

FFR

Hyperemia and Standardization

**Bernard De Bruyne
Cardiovascular Center Aalst
Belgium**

Hyperemic Stimuli

Why ?

How ?

FAQ !

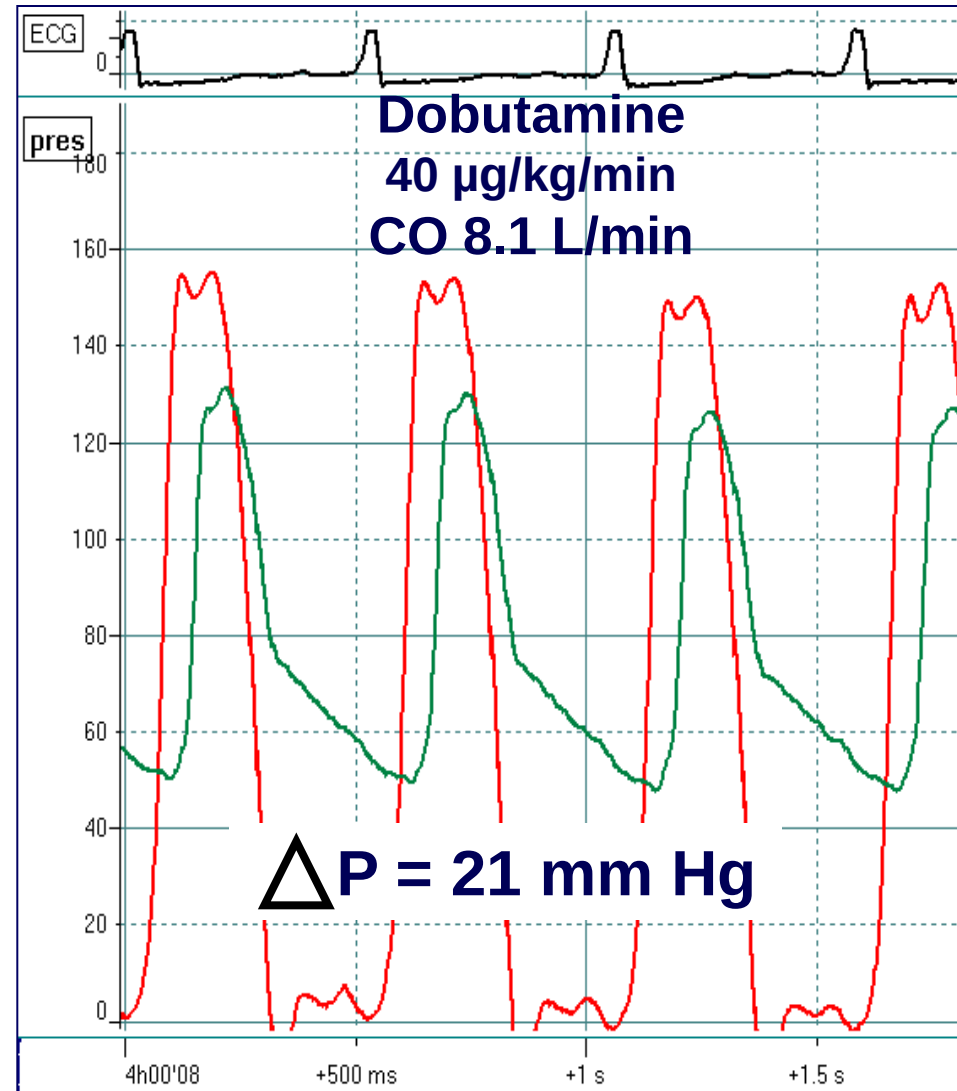
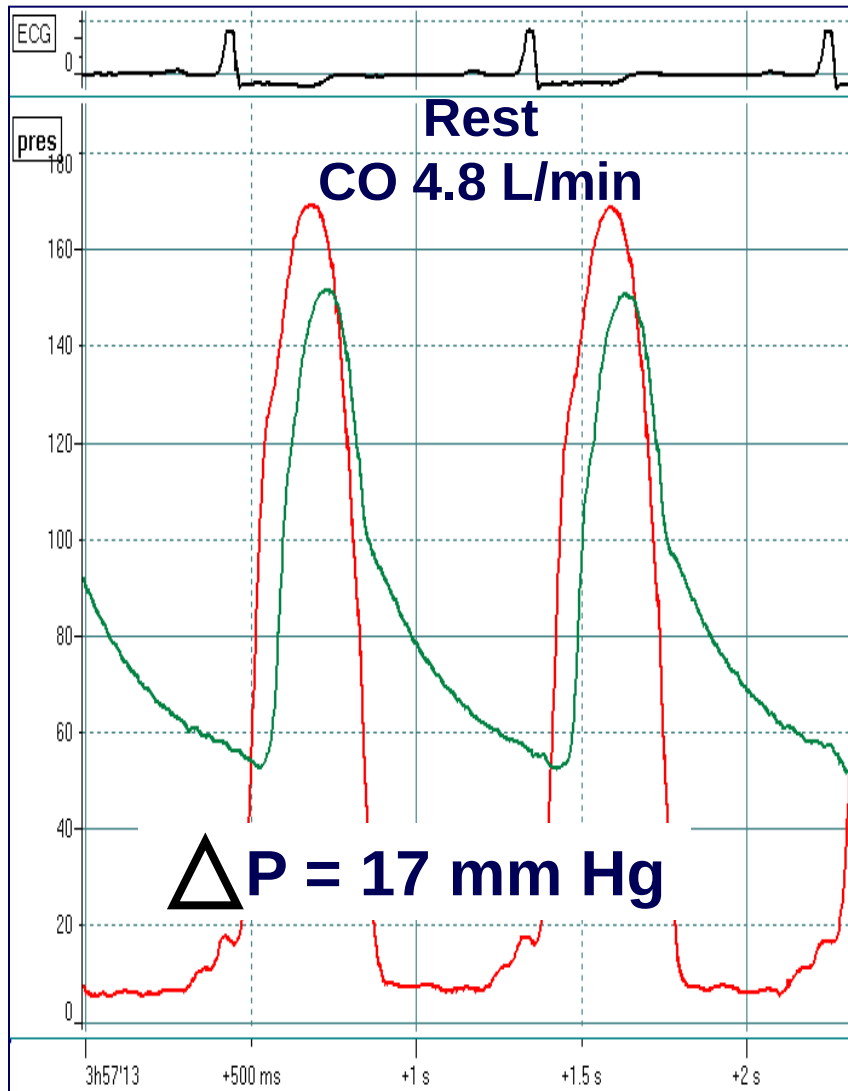
**Bernard De Bruyne, MD, PhD
Cardiovascular Center Aalst
OLV-Clinic Aalst, Belgium**

Why?

1. **General concept of stress test (as opposed to “rest test”)**
2. **Standardized measurements (as opposed to “moving target”)**
3. **Rest vs hyperemia = window towards the microvasculature**
4. **All clinical outcome data are based on hyperemic data (FFR)**

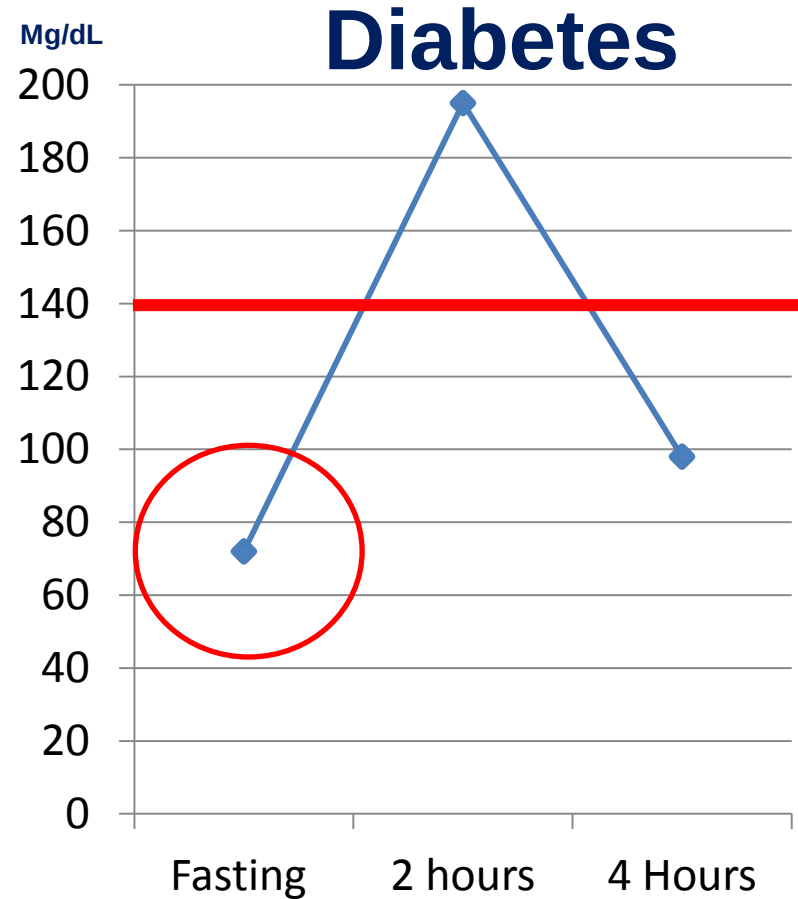
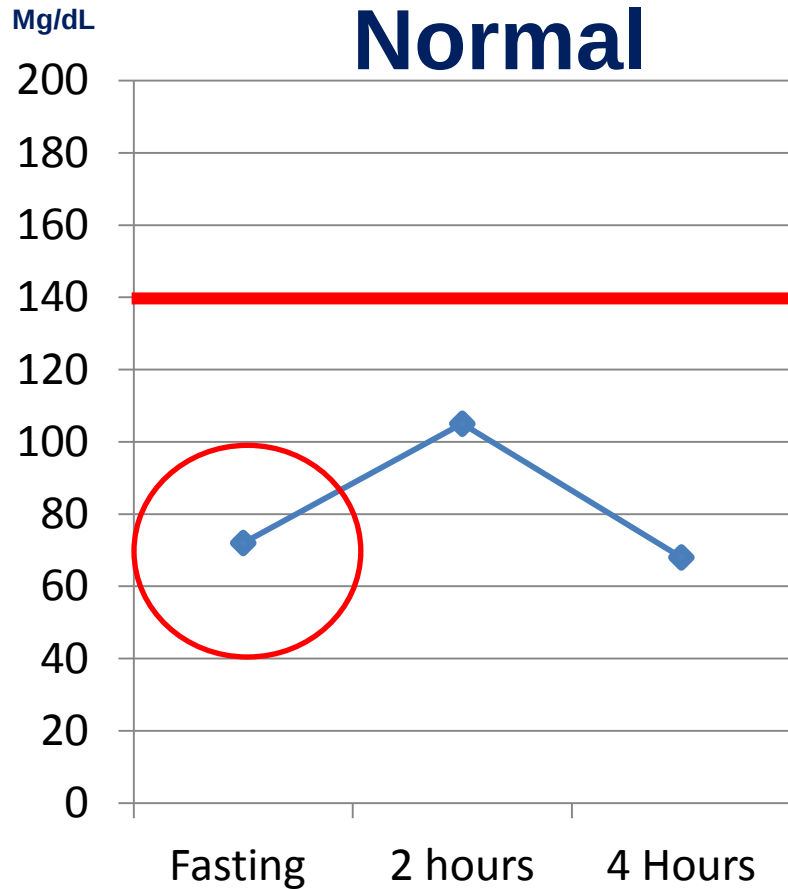
General concept of stress test

Mild Aortic Stenosis



General concept of stress test Diabetes

Oral Glucose Tolerance Test:
75 g of sugar to be drunk within 5 minutes



General concept of stress test

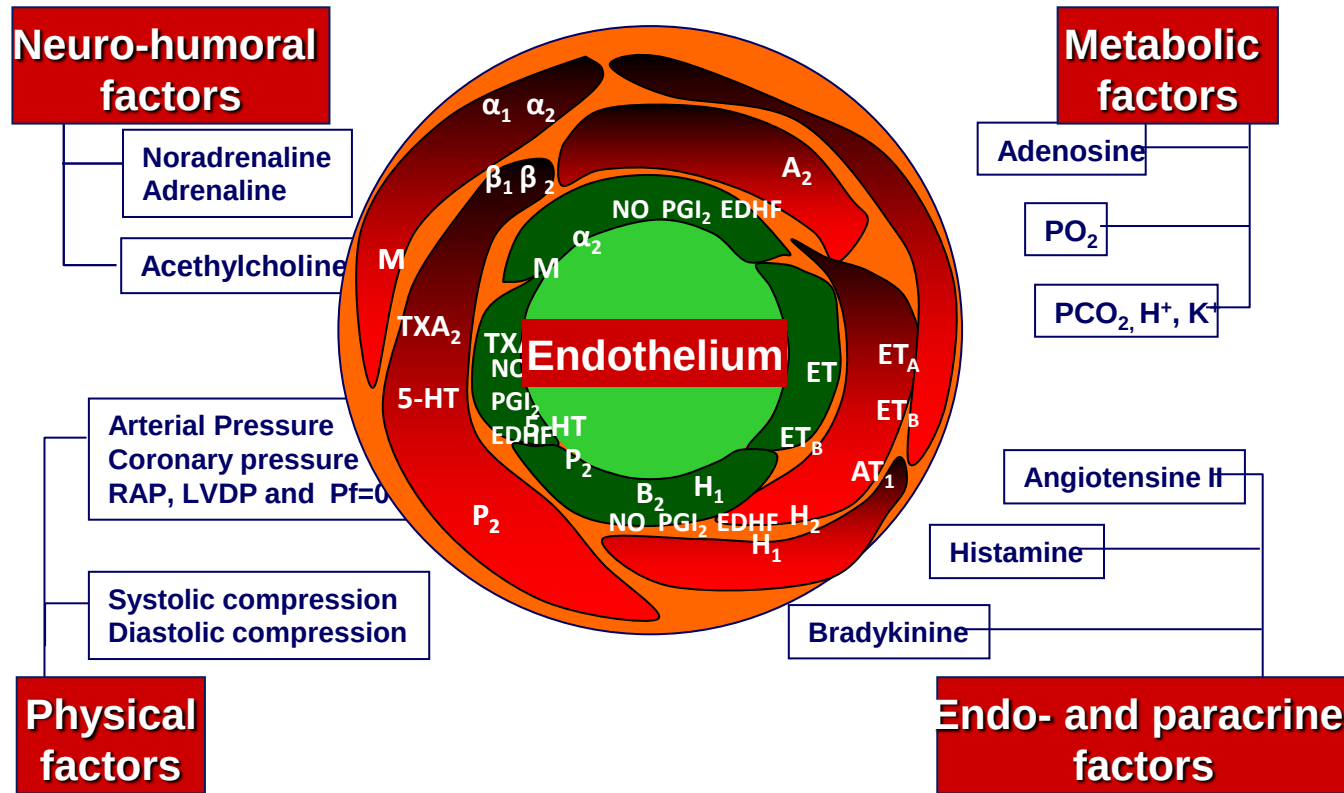
The Wind Tunnel



Why?

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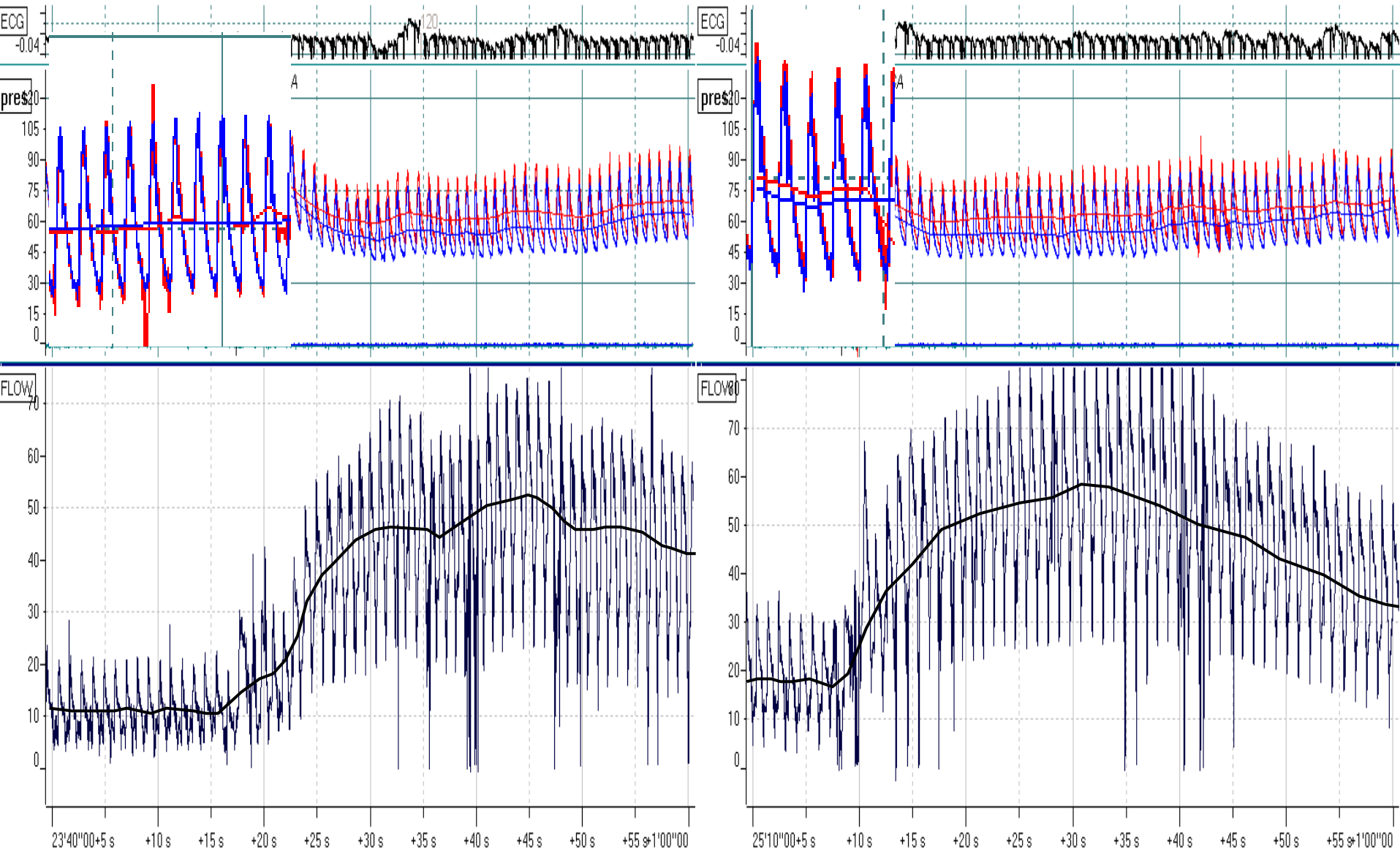
The Control of Resting Myocardial Blood Flow



The “resting state” in biology is wishful thinking of biologists

‘Rest’ is almost never ‘steady state’

The Control of Resting Myocardial Blood Flow

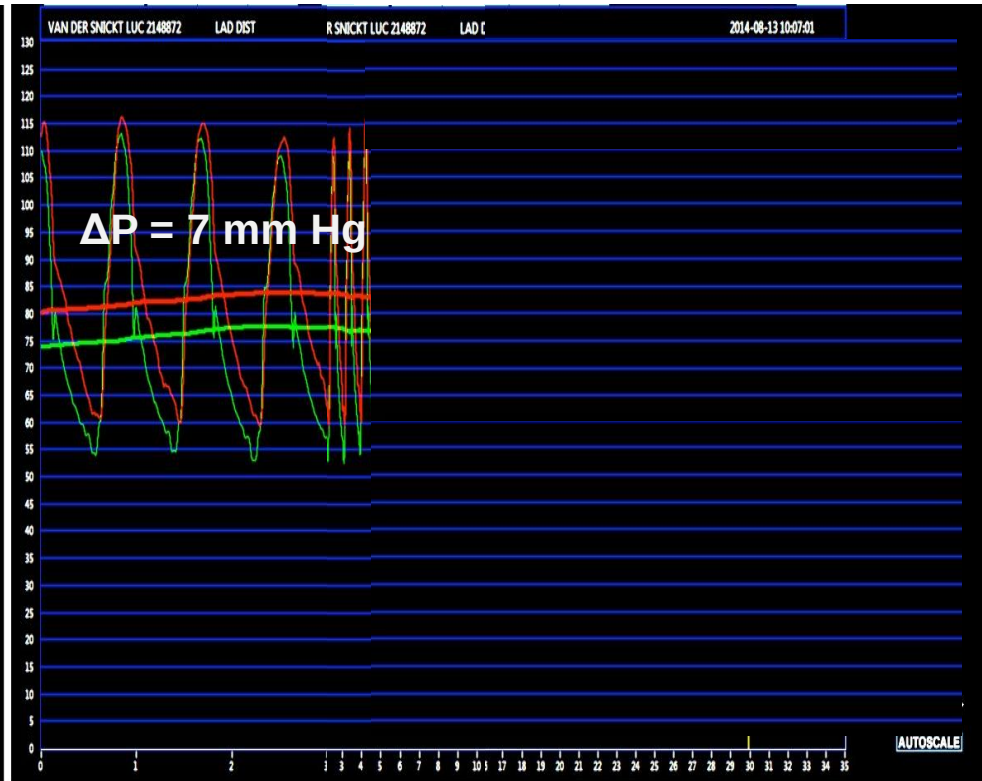
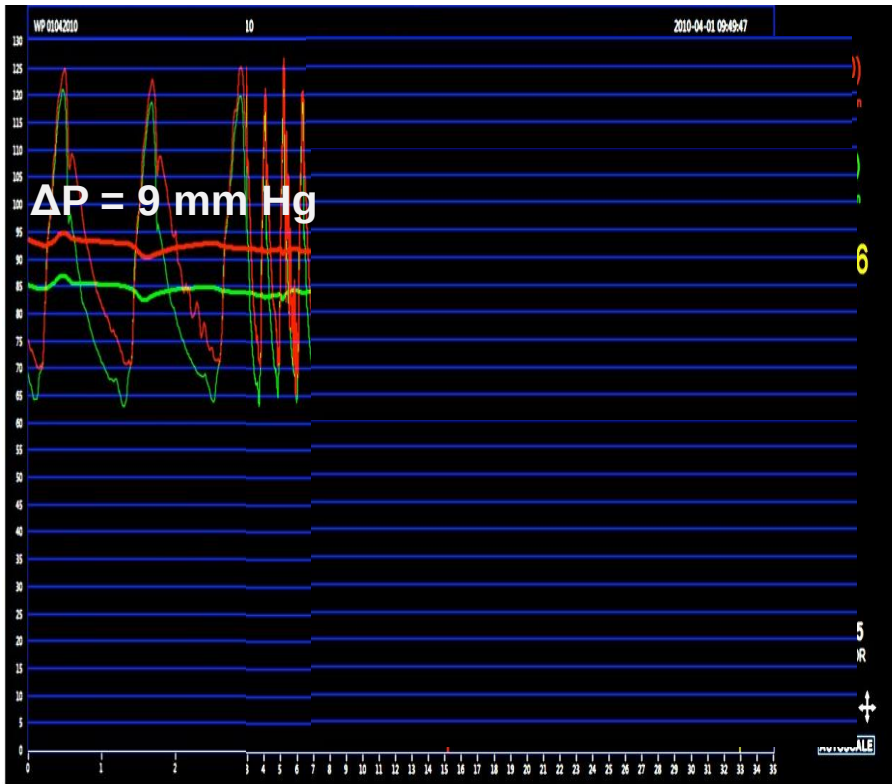


Why?

