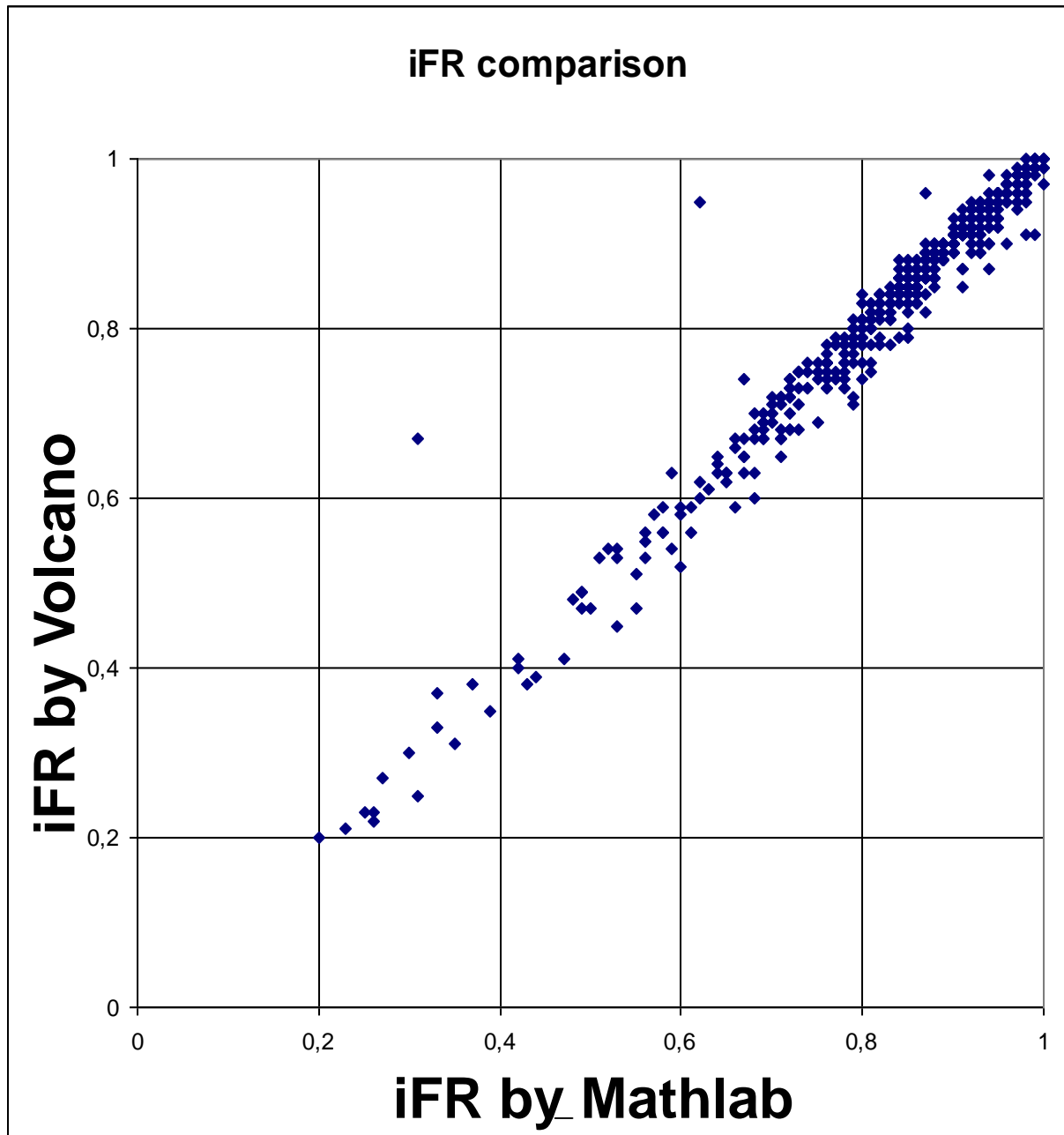
# CALCULATION OF iFR: VOLCANO BOX vs MATLAB *DOES IT MATTER ?*

VERIFY STUDY: 705 resting and hyperemic tracings

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

Calculation by the Volcano algorithm blinded for the  
results by Matlab  
(CRF, New York)

