CORONARY PHYSIOLOGY IN THE CATHLAB:

ABSOLUTE BLOOD FLOW MEASUREMENTS:

PRINCIPLES

Educational Training Program ESC
European Heart House
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PROBLEMS WITH ABSOLUTE FLOW (and FLOW VELOCITY)

- ***absolute blood flow*** has no meaning without knowledge of the extent of the perfusion area or without knowing a normal value

- absolute flow and all ***flow-derived parameters*** are dependant on perfusion pressure, which is highly variable within the same patient

- ***coronary*** blood flow is often not representative for ***myocardial*** perfusion, especially not in case of severe stenosis

- coronary flow, velocity, and CFR do not discriminate ***epicardial or microvascular disease***

Consequently, for *routine interventional practice* and decision making in the catheterization lab, absolute flow or flow velocity has little value.

Fractional Flow Reserve (FFR) perfectly describes the influence of the epicardial stenosis on myocardial perfusion

For *scientific purposes* and assessing the *microcirculation*, things might be different

If you know absolute maximum blood flow
in ml/min for an arbitrary stenosis, arbitrary myocardial distribution and any blood pressure and heart rate (***e.g. 80 ml / min***)

<u>AND</u> you know FFR
(***e.g. 0.50***)

you also know the normal maximum flow for that respective distribution under those specific hemodynamic conditions:

⟶ ***160 ml / min (!)***

……and if you also know ***coronary wedge pressure (Pw)*** , you know both the ***absolute myocardial, coronary, and collateral flow***

(because FFR gives the relative contribution of coronary arterial and collateral flow to myocardial flow)

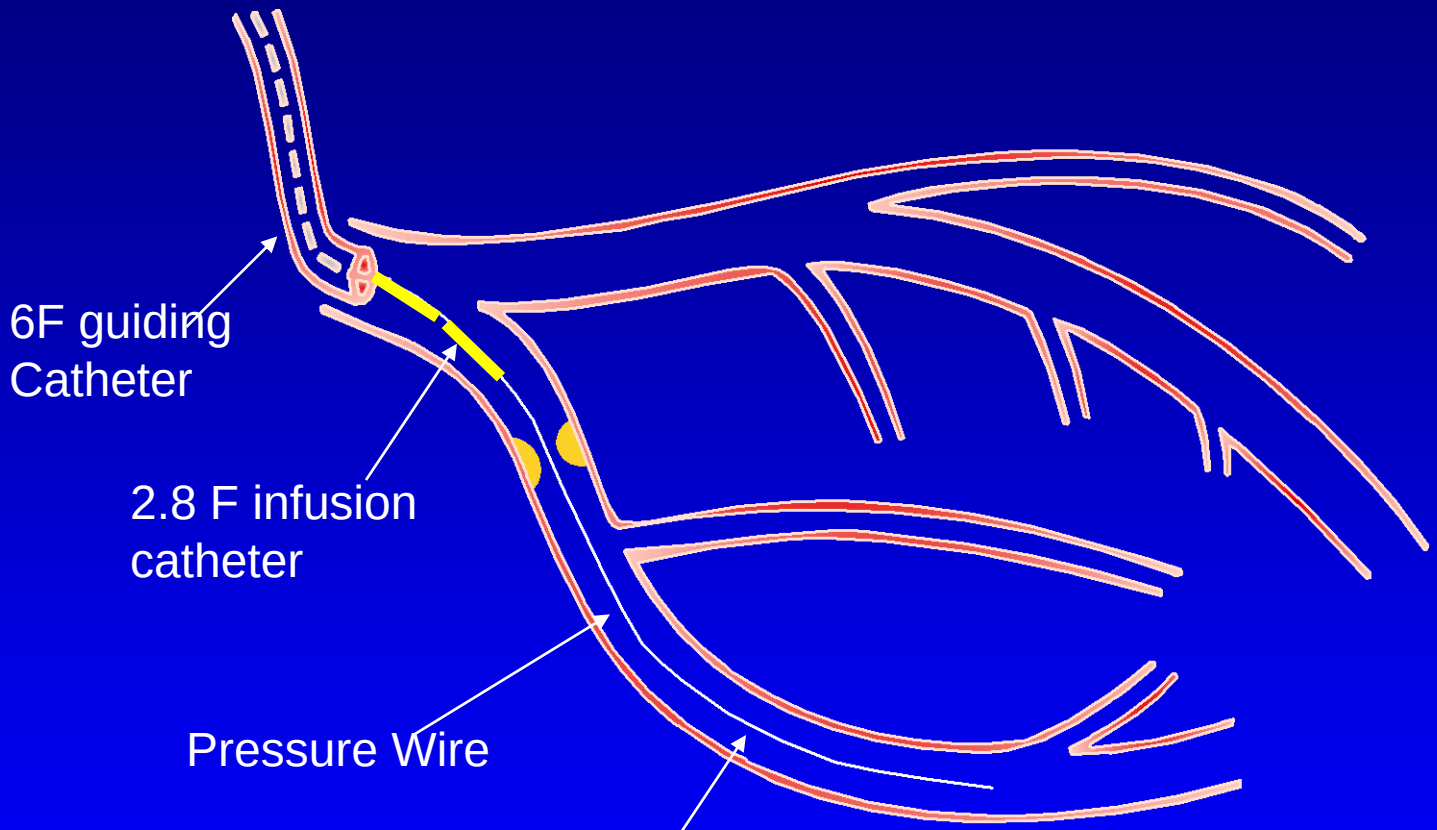
…….and if you measure ***coronary pressure*** simultaneously, you know ***all resistances quantitatively*** for any arbitrary coronary segment, myocardial distribution, or collateral bed