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Hyperemia

A window towards the microvasculature



Resting gradient is similar but the hyperemic gradient is very different

Largely due to a difference in microvascular function

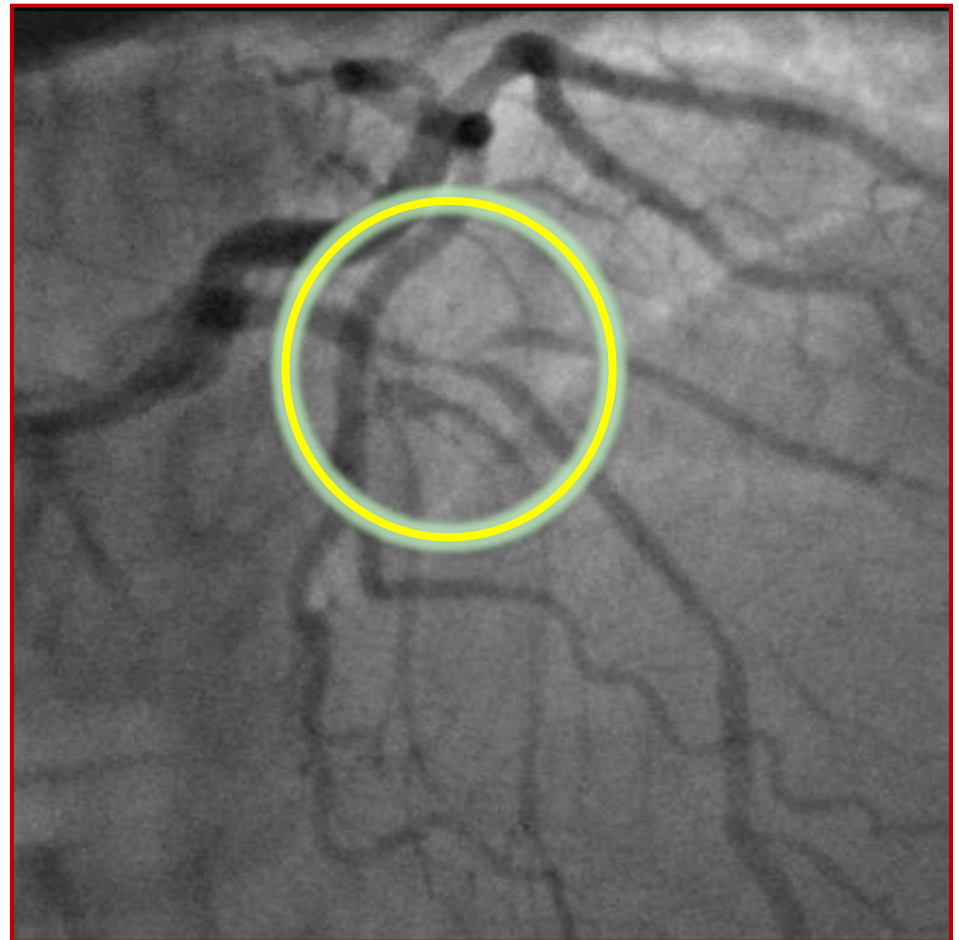
D.R.J. 55 y/o male
86 Kg – 1,79 cm – 26,8 Kg/m²

Risk factors:

- **Dyslipidemia**
- **Family history of CAD**
- **Hypertension**
- **Obesity**

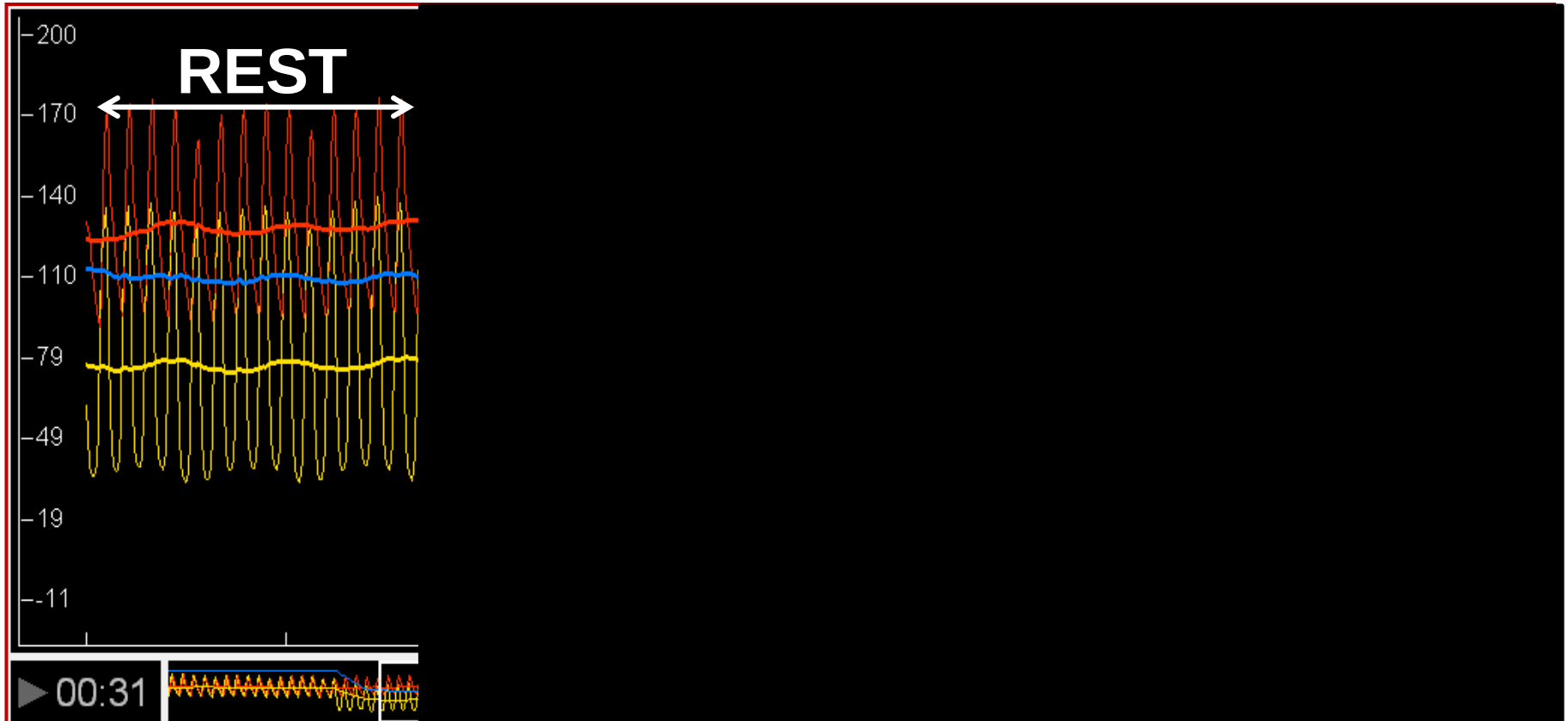
Clinical presentation

- **NSTEMI**
- **LVH on angiography**



Hyperemia

A window towards the microvasculature



Large resting gradient which does not increase during hyperemia

Suggests microvascular dysfunction

Why?

1. **General concept of stress test (as opposed to “rest test”)**
2. **Standardized measurements (as opposed to “moving target”)**
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How?

“Keep it **Simple** and **Standardized**”

The KISS principle

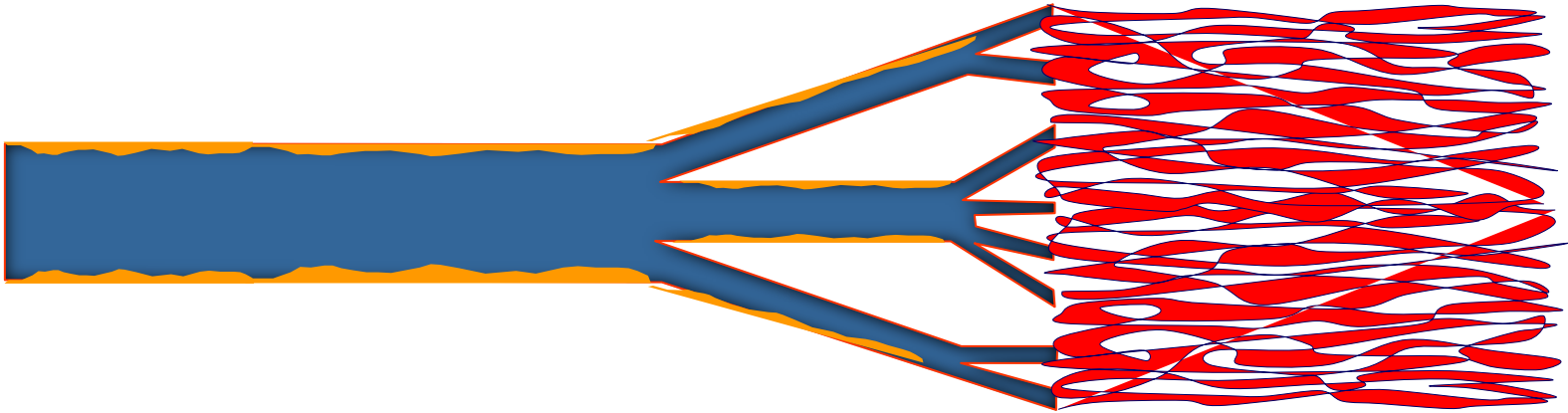
Maximal Vasodilation

Epicardial

= Conductance
Arteries $> 550 \mu$

Microvasculature

= Resistance
Arteries $< 550 \mu$



~~Vasospasm~~

~~Autoregulation~~

Maximal Vasodilation

- 1. Nitrates → Epicardial arteries**
- 2. Adenosine → Microvasculature**
 - **IV: 140 $\mu\text{g/kg/min}$**
 - **IC: 100 – 200 μg in bolus**

Maximal Vasodilation

1. Nitrates → Epicardial arteries

2. Adenosine → Microvasculature

3. Papaverine
4. Regadenoson
5. Apadenoson
6. Binodenoson
7. Nitroprusside
8. Nicorandil
9. Dopamine
10. Exercise
11. Coronary occlusion

inhibition of phosphodiesterase → cyclic **adenosine** MP ↑
precursor of **adenosine**
precursor of **adenosine**
precursor of **adenosine**
NO pathways direct non-selective vasodilator
↑ guanylate cyclase to increase formation of cyclic GMP
 β_1 -agonist → ↑ O_2 consumption → **adenosine** ↑
Adren stimulation → ↑ O_2 consumption → **Adenosine** ↑
Ischemia → release of **adenosine**

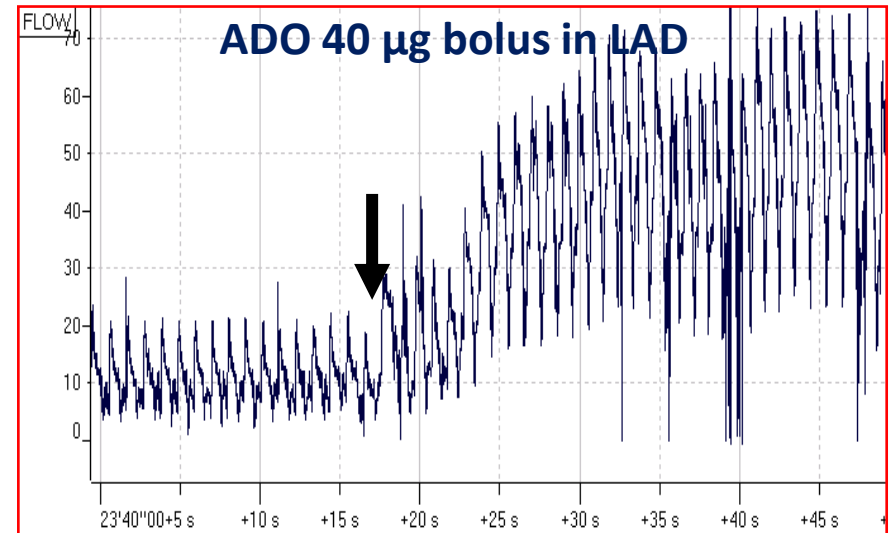
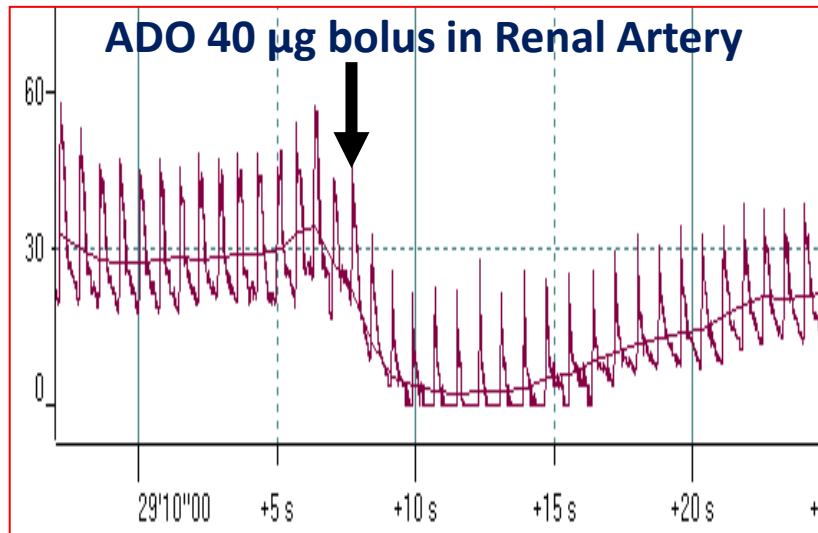
Adenosine: Mechanisms of Action

Target organs

- Coronary arteriolar smooth muscle cells
- Renal arteries (organ level)
- Peripheral and central nervous system
- Myocardium
- Cardiac Conduction system
- Respiratory tract
- Fibroblast, Adipocytes, Immune System

Receptors (A_1 , A_{2A} , A_{2B} , A_3)

A_{2A}
 A_1
 $A_1 A_{2A}$
 A_3
 A_1
 A_1
 A_{2B}



Half Life = 4 to 10 s

Maximal Vasodilation

- 1. Nitrates → Epicardial arteries**
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 - **IV: 140 $\mu\text{g/kg/min}$**
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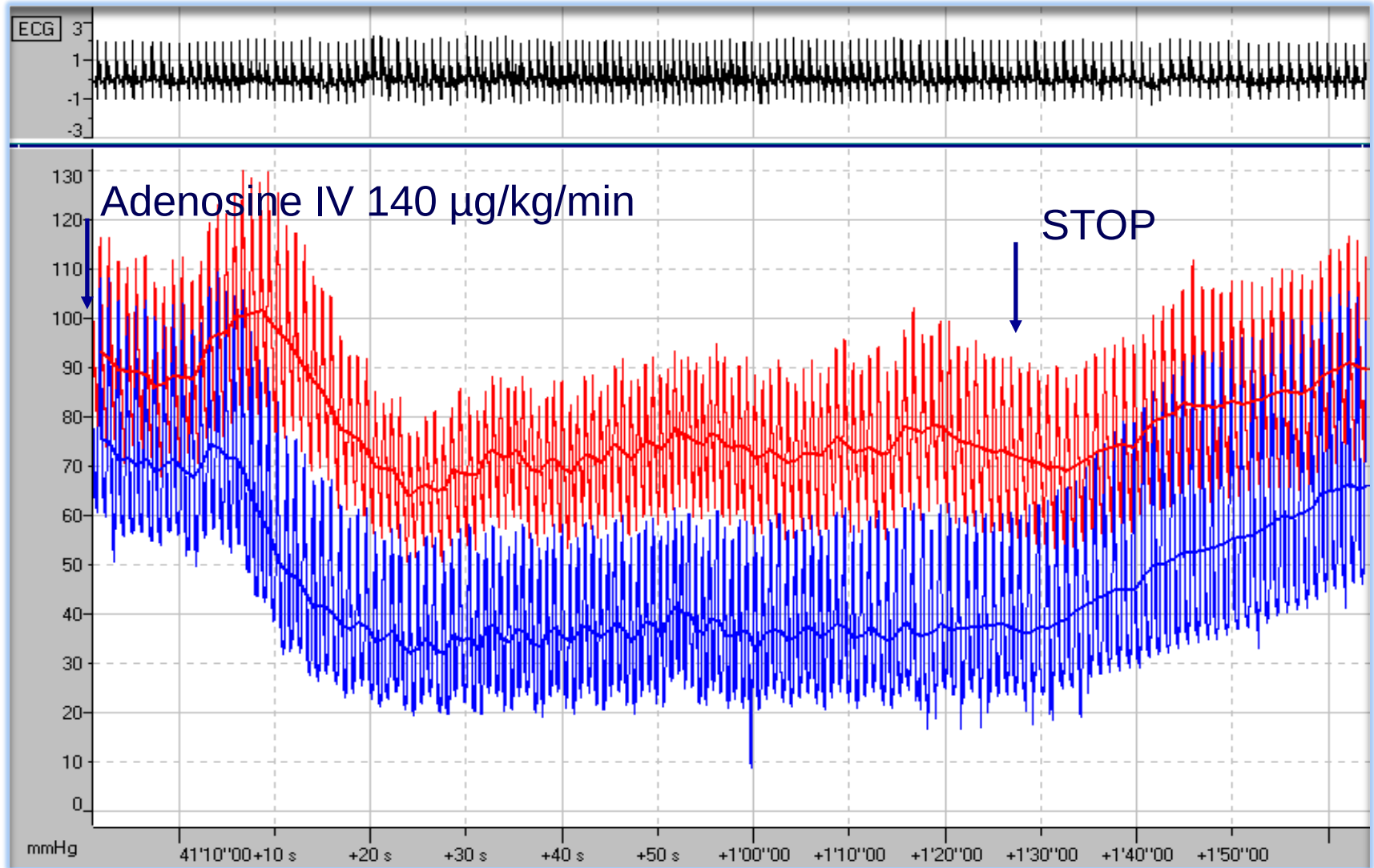
Adenosine IV

Specificities of IV Adenosine (140 µg/kg/min)

- 1. Preferred route when a pressure pull back is needed**
- 2. Induces a brief increase in systemic pressure followed by a decrease in systemic pressure by 10-20%**
- 3. Is almost uniformly accompanied by a burning sensation**
- 4. Fluctuation of the P_d/P_a ratio are observed in some cases**
- 5. A-V blocks are relatively frequent, always transient**

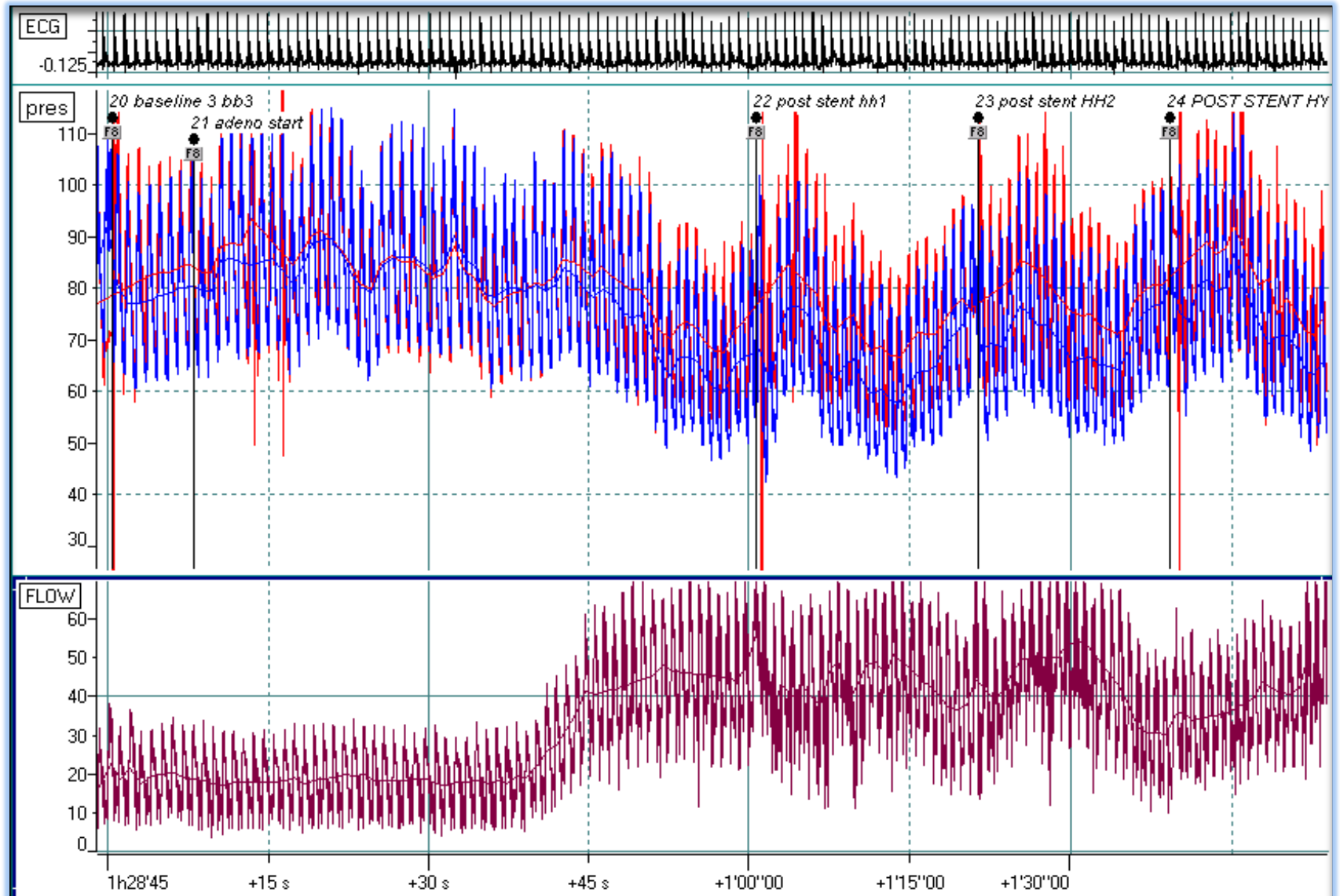
Adenosine IV

“Classic Appearance”