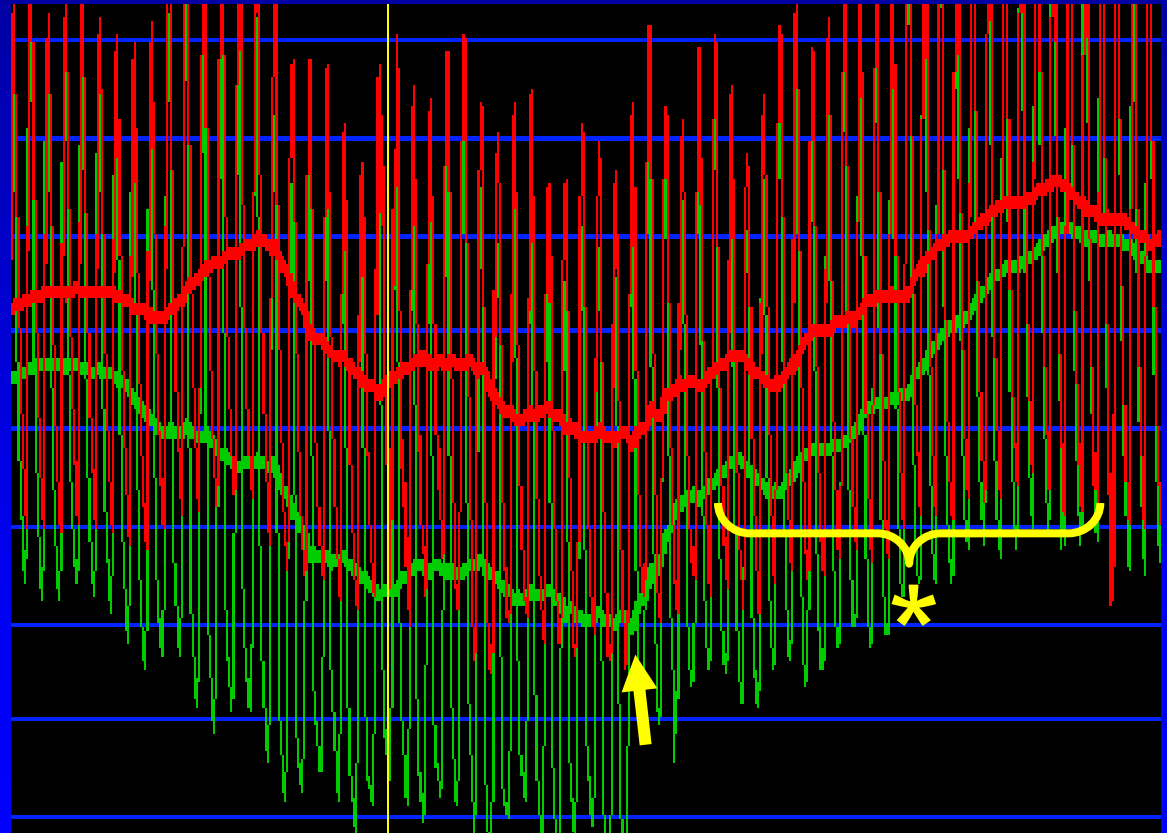
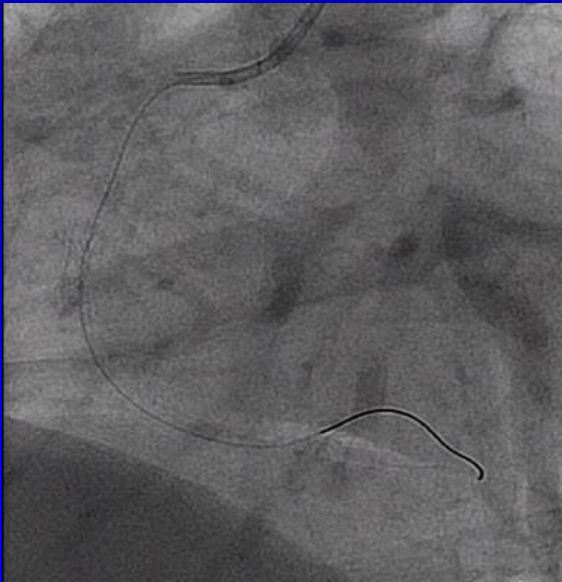
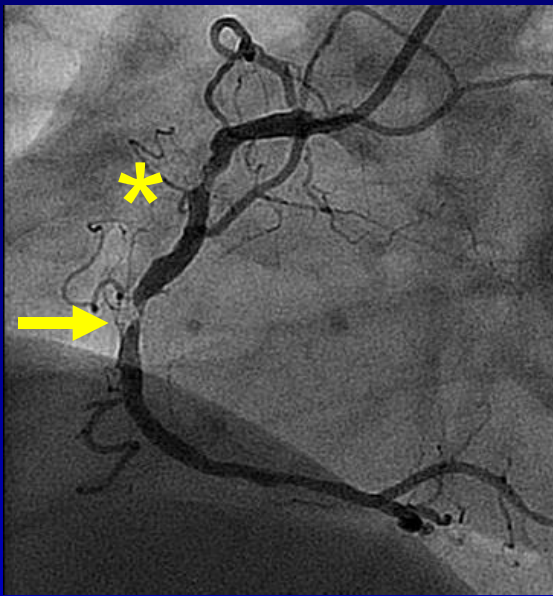
**From:  
VERIFY  
N=705**



Berry et al  
JACC 2013;

# “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

# 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  $\Delta P$ ,  $P_d/P_a$  *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***