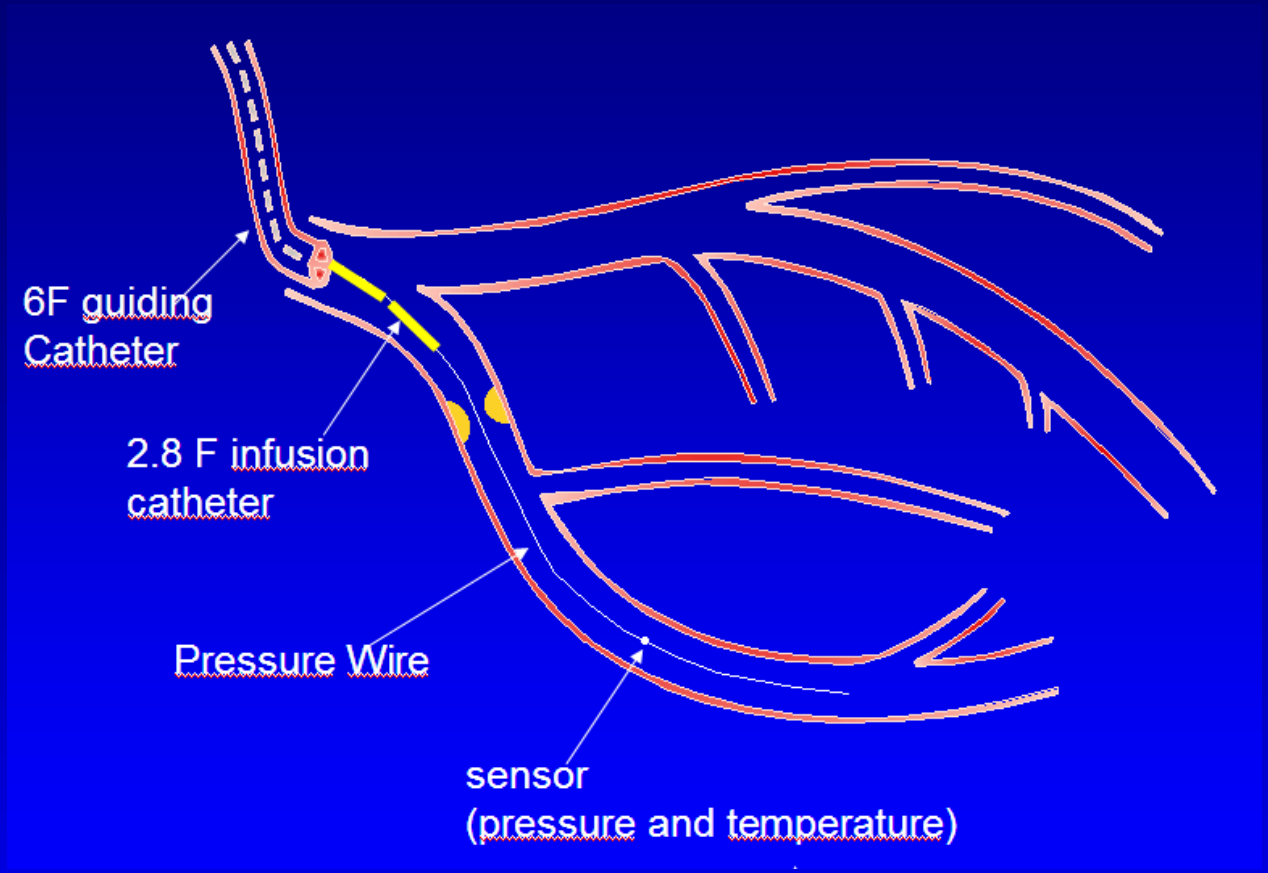
⟶ ***Easy assessment of microcirculation and collaterals***

So, from the scientific and physiologic point of view, it would be attractive to measure hyperemic absolute flow (in conjunction with pressure)…