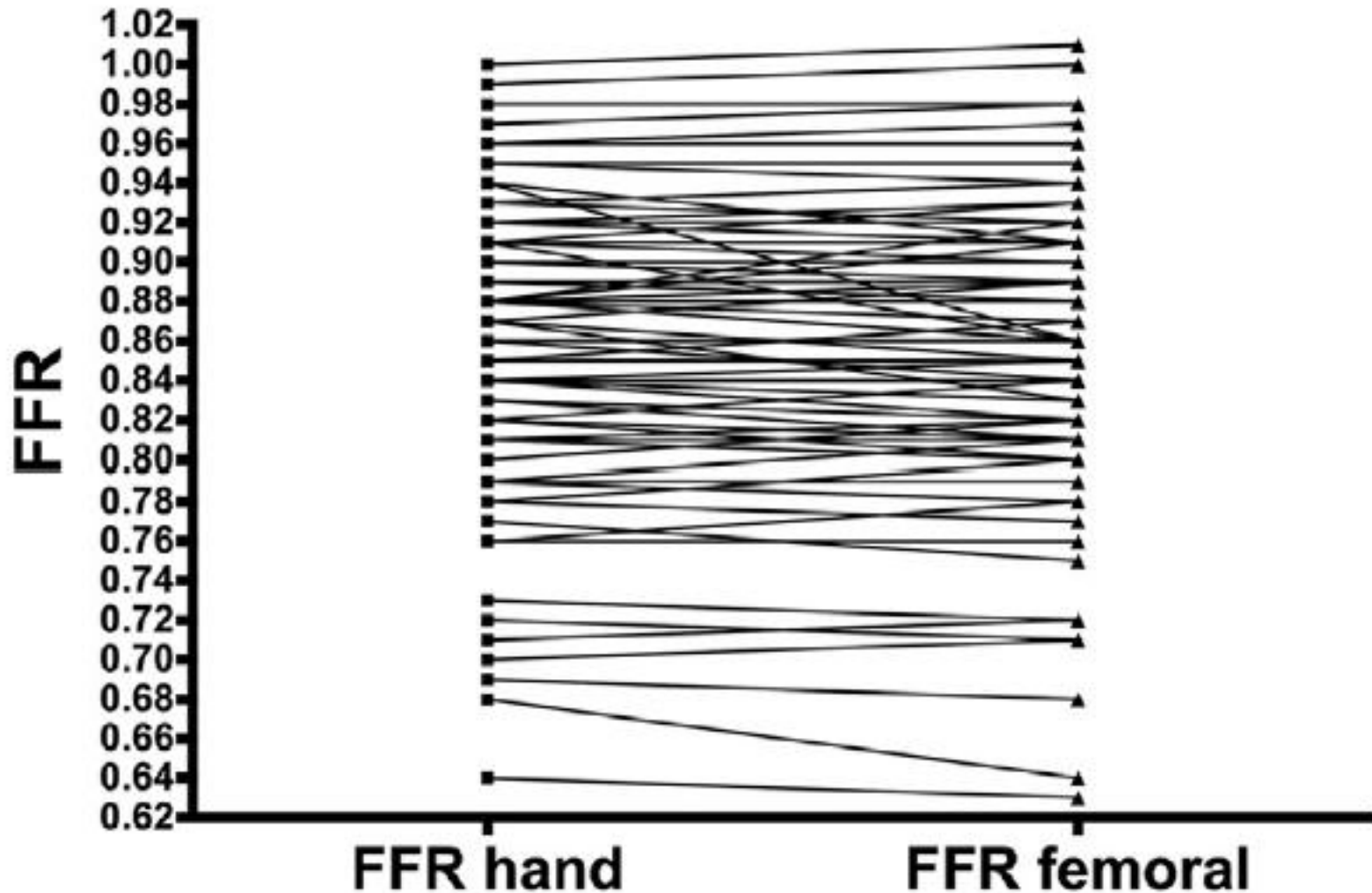


Adenosine IV

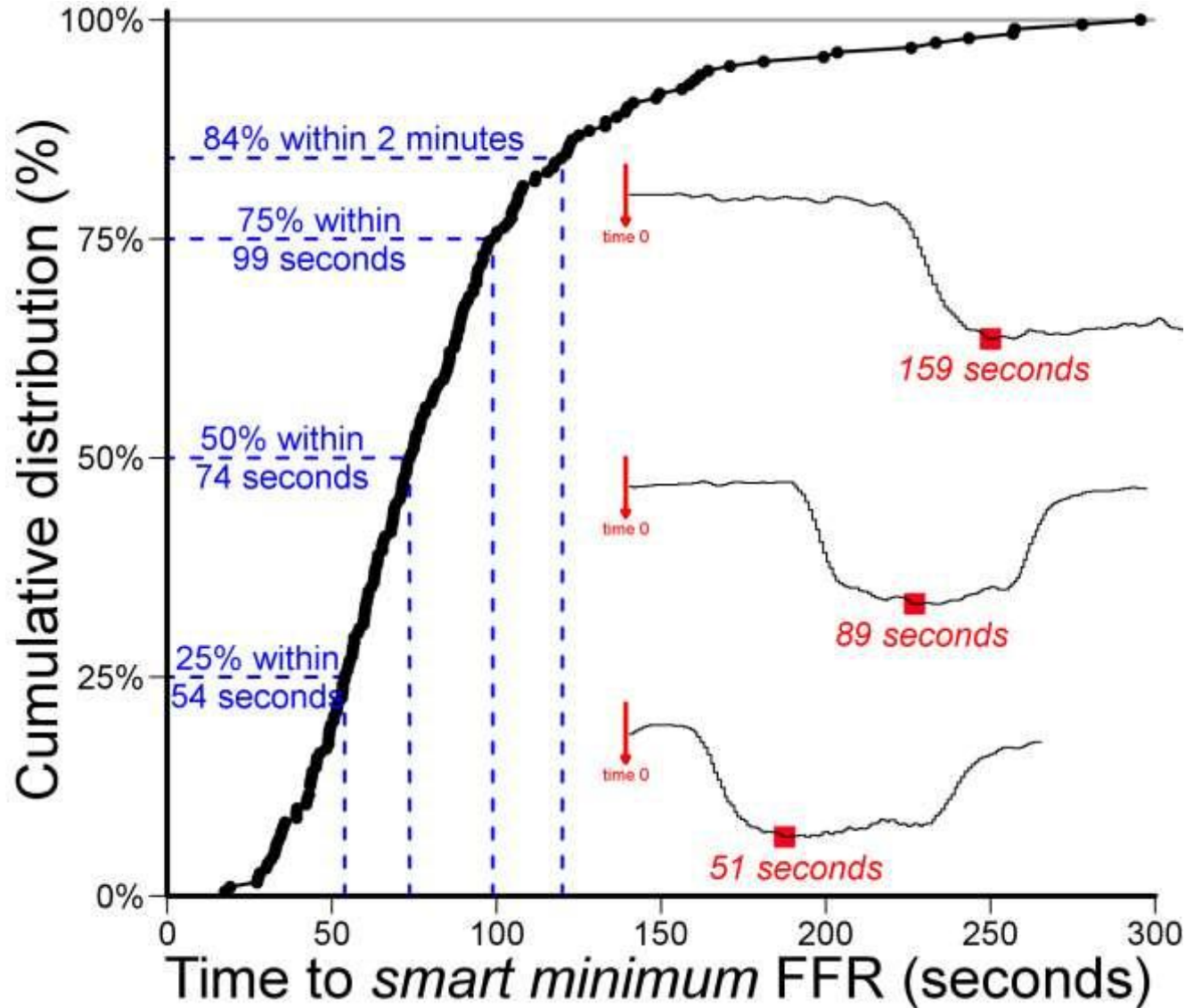
“Humped Appearance”



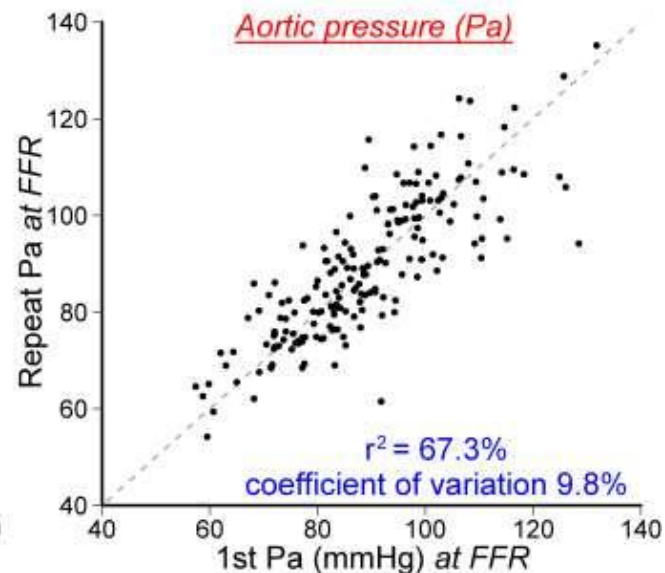
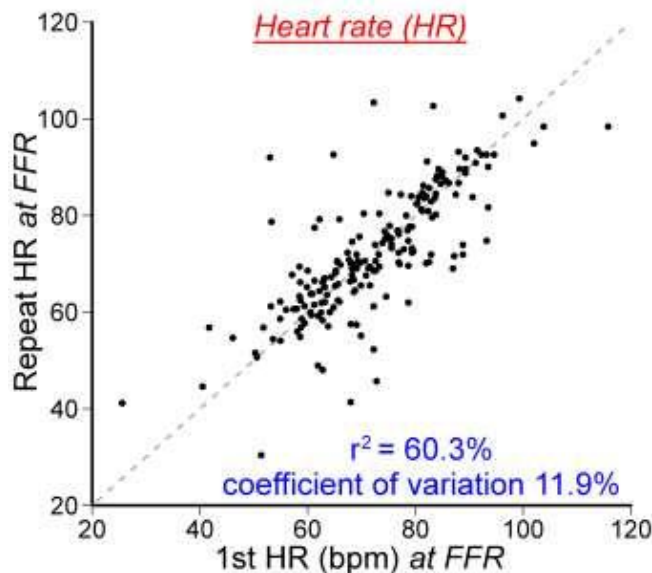
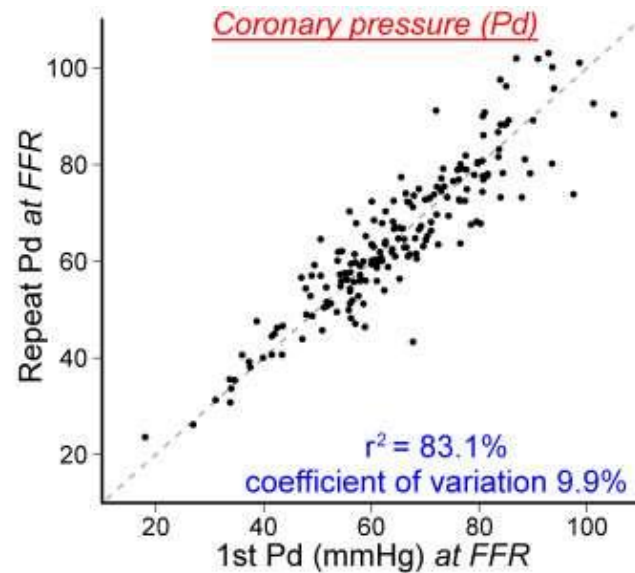
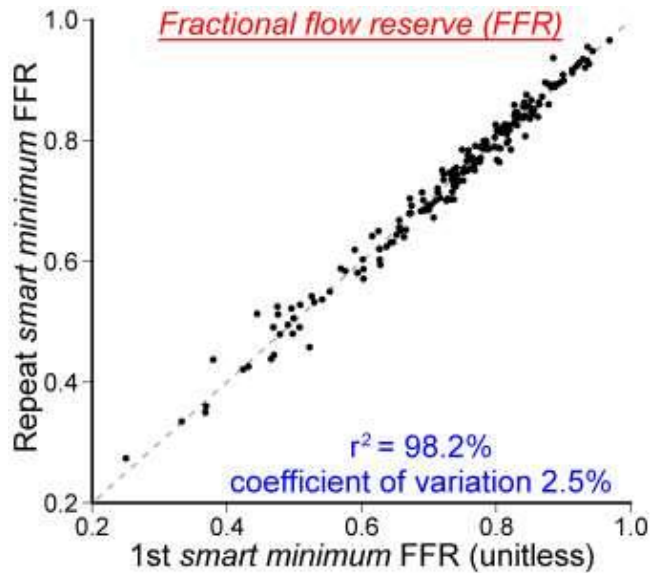
Adenosine IV: Femoral or Hand vein ?



Time to “Smart Minimum”



Repeatability of FFR (“Smart Minimum”)

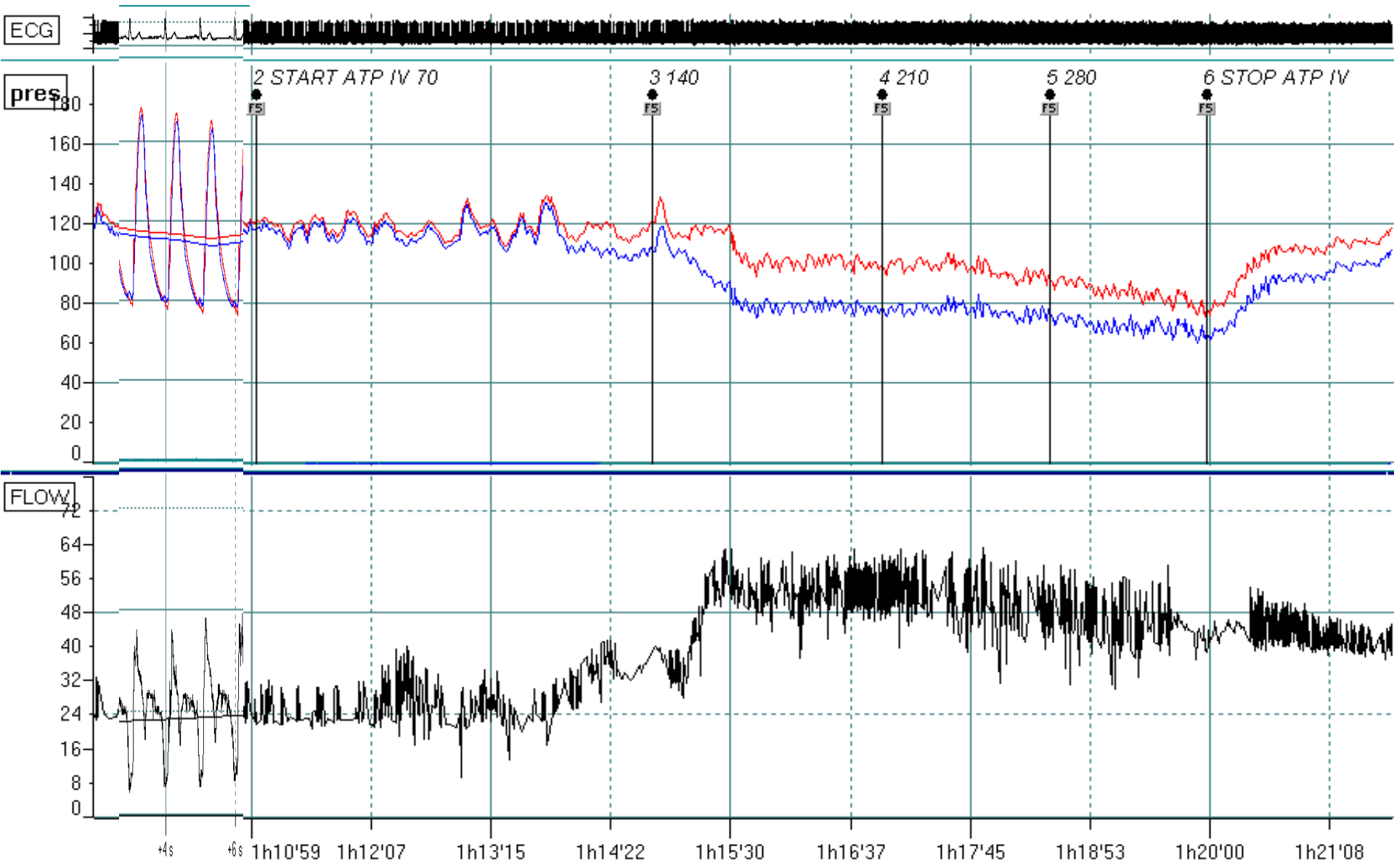


FAQ

**Useful to increase the dose of
IV ado > 140 µg/kg/min ?**

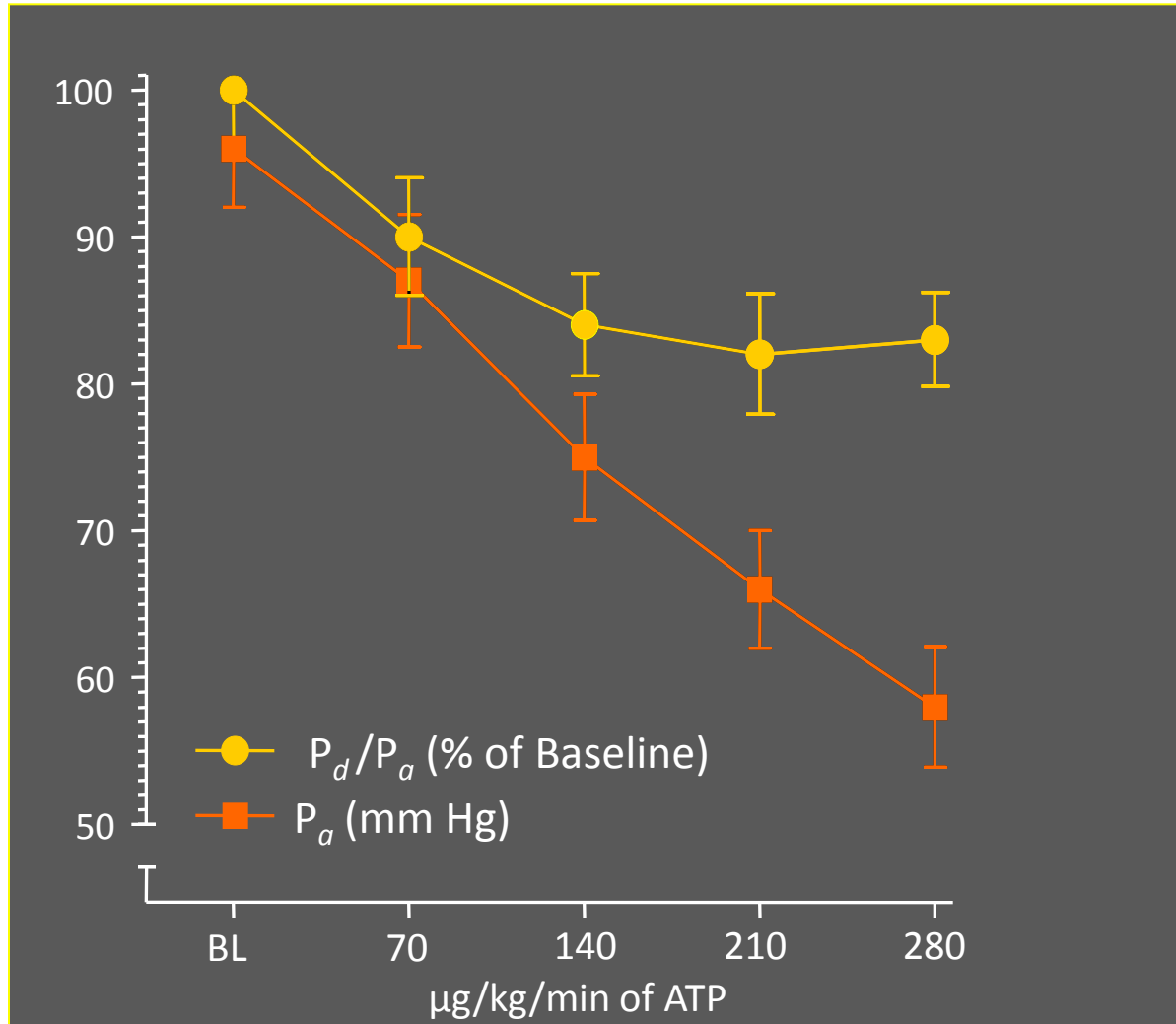
NO

Is it Useful to increase the dose of IV ado > 140 $\mu\text{g/kg/min}$?