- assessing the microcirculation
- quantitation of collateral flow
- quantitation of microvascular flow and resistance in specific patient groups:
  - *heart-transplant follow-up*
  - *stem cell therapy*
  - *syndrome X (whatever it might be)*
  - *prognostic stratification after STEMI*

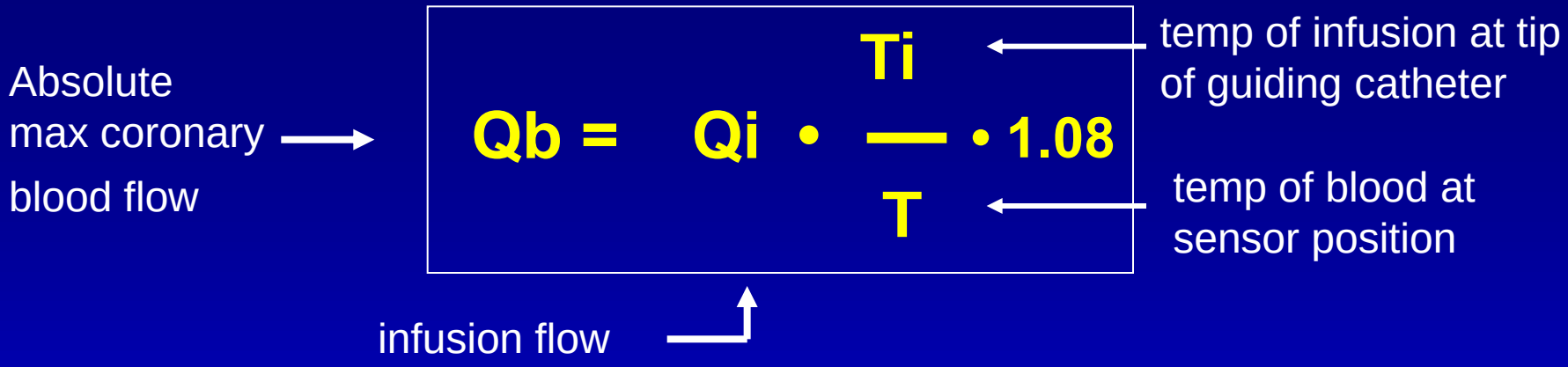
continuous infusion of saline to determine absolute maximum coronary blood flow





saline infused at 20 ml/min
temperature of saline is 5° below blood temperature
after mixing, temperature of mixtate is 1° below blood temp

⟶ blood flow must be 5 x infusion flow of saline



saline infused at 20 ml/min
temperature of saline is 5° below blood temperature
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→ blood flow must be 5 x infusion flow of saline

continuous infusion of saline to determine absolute maximum coronary blood flow

Prerequisites :

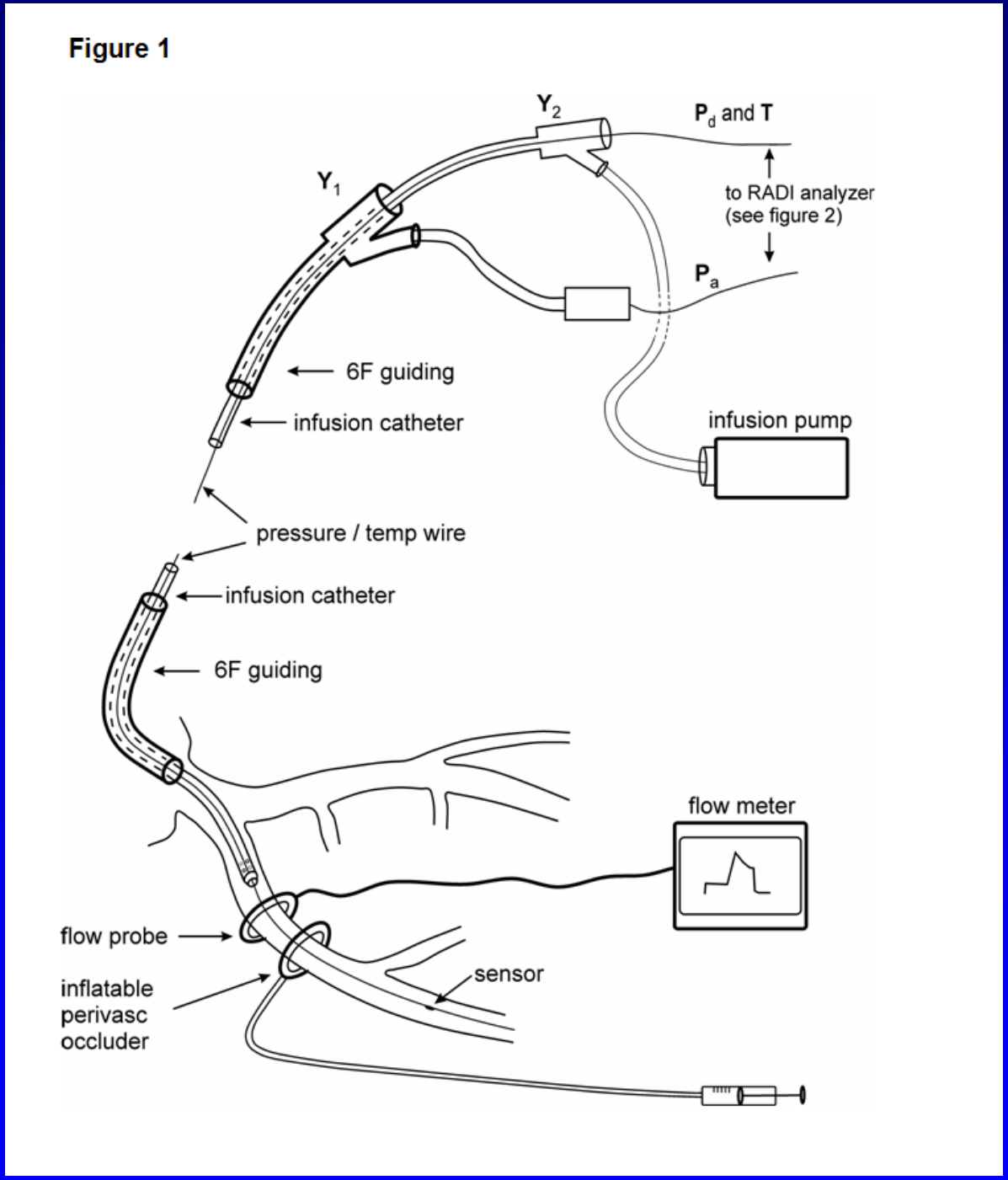
- decrease of coronary temperature should be large enough to be detected and stable (or stated another way: temperature sensor should be sensitive enough to detect changes) , given a reasonable injectate flow *(adequate signal/noise ratio)*