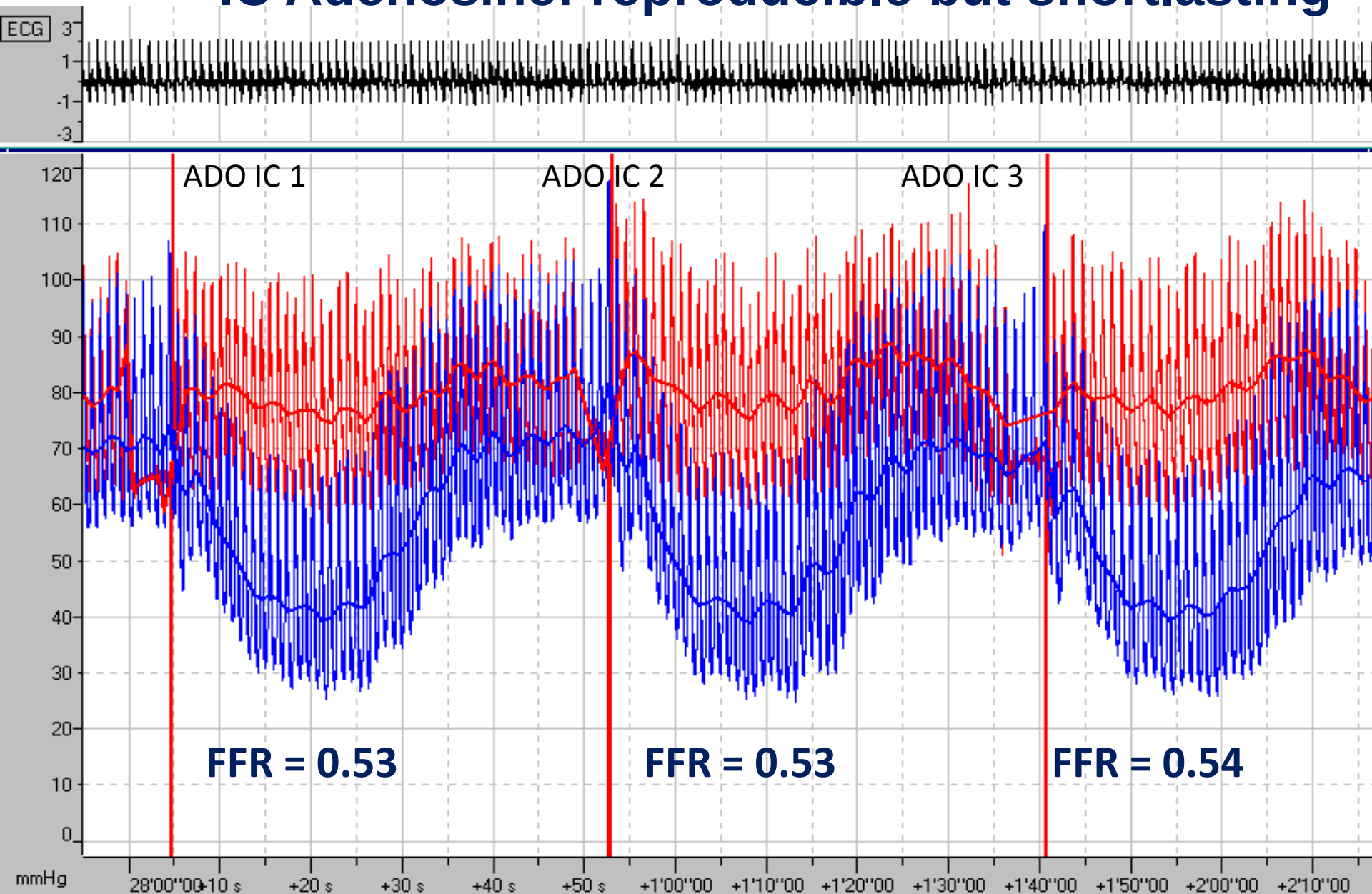
Is it Useful to increase the dose of IV ado > 140 $\mu\text{g/kg/min}$?

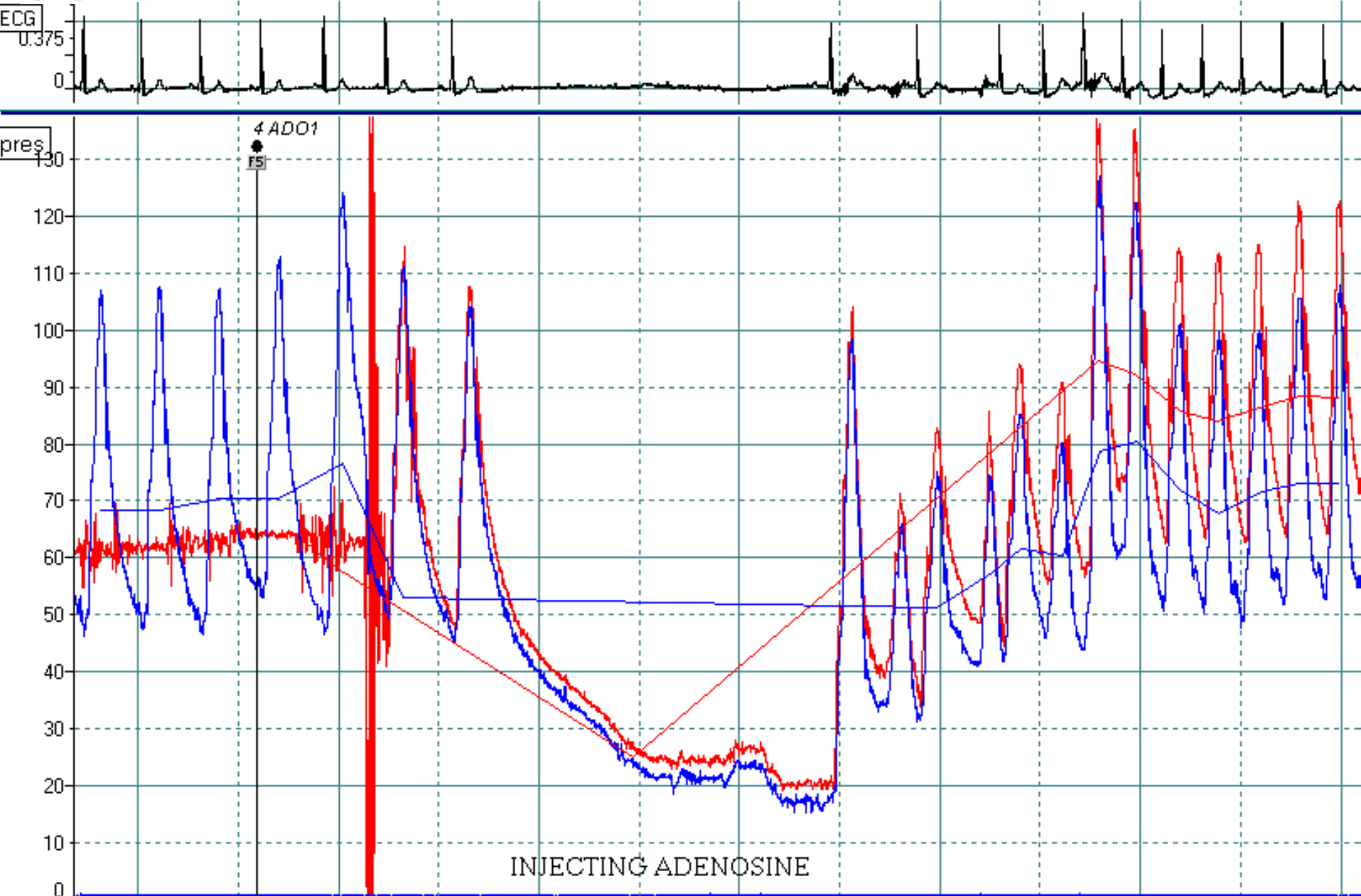
- 12 patients
- Increasing dosages of ATP intravenously (from 0 to 280 $\mu\text{g/kg/min}$)



Adenosine IC

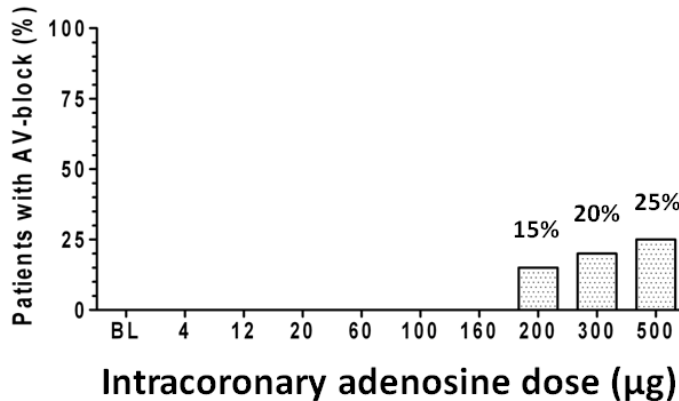
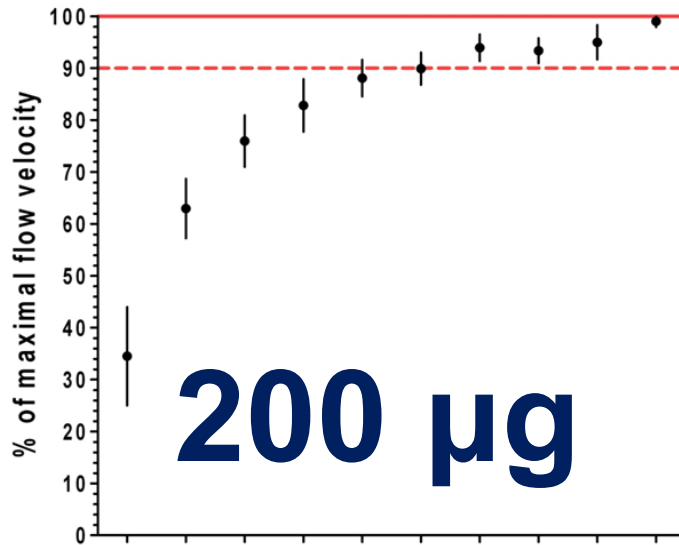
IC Adenosine: reproducible but shortlasting



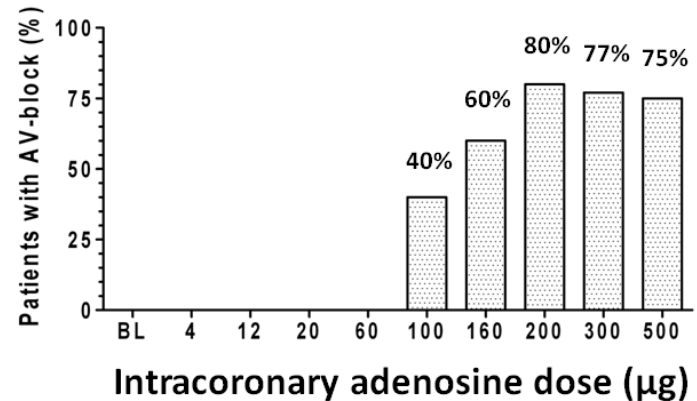
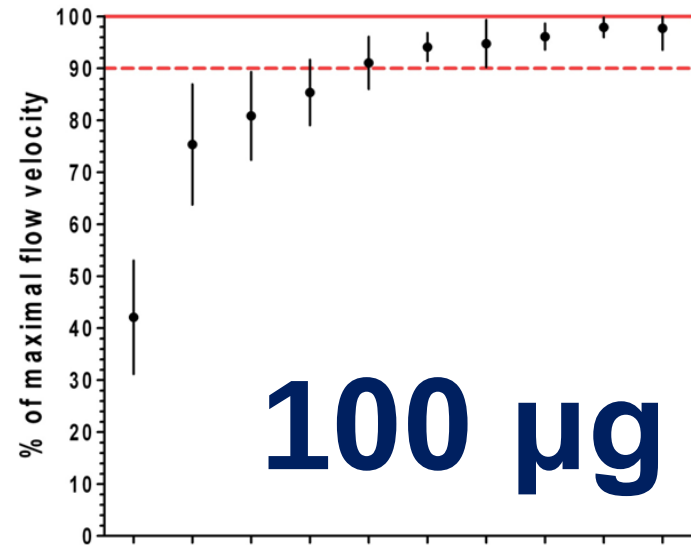


Dose-Response Curve of IC Adenosine

Left coronary artery



Right coronary artery

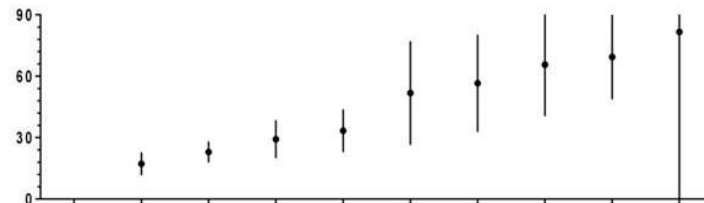
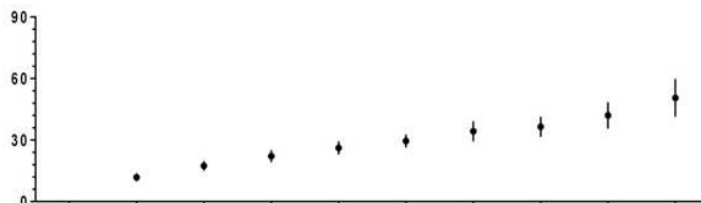


Hemodynamic Effect of IC Adenosine

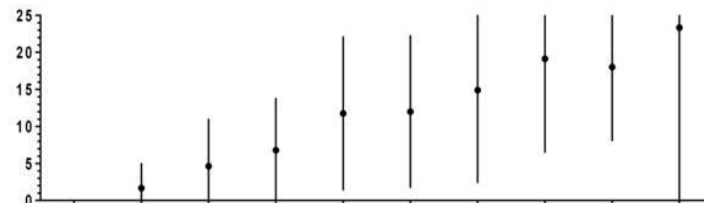
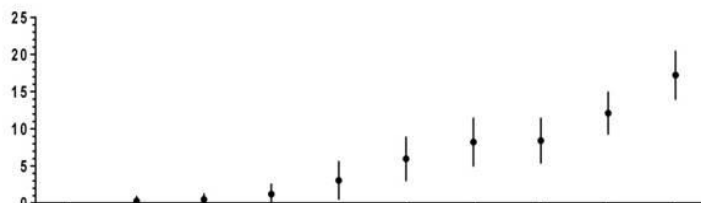
Left coronary artery

Right coronary artery

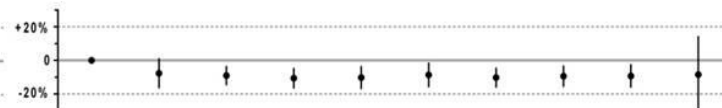
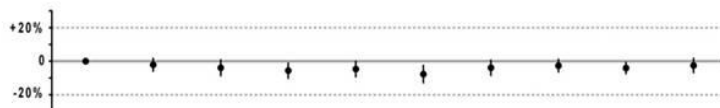
Time to return
to baseline (s)



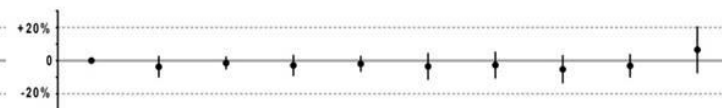
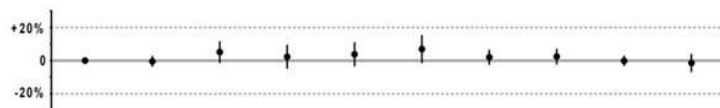
Duration of the
hyperemic plateau (s)



Changes in
Blood pressure (%)



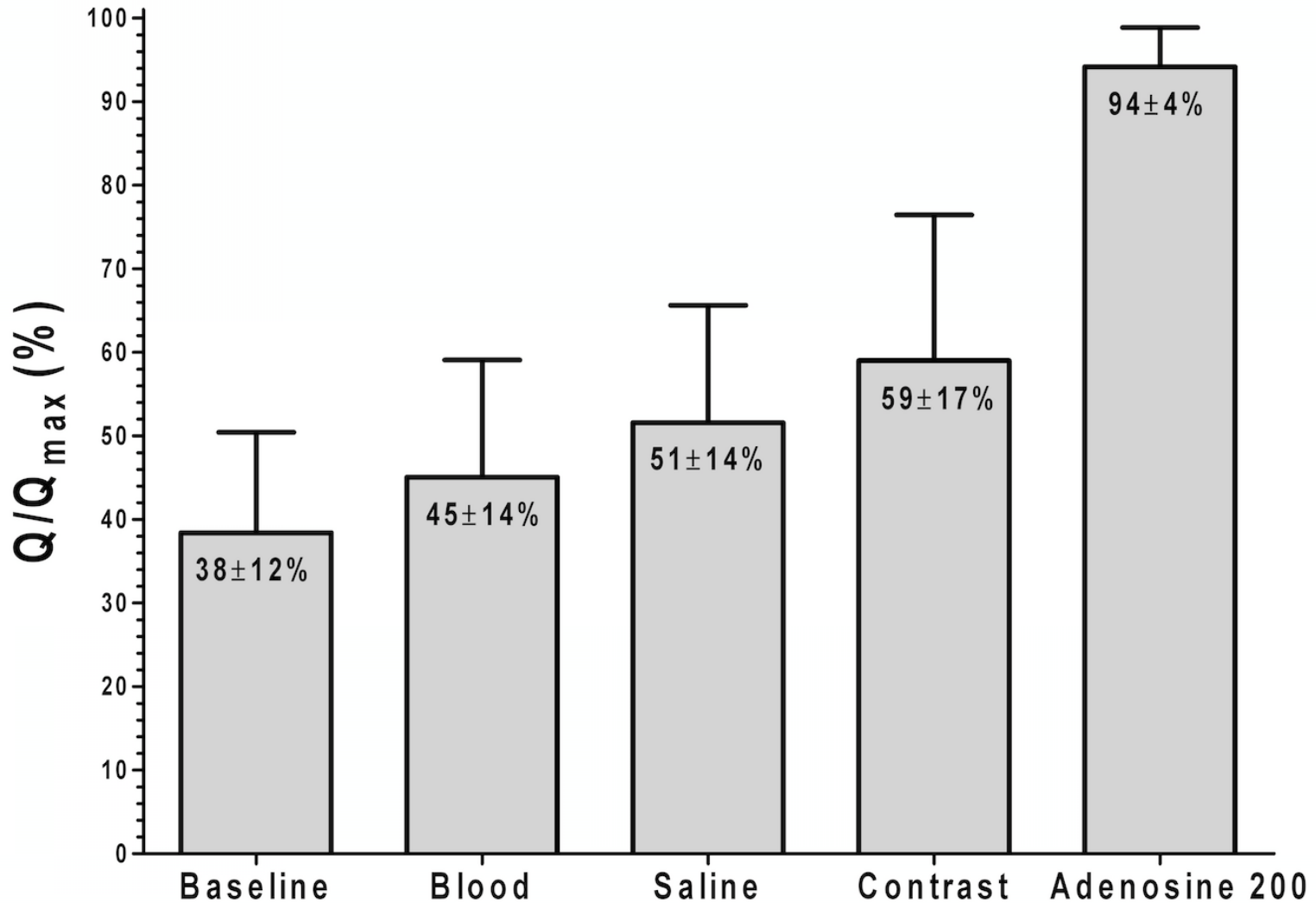
Changes in
heart rate (%)



Intracoronary adenosine dose (μg)

Intracoronary adenosine dose (μg)

Effect on Blood Flow Velocity (% of Max) of Various Stimuli



Specificities of IC Adenosine (100-200 µg)

- 1. Can be used in the vast majority of lesions**
- 2. Short half live**
- 3. Rare AV blocks, always transient**
- 4. Extremely reproducible: do it twice (or more!)**

Cost of Adenosine

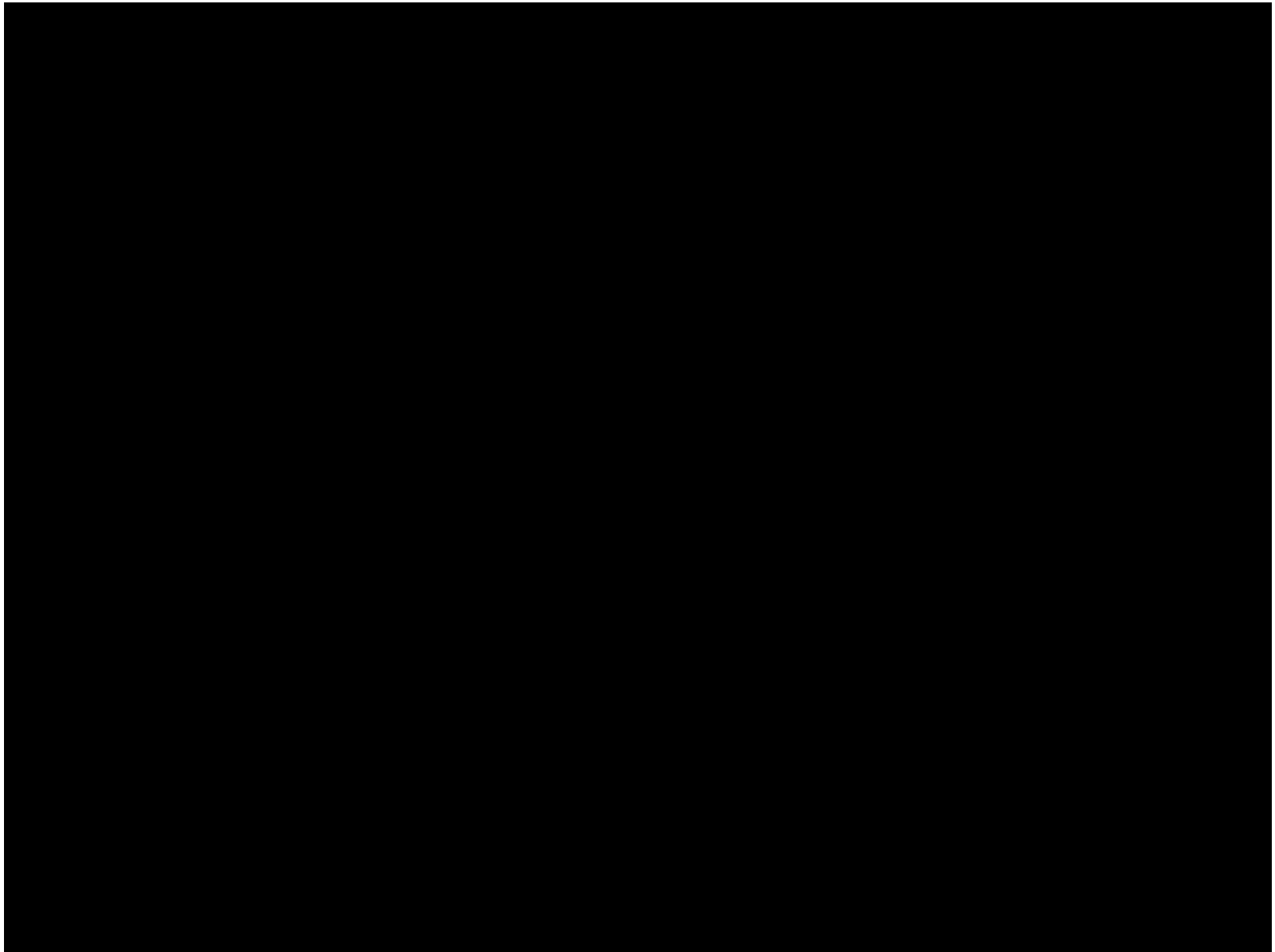
Adenocor, Sanofi	Belgique, Bulgarie, Danemark, Royaume Uni, Hongrie, Irlande, Pays- Bas, Portugal	3 mg/ml (2ml)	6-16 €
Krenosin, Sanofi	France, Italie, Suisse	3 mg/ml (2 ml)	6-16 €
Adenoscan, Sanofi	France, Allemagne, Italie, Japon, Portugal, Espagne, USA, Royaume Uni	3mg / ml (10 ml)	30-50 €
Adenosin, Life Medical	Allemagne	5 mg/ml (10 ml)	26 €
Adenosin Injection, USP	Canada	3 mg/l (2 ml)	11 C\$