- *complete mixing* of blood and saline between injection site (= tip of infusion catheter) and sensor position

- *heat (“cold”) loss through the wall* of the artery must be small compared to convection by blood

Animal study:

instrumentation



ANIMAL STUDY: methods

- five mongrel dogs, 28-43 kg
- instrumentation of LCX by perivascular flow probe and perivascular balloon occluder at day 0
- cardiac catherization at day 7, Amplatz guiding catheter
- 0.014” pressure wire *(RADI)* distal to flow probe/occluder for coronary pressure & temperature measurement
- 2.8 F special infusion catheter *(AMT, Inc)* over wire, position just proximal to occluder
- creation of different degrees of stenosis *(corresponding with FFR of 0.85, 0.70, 0.55, 0.40)*
- measurements with continuous saline infusion at 2 different infusion rates and 2 different sensor positions
- in-duplo measurements for all degrees of stenosis, both infusion rates, and both sensor positions:

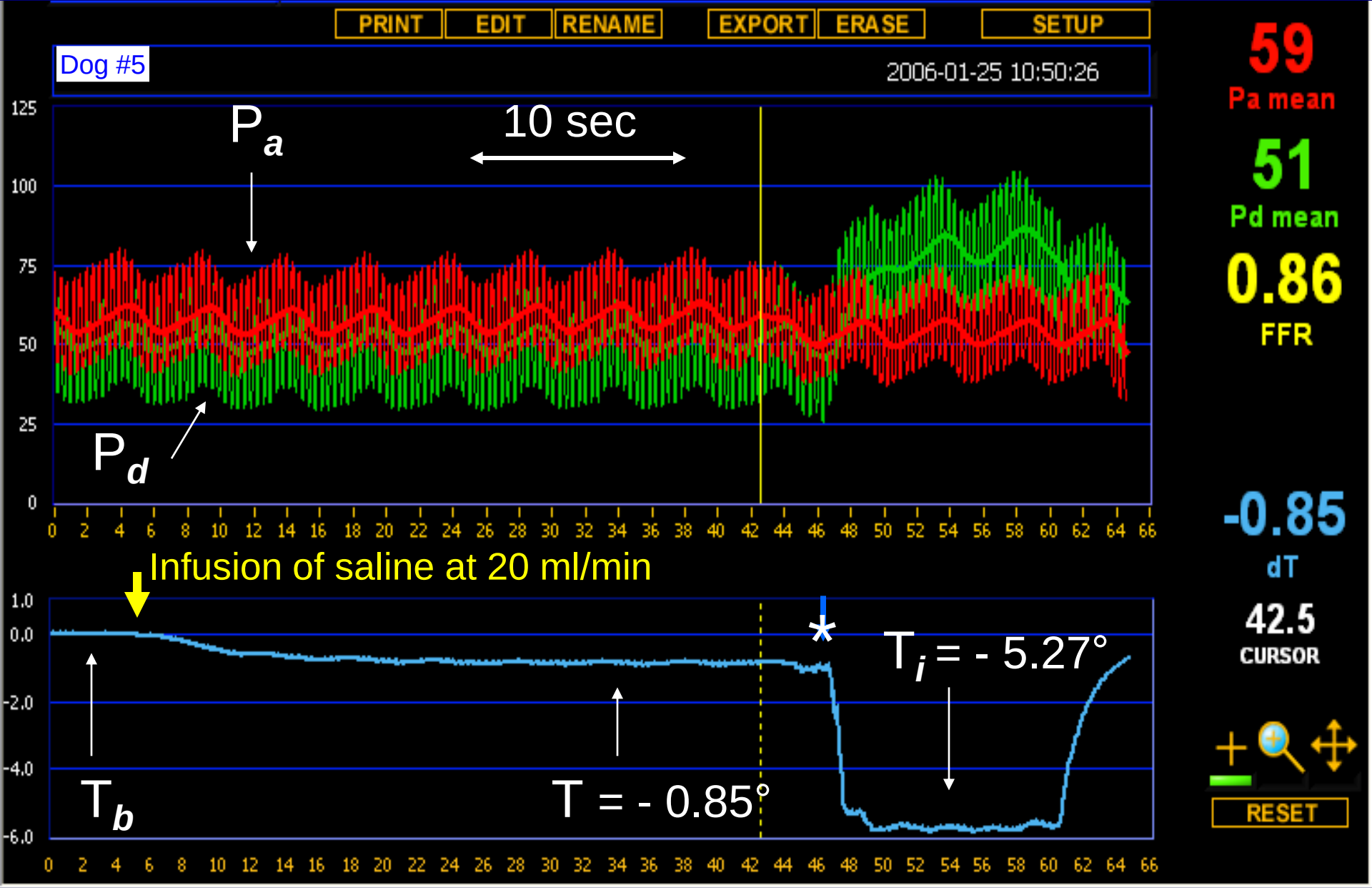
⟶ ***4 x 2 x 2 x2 = 32 measurements per dog***

Infusion Catheter For Thermodilution (Hexacath ®)

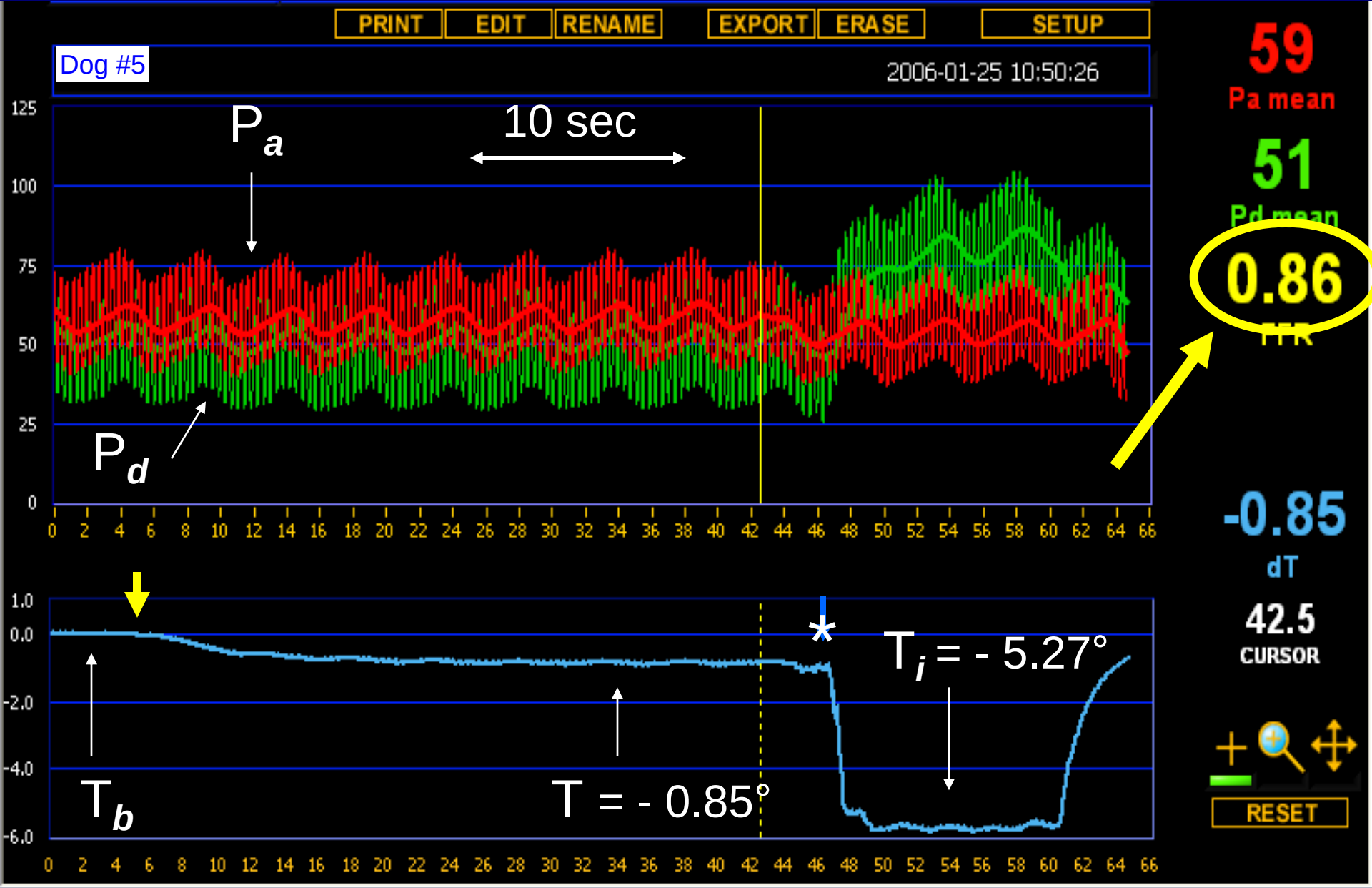
(complete mixing of blood and saline)