Adenosine prepared by your own pharmacy:

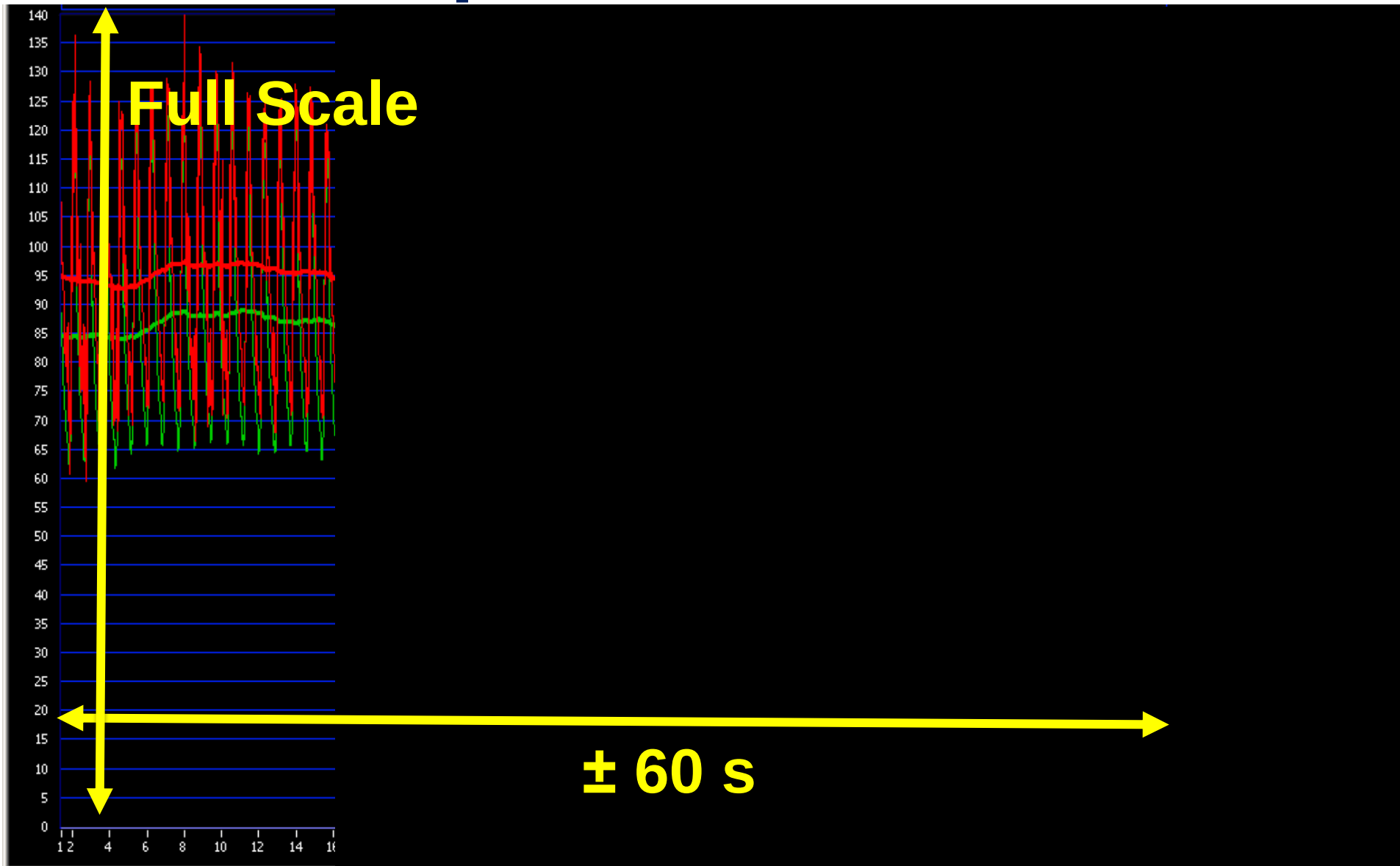
- IV ± 8 € / seringue
- IC ± 0.30 € / bolus

Quality of the Pressure Recordings

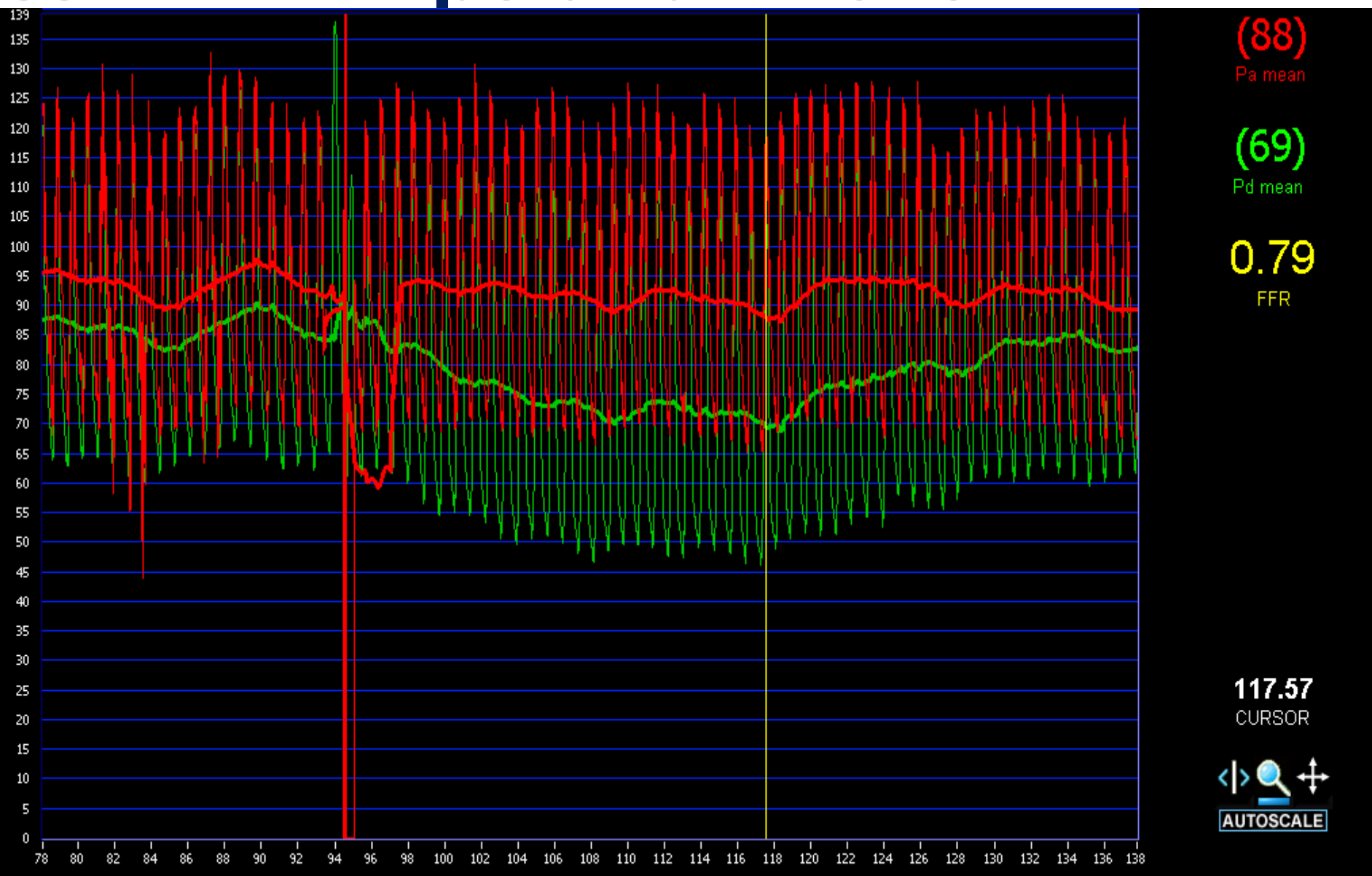
- *Recording of 12 beats steady state at rest*
- *Very short (1-2 s) injections of adenosine*
- *Total recording of 45-60 s*

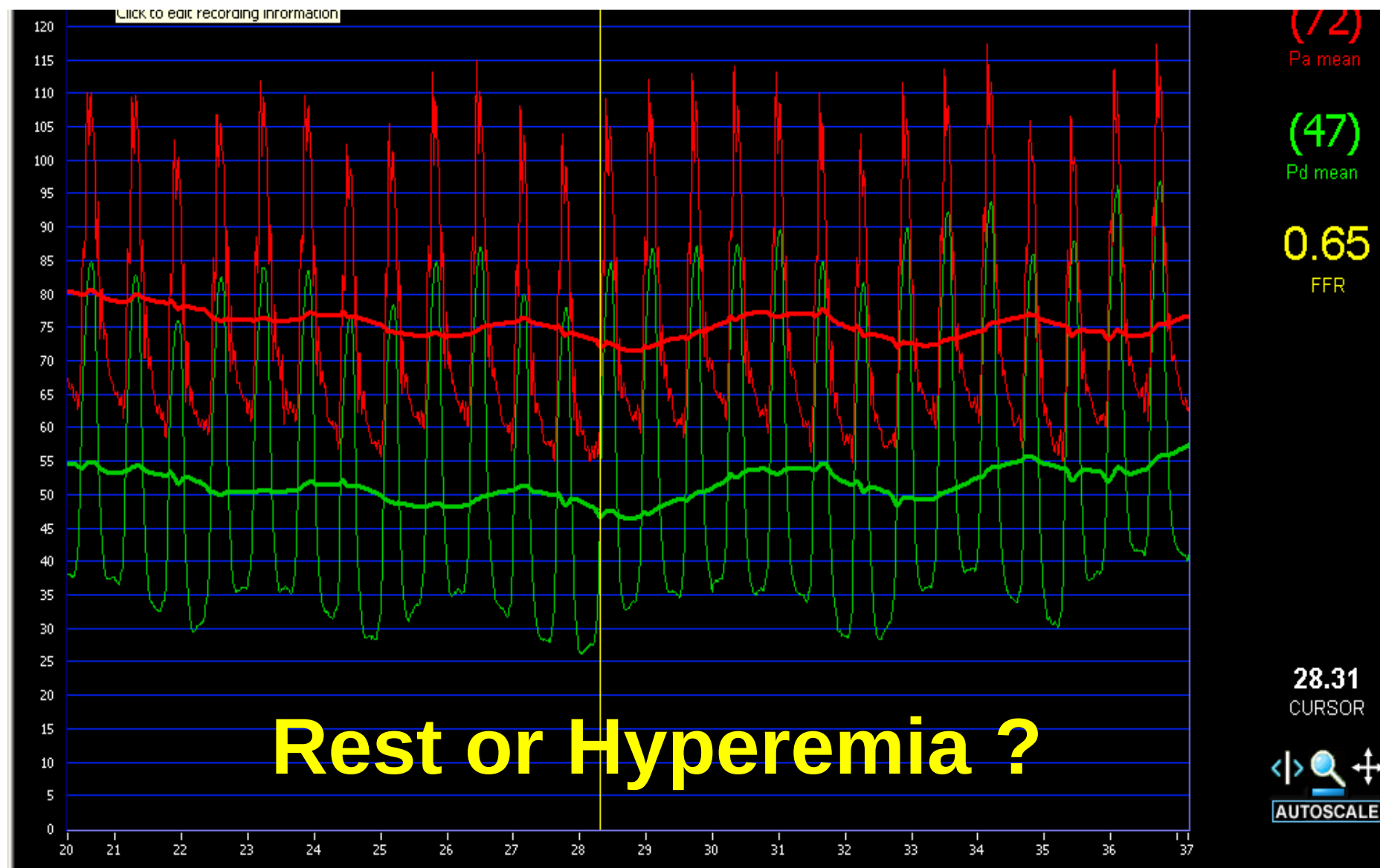


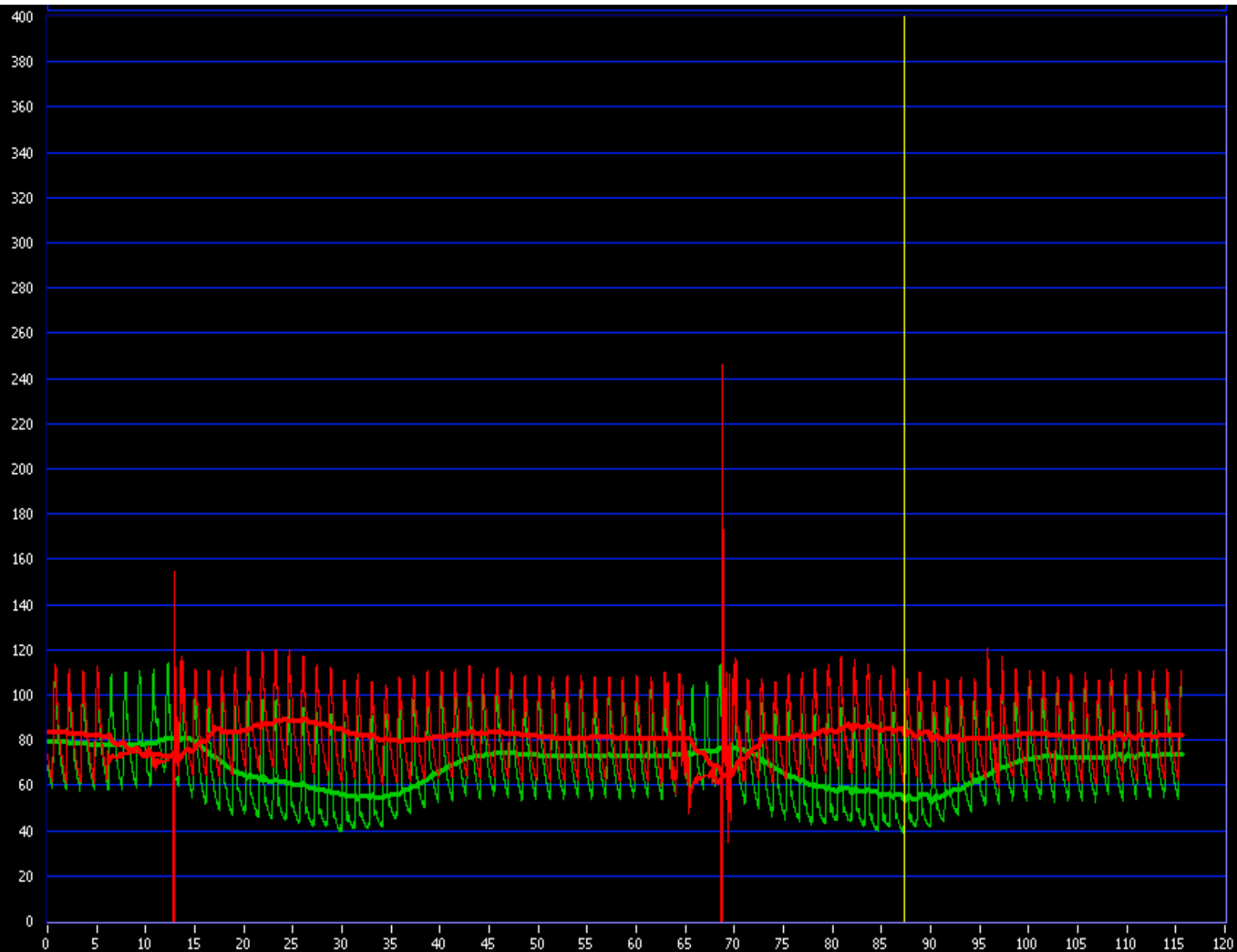
Tips and Tricks



Tips and Tricks





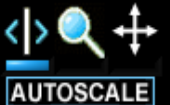


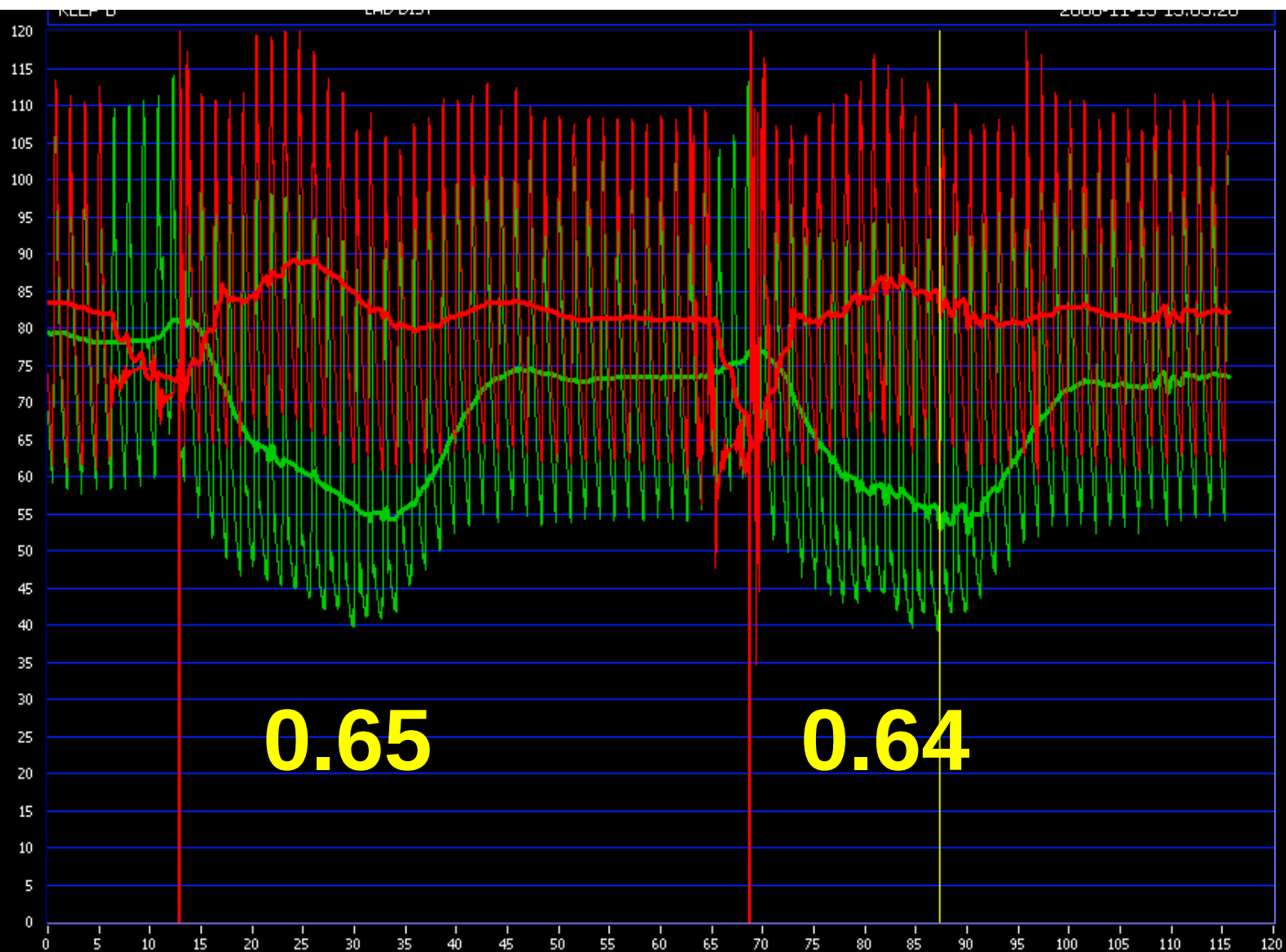
(82)
Pa mean

(53)
Pd mean

0.64
FFR

87.35
CURSOR





(82)

Pa mean

(53)