without guidewire

with guidewire



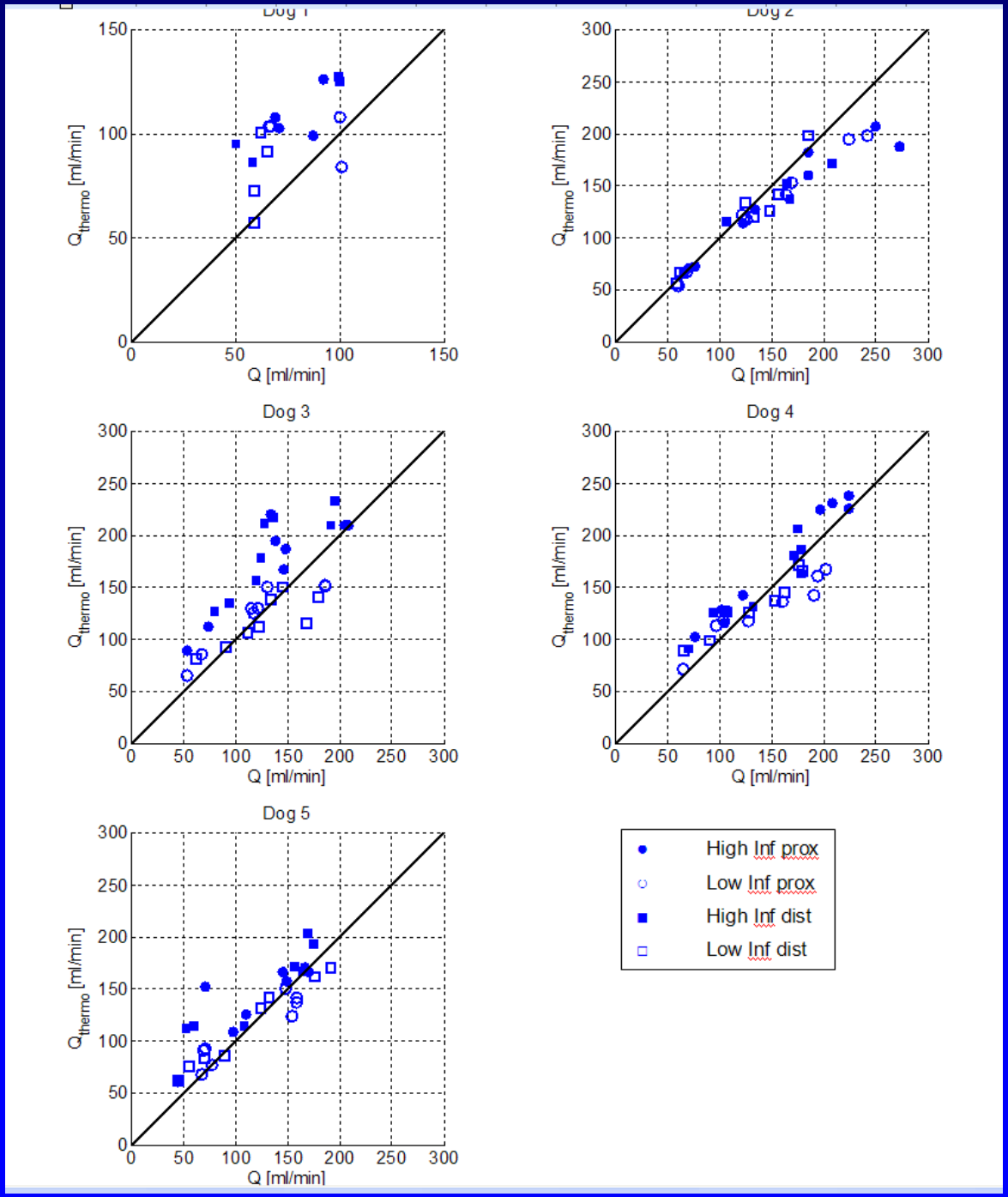
$$Q\boldsymbol{b} = 20 \times (-5.27\ \boldsymbol{I}\ -0.85) \times 1.08 = 134\ \text{ml/min}$$

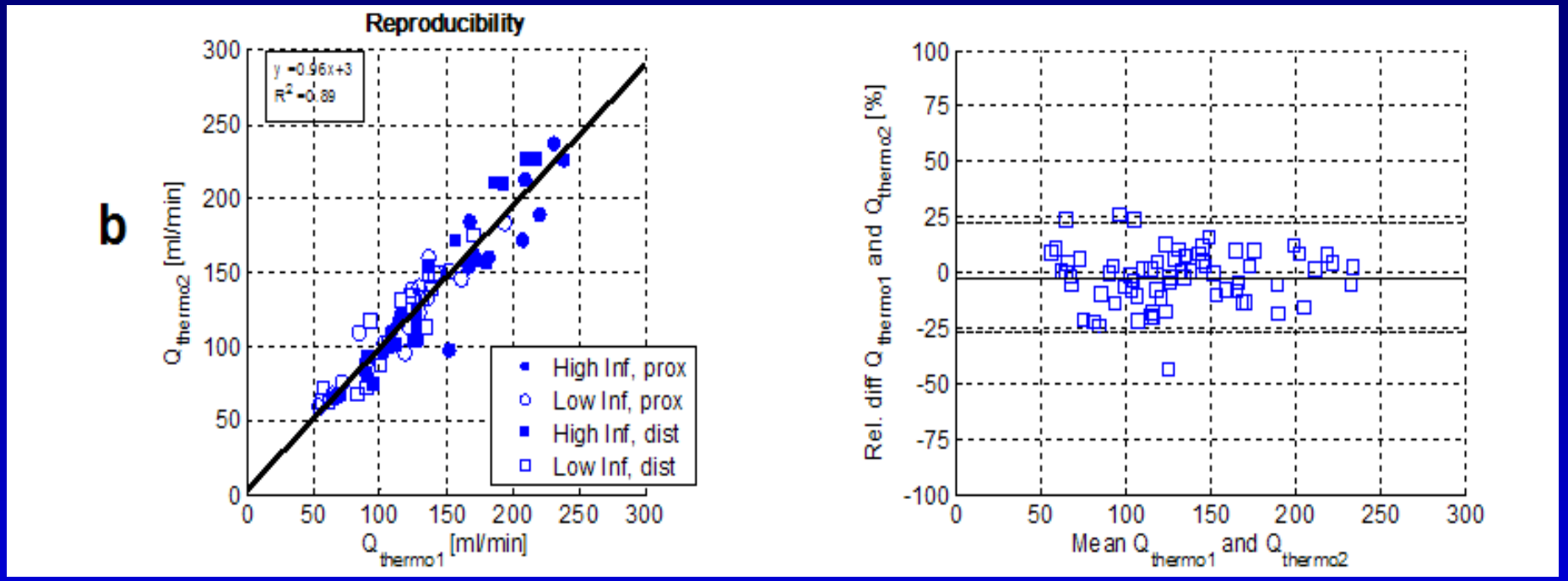


Q***b*** = 134 ml/min ⟶ <u>normal</u> max flow = 100/86 x 134 = 156 ml/min

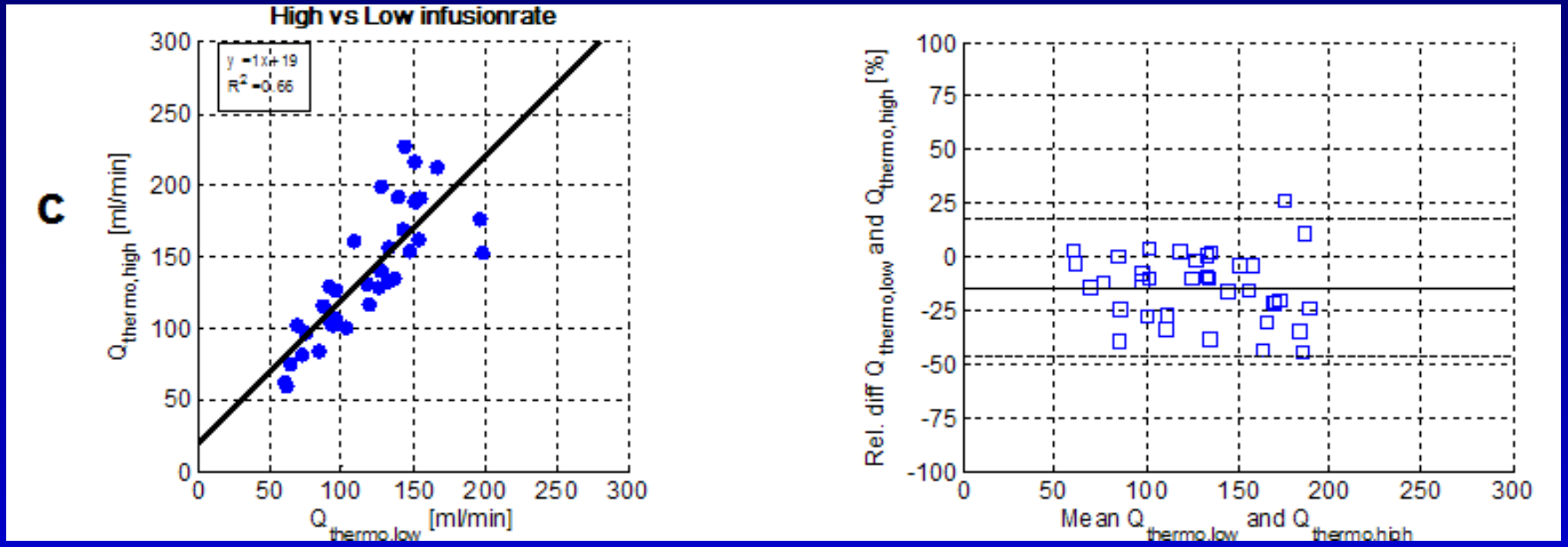
Animal study:

results in the individual dogs





Animal study: *reproducibilty* (N=72)