Pd mean

0.64

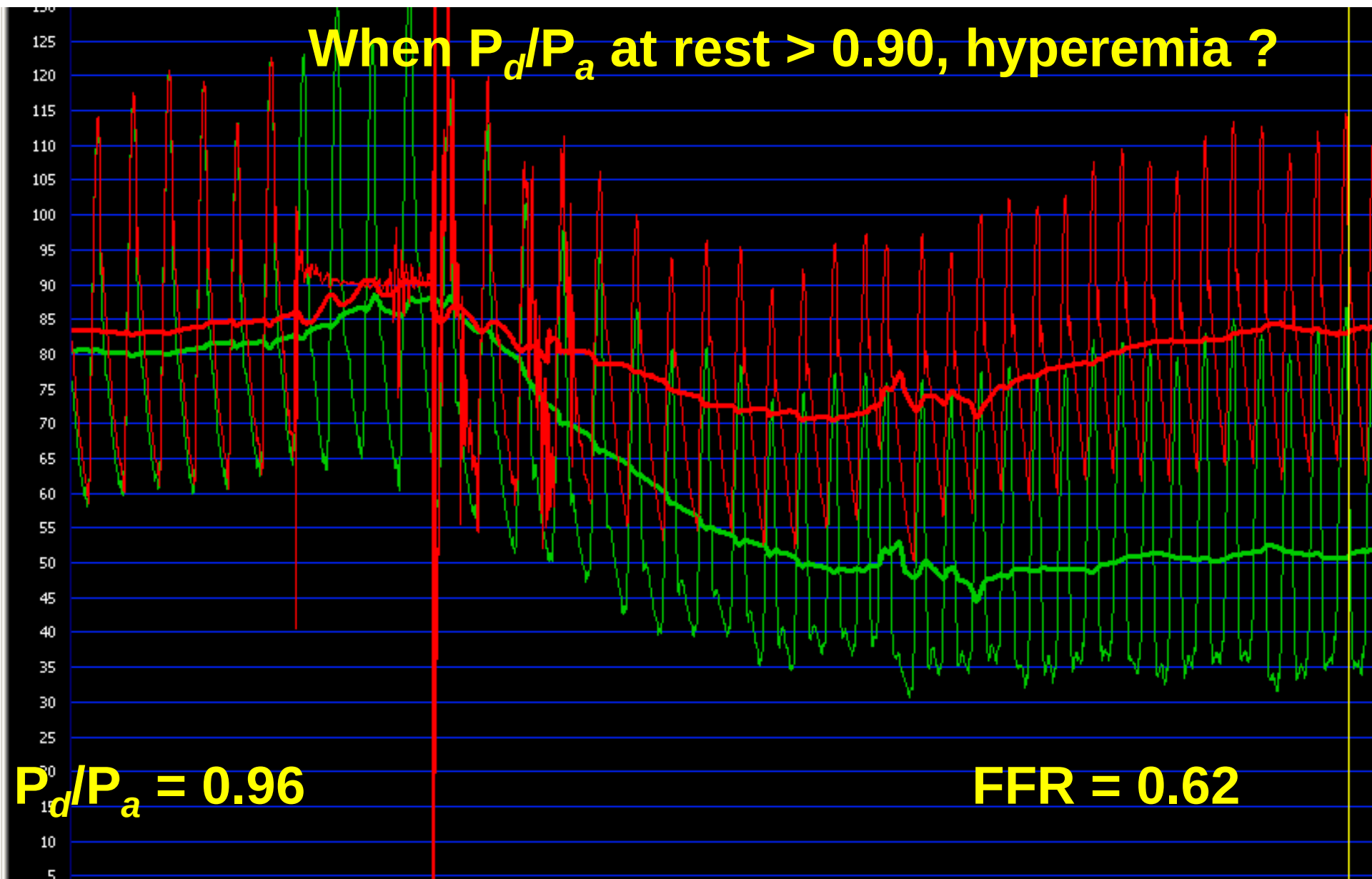
FFR

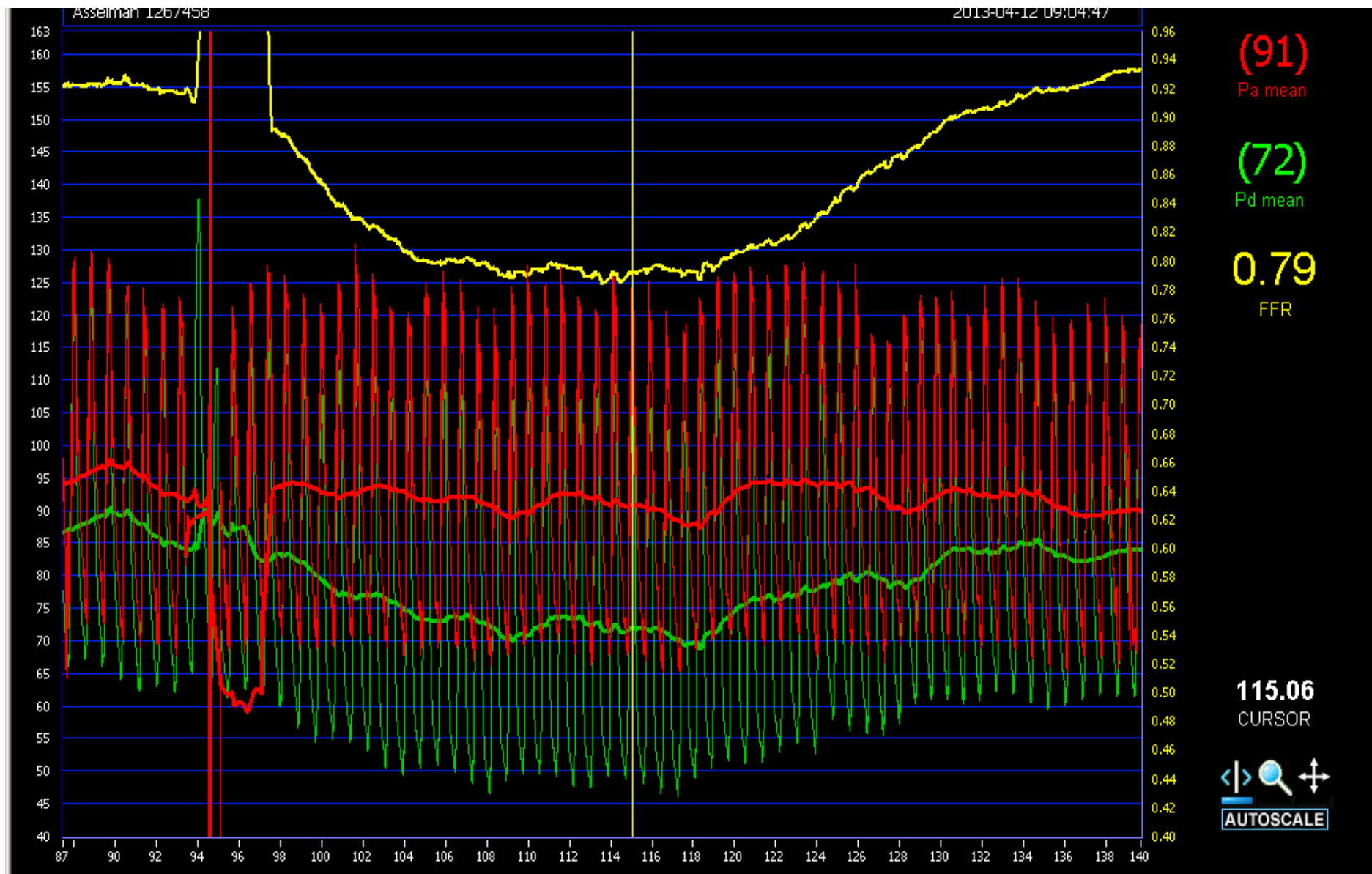
87.35

CURSOR



When P_d/P_a at rest > 0.90 , hyperemia ?





Conclusive Remarks

- 1. Hyperemia is mandatory to “interrogate” a lesion properly**
- 2. Can be obtained very easily, safely, cheaply, ...**
- 3. Provided it is standardized in each laboratory**

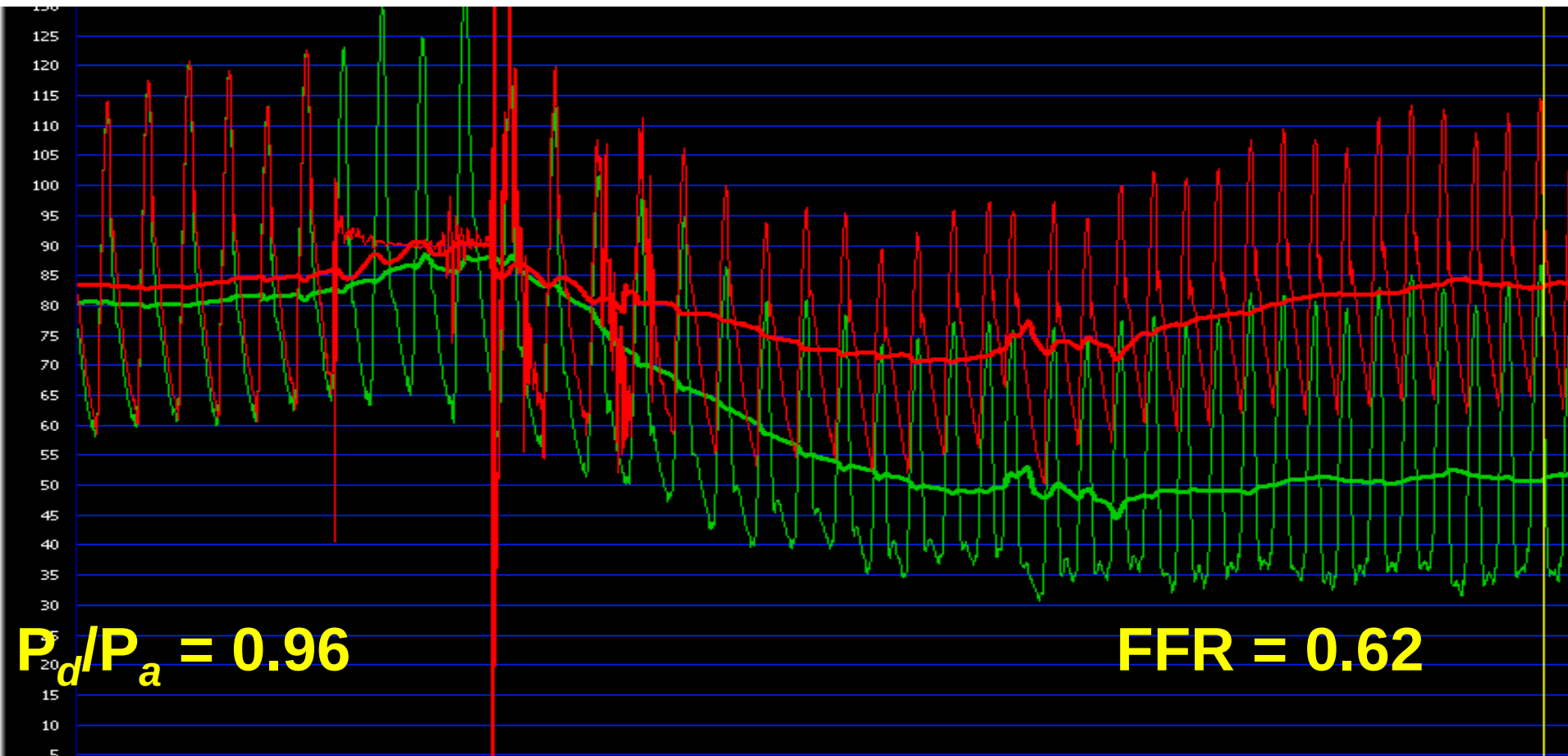
FAQ

- ✓ When P_d/P_a at rest > 0.90 , do we have to induce hyperemia ?
- ✓ When P_d/P_a at rest < 0.80 , do we have to induce hyperemia ?
- ✓ Useful to increase the dose of IV ado $> 140 \mu\text{g/kg/min}$?
- ✓ Useful to increase the dose of IC ado $> 200 \mu\text{g}$ (bolus) ?
- ✓ Is the burning sensation related to ischemia ?
- ✓ Are some patients resistant to Adenosine ?
- ✓ Can Papaverine be used instead of Adenosine ?
- ✓ Is hyperemia expensive ?
- ✓ What to do with radial procedures ?
- ✓ Interference with some medications ?
- ✓ Is adenosine contraindicated in patients with lung disease?

FAQ

When P_d/P_a at rest > 0.90 , do we have to induce hyperemia ?

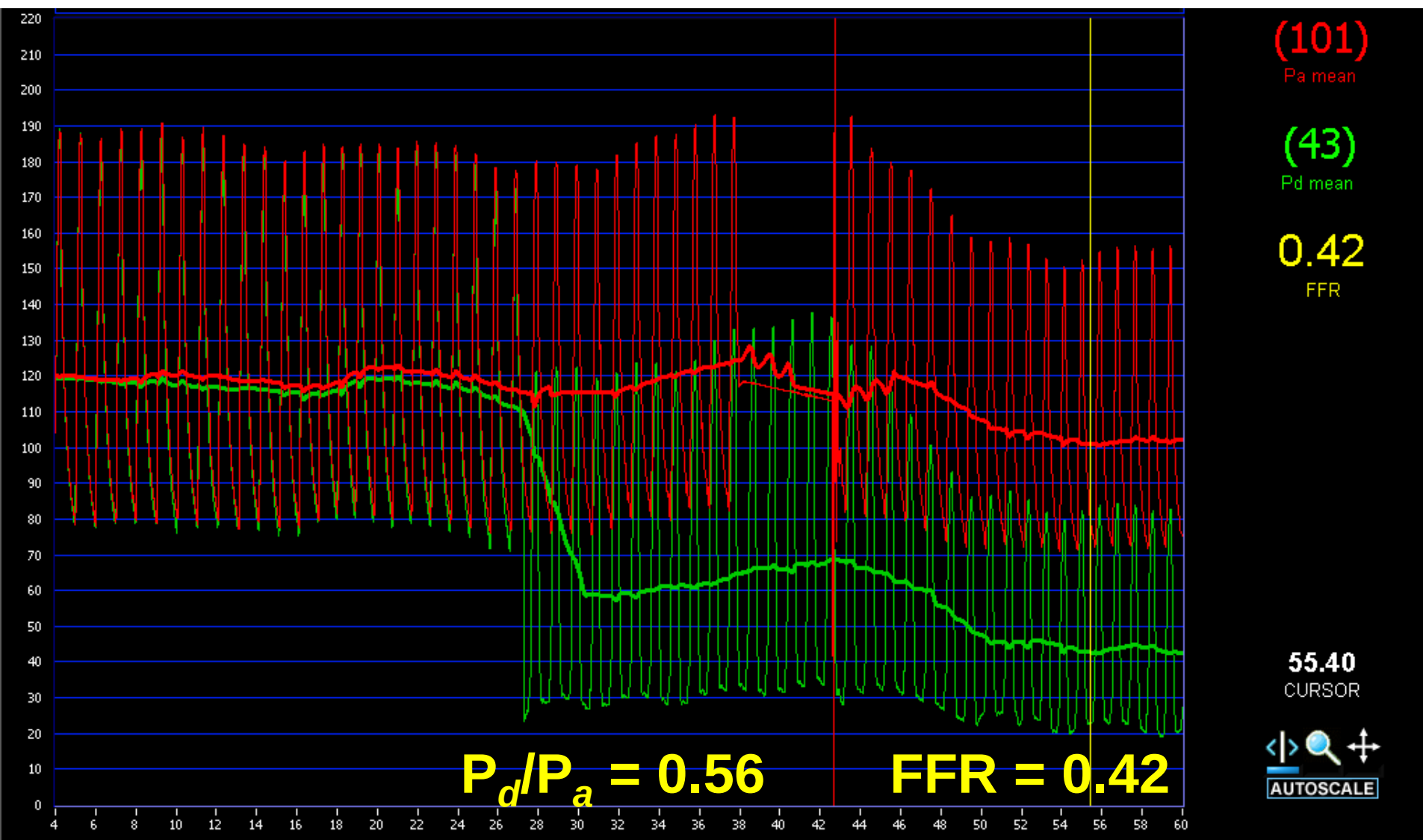
YES



FAQ

When Pd/Pa at rest < 0.80, do we have to induce hyperemia ?

When P_d/P_a at rest < 0.80 , do we have to induce hyperemia ?

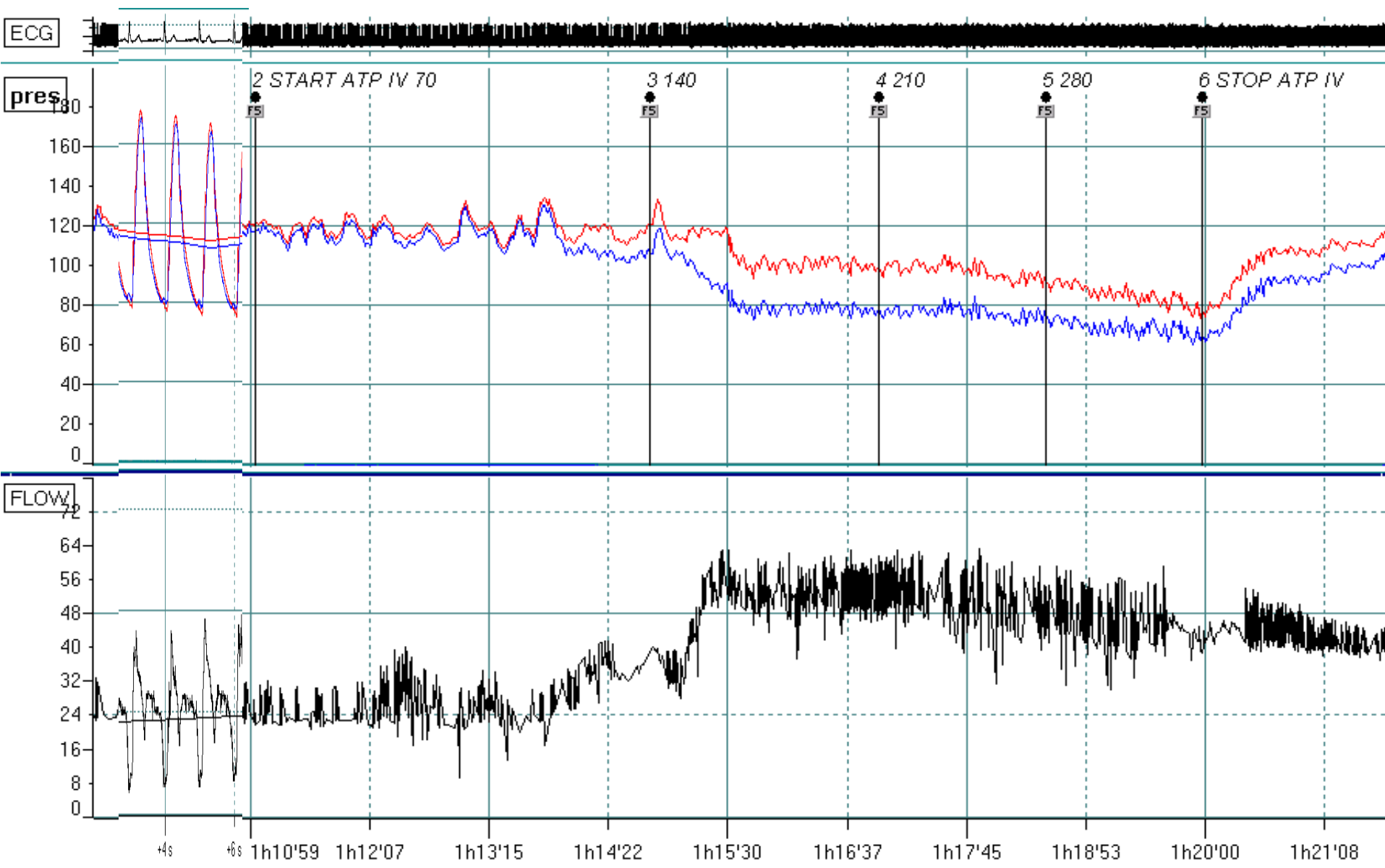


FAQ

Useful to increase the dose of IV ado > 140 µg/kg/min ?

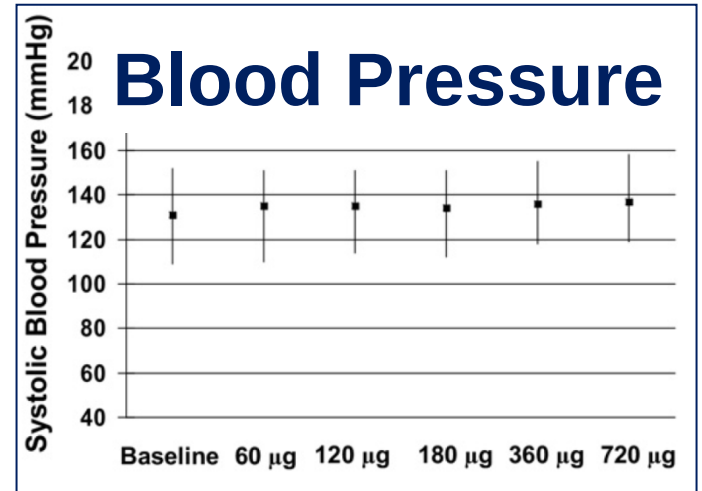
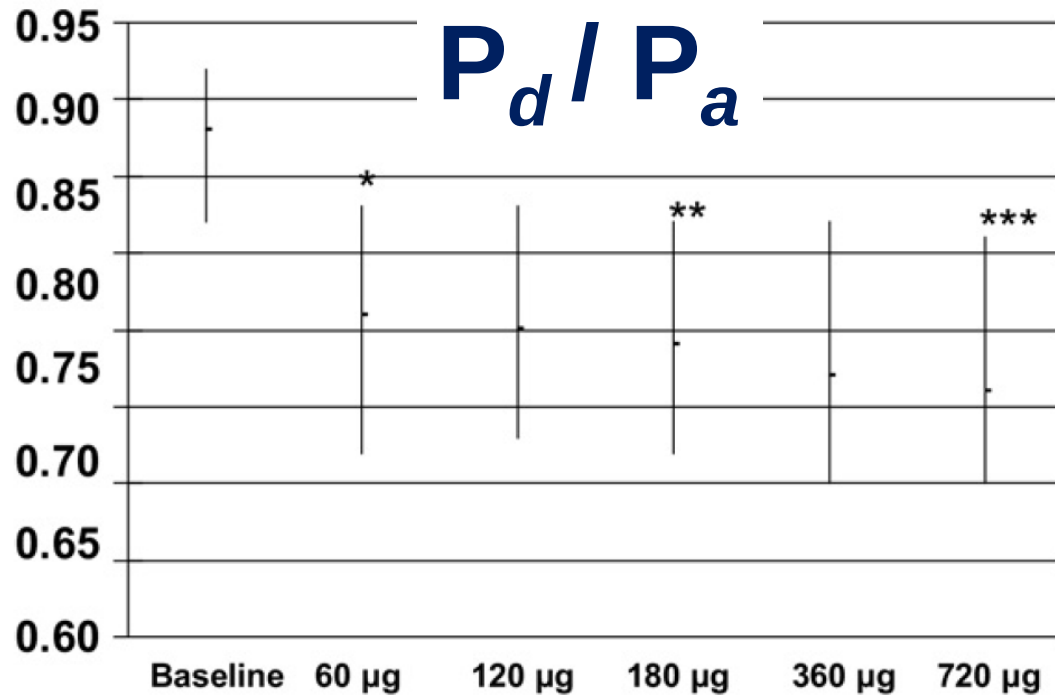
NO

Increasing the dose above 140 $\mu\text{g/kg/min}$ decreases systematic BP and increases the thoracic pain



FAQ

Useful to increase the dose of IC ado > 200 µg (bolus) ?



N=46

720 µg decreases P_d/P_a a bit further w/o any decrease in BP, any increase in HR and no heart blocks ????

FAQ

Is the burning sensation related to ischemia ?

NO

Adenosine is an algesic substance which stimulates the same nerves than those responsible for angina ... which is also due to the local release of adenosine during ischemia

FAQ

Are some patients resistant to Adenosine ?

NO,

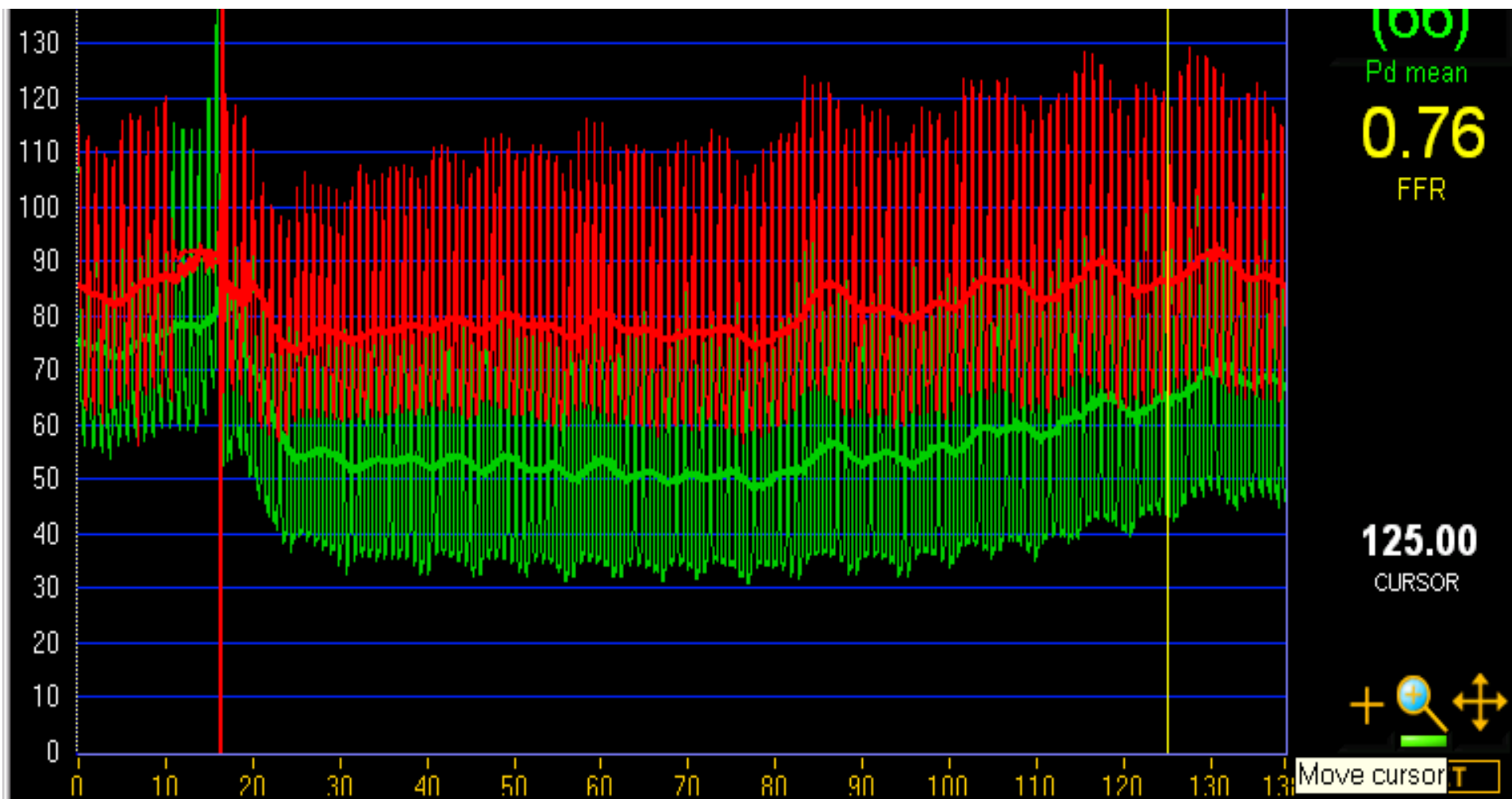
Resistance to exogenous Adenosine does not exist

FAQ

Can Papaverine be used instead of Adenosine ?

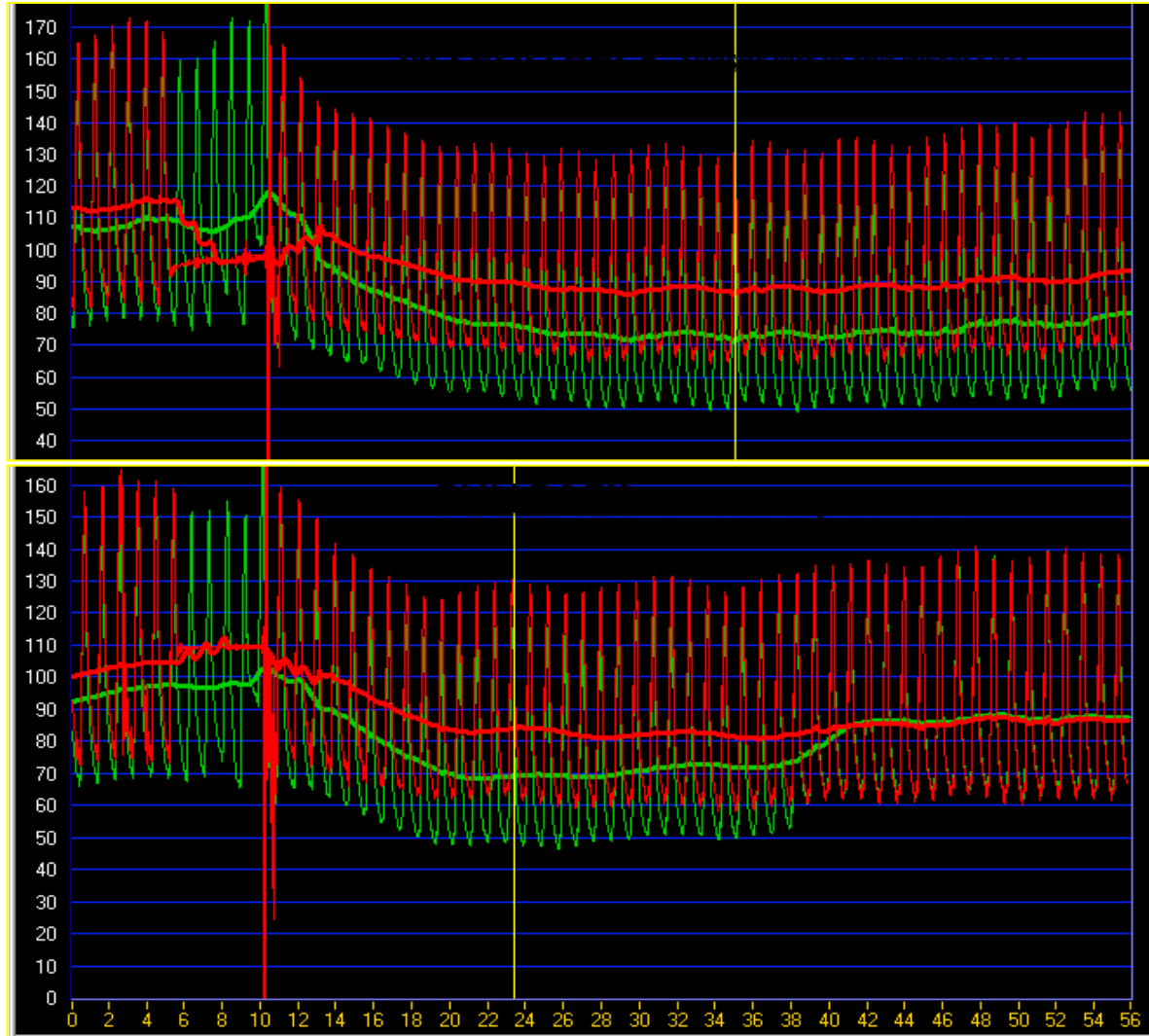
Papaverine IC

16 mg IC in LCA 12 mg IC in RCA



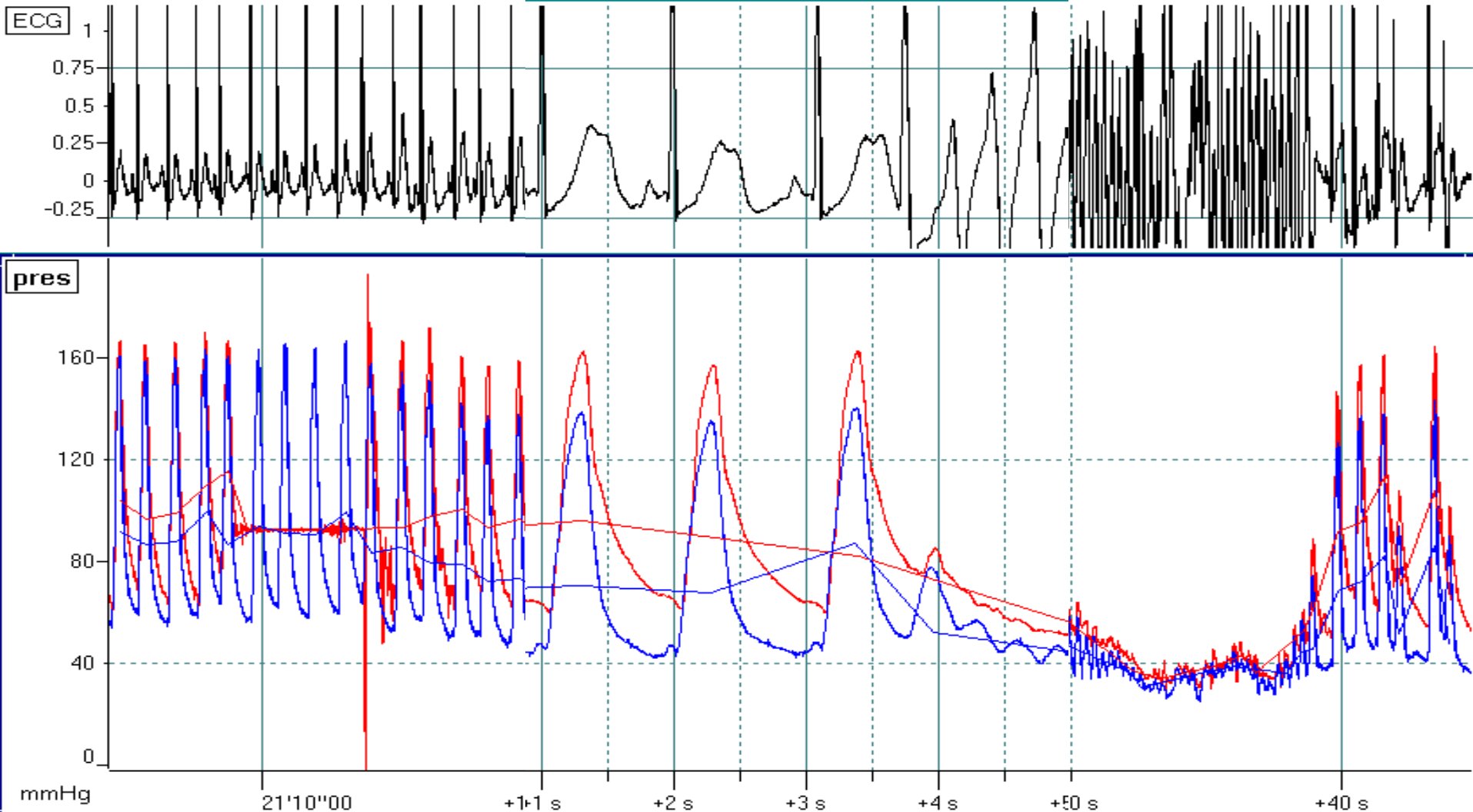
Papaverine IC

16 mg IC in LCA 12 mg IC in RCA



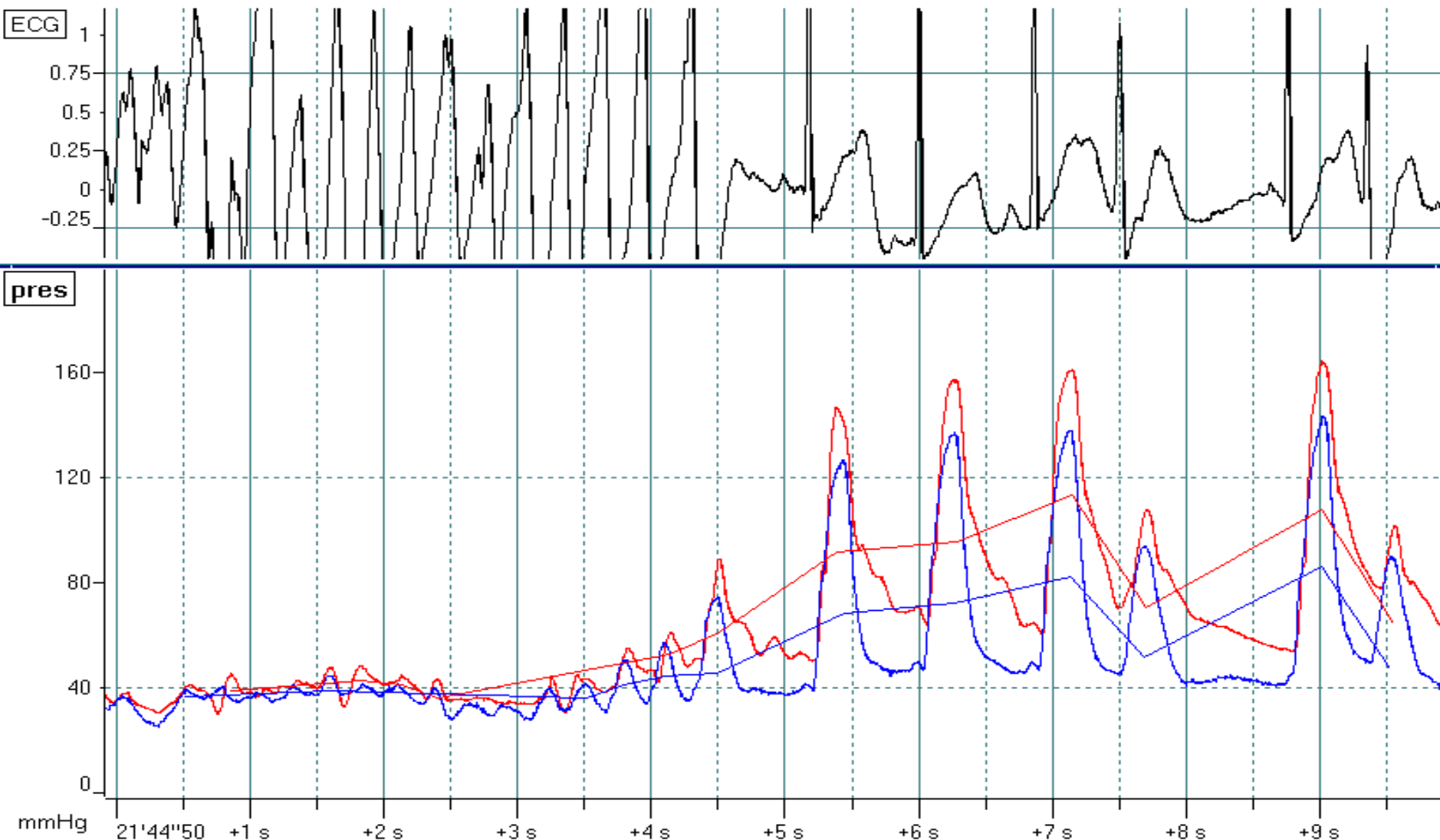
Papaverine IC

16 mg IC in LCA 12 mg IC in RCA



Papaverine IC

16 mg IC in LCA 12 mg IC in RCA



FAQ

Is hyperemia expensive ?

... NOT REALLY:

0.12 € / bolus of 100 µg IC; 0.24 € / bolus of 200 µg

1.34 € / syringe needed for approx 15 minutes of IV administration

FAQ

What to do with radial procedures ?

IC BOLUS

IV adenosine INFUSION

IV Regadenosone BOLUS

FAQ

Some medications interfere with Adenosine

Beta-blockers
Alpha-blockers
Caffeine
Ticagrelor
ACE-inhibitors

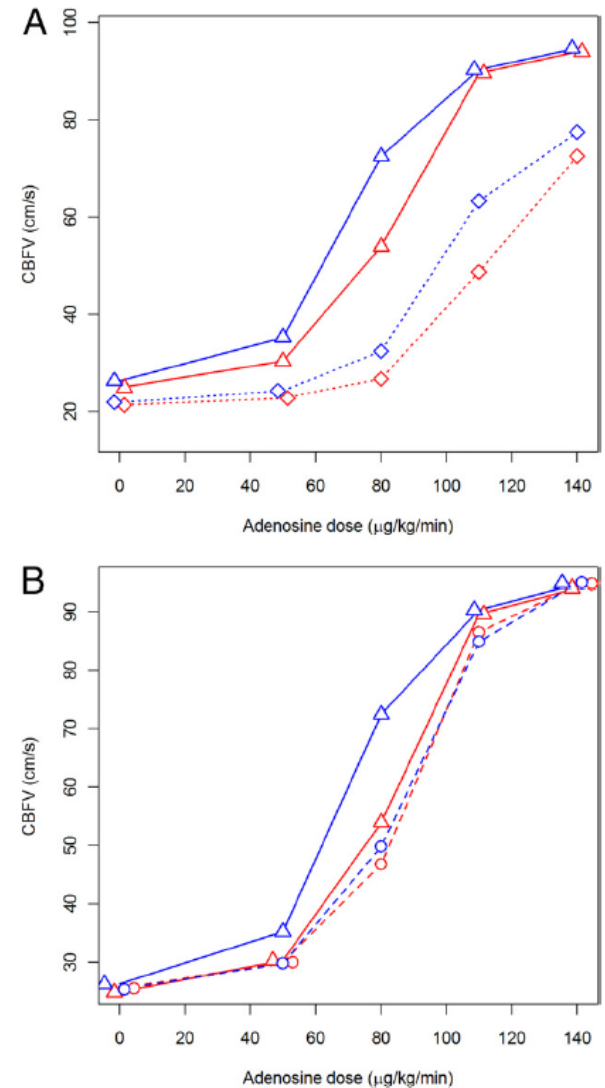
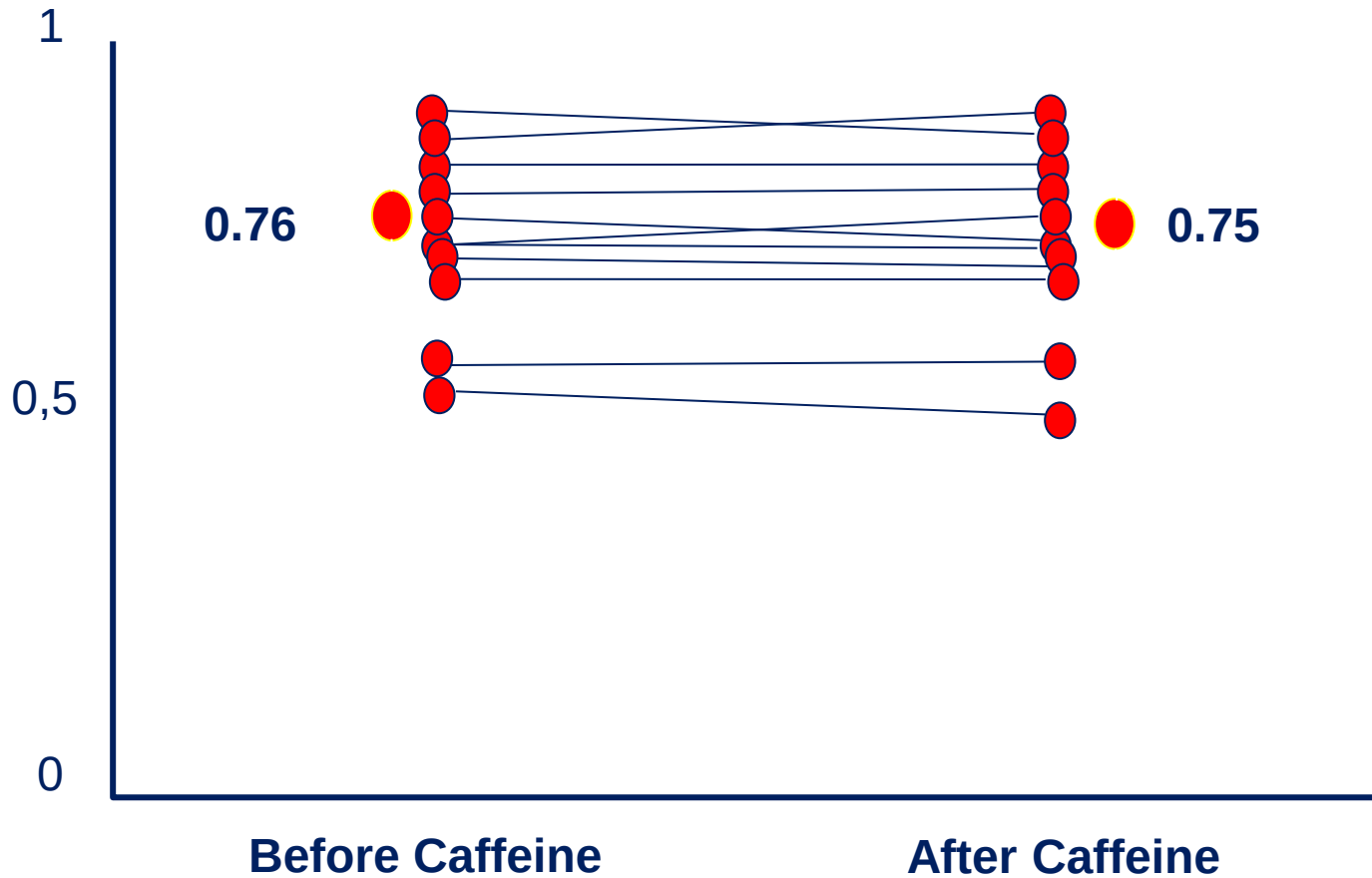


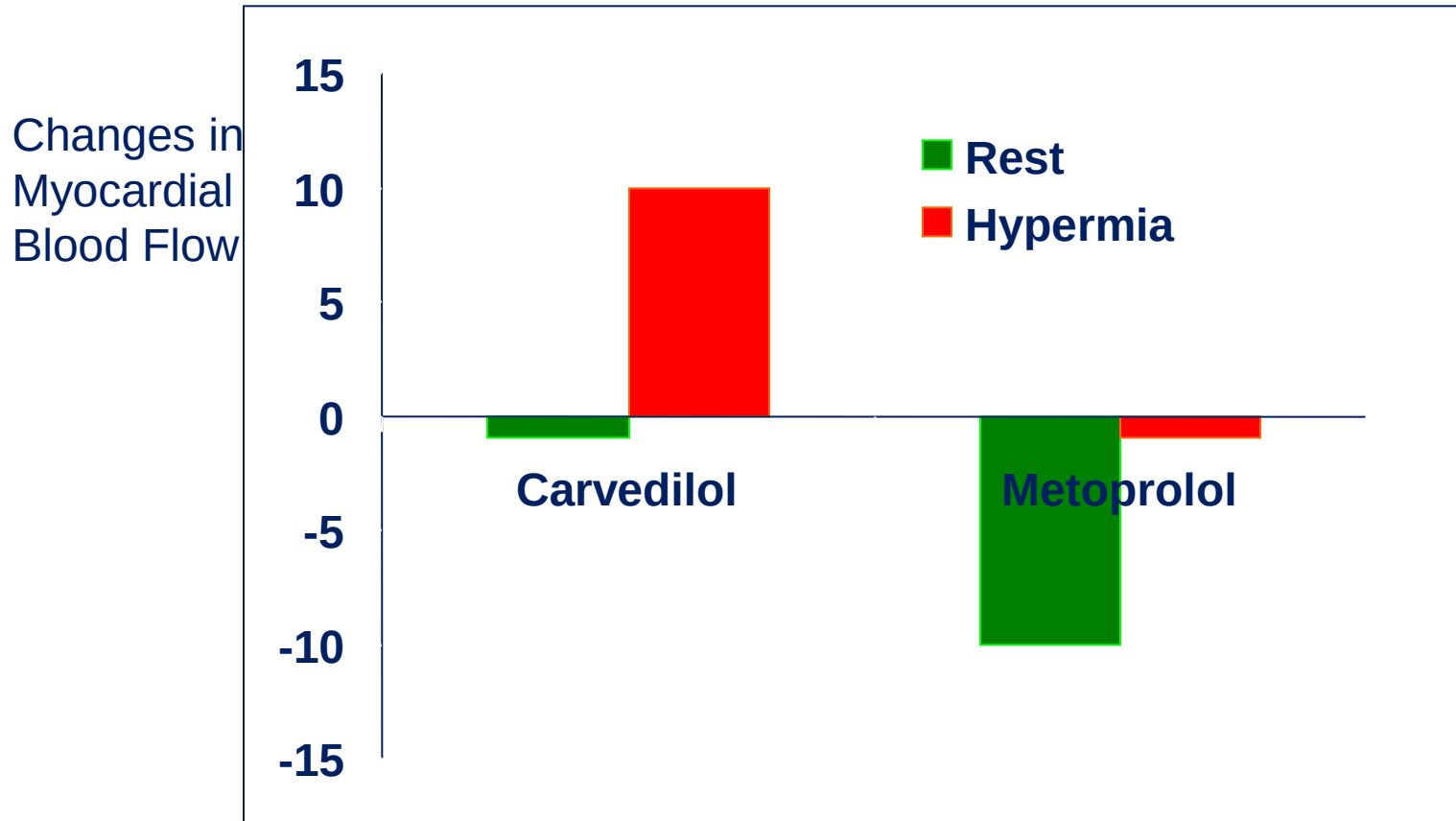
Figure 3 Treatment Effect on Adenosine-Induced CBFV

(A) Adenosine-induced mean coronary blood flow velocity (CBFV) and (B) mean CBFV after theophylline. Symbols are given by pre-placebo (red dashed line, ○), post-placebo (red solid line, Δ), pre-ticagrelor (blue dashed line, ○), post-ticagrelor (blue solid line, Δ), post-theophylline-placebo (red dotted line, ◇), and post-theophylline-ticagrelor (blue dotted line, ◇). Overlapping symbols have been slightly separated for visibility.

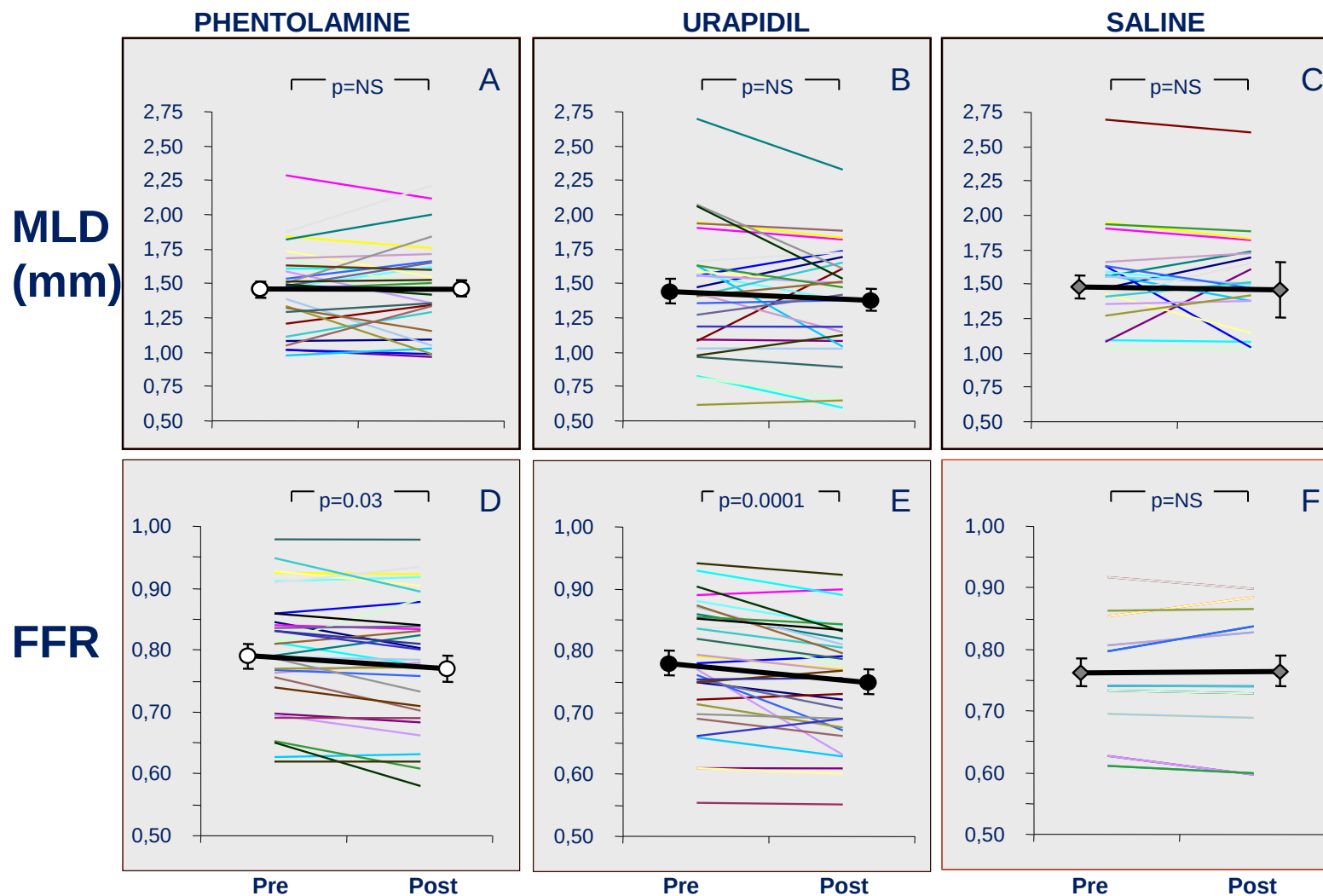
Effect of Caffeine on FFR



Beta-Adrenergic Blockade and Myocardial Flow



Effect of α -Blockers on Diameter and FFR

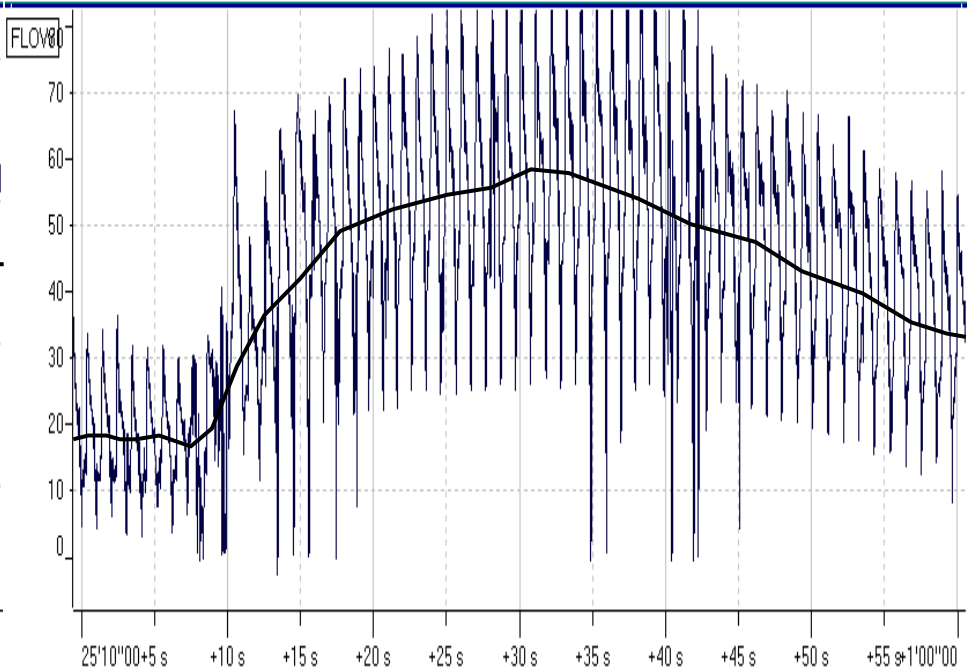
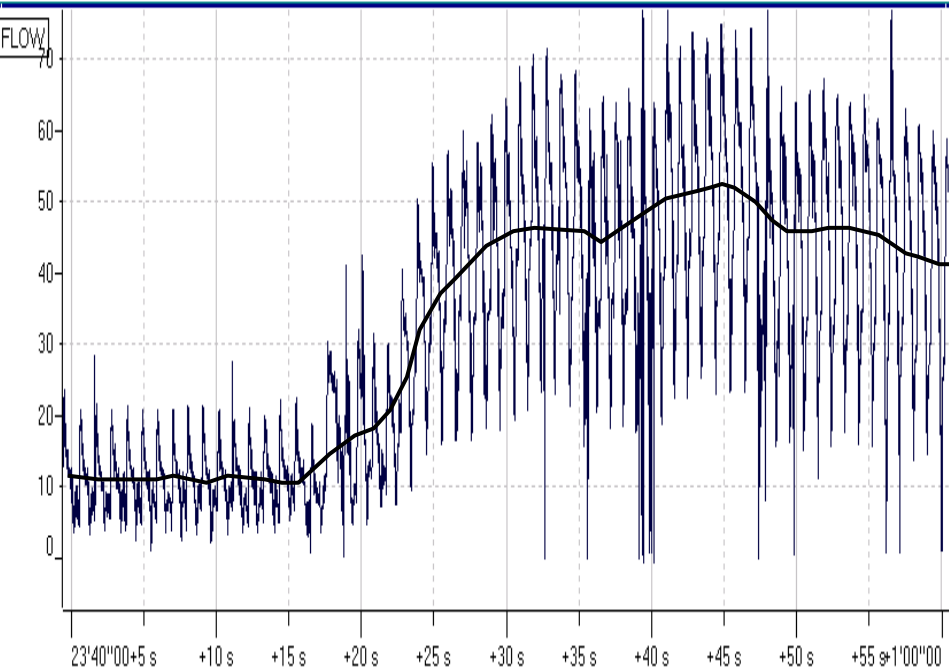
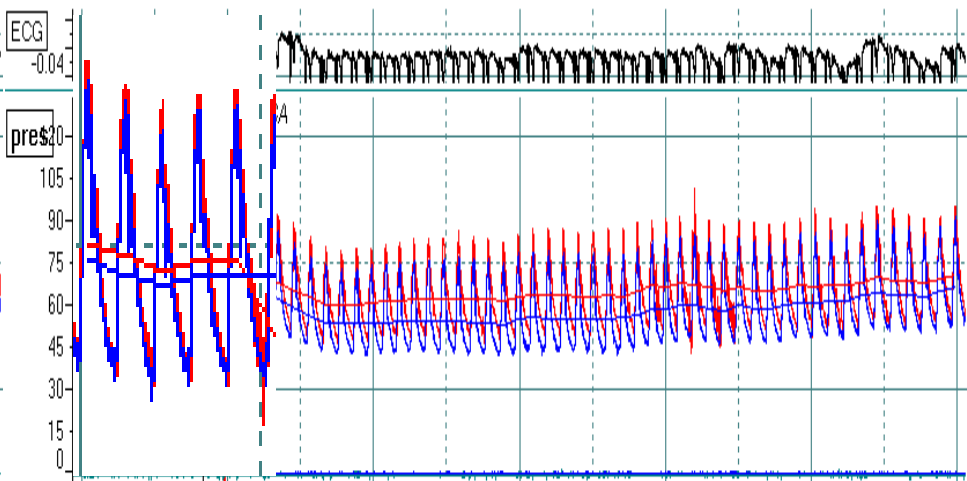
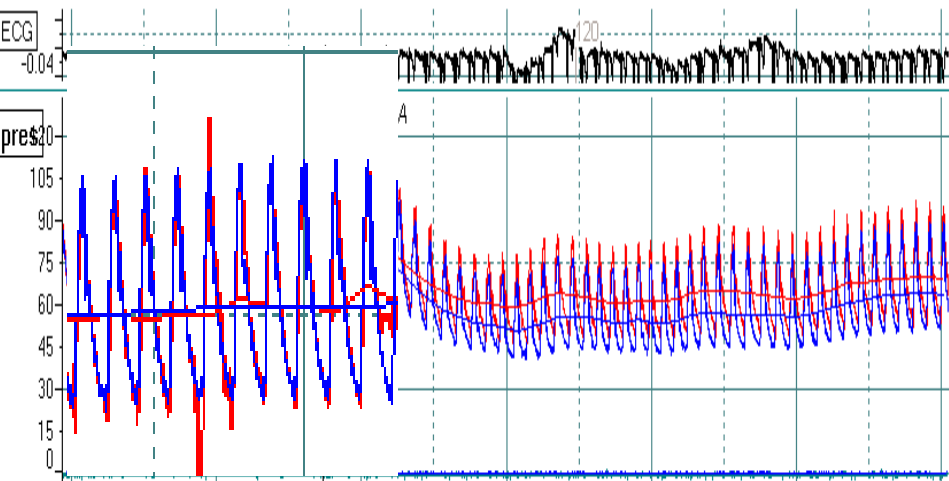


FAQ

Is adenosine contraindicated in all patients with lung disease ?

NO

- 1. Adenosine is strictly contra indicated in asthma**
- 2. Adenosine is NOT contra indicated in COPD**



Regadenosone IV peripheral



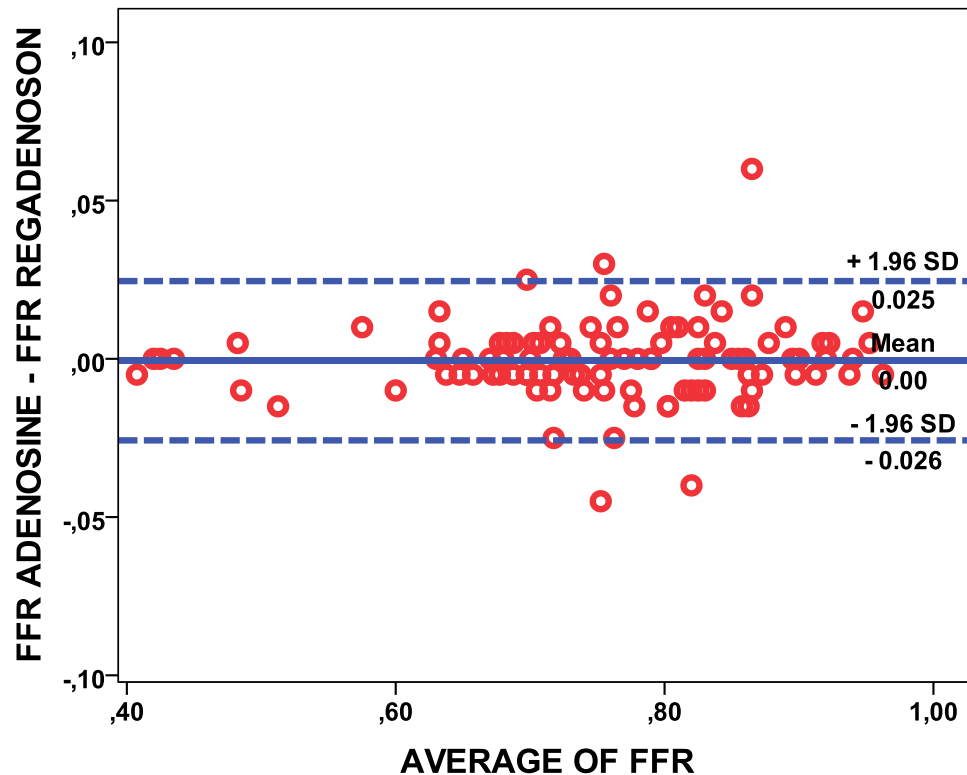
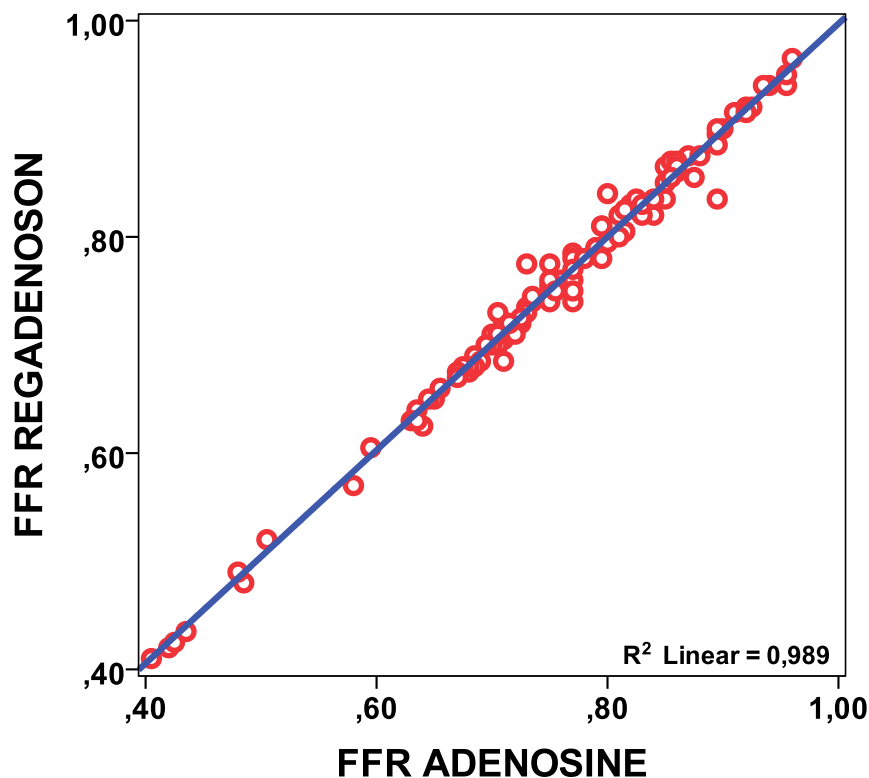
Regadenoson (= Rapiscan ®)

Regadenoson as single peripheral i.v. bolus 400 µg

- maximum hyperemia within 60 sec and lasting for at least 30 seconds (sufficient for pull-back recording)
- can be safely repeated after 10 min
- hyperemia completely comparable to i.v. adenosine

➔ *ideal in radial procedures or ad-hoc FFR*

Regadenoson vs Adenosine (N=100)



- Mean Difference 0.00 ± 0.01