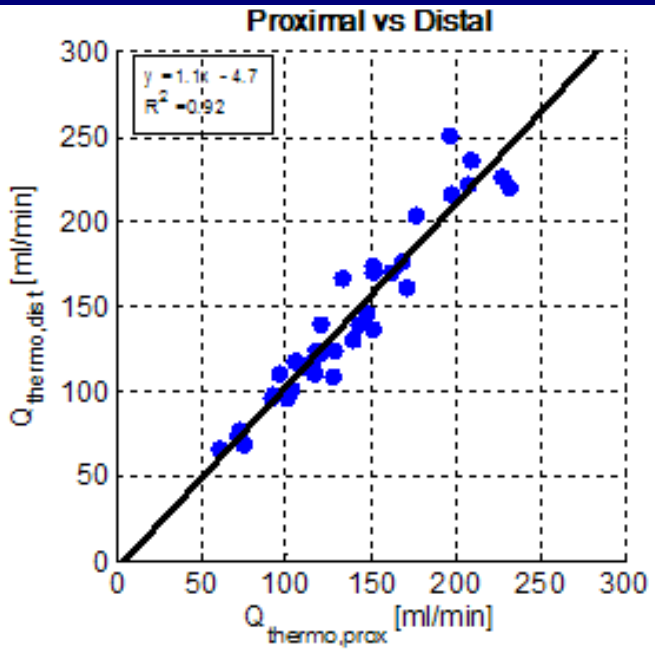


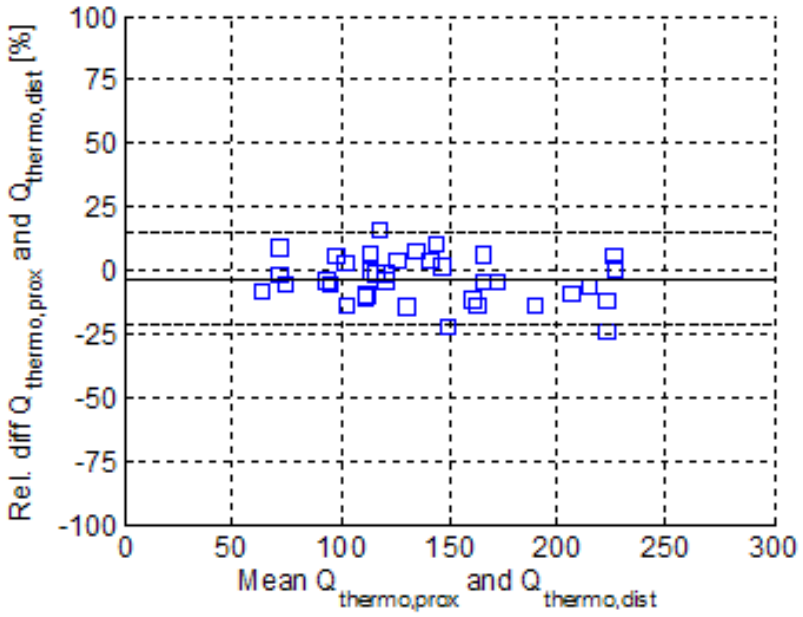
Animal study: *high versus low infusion rate*

15-25 ml/min

8-15 ml/min

saline room temp





Animal study: *proximal versus distal sensor position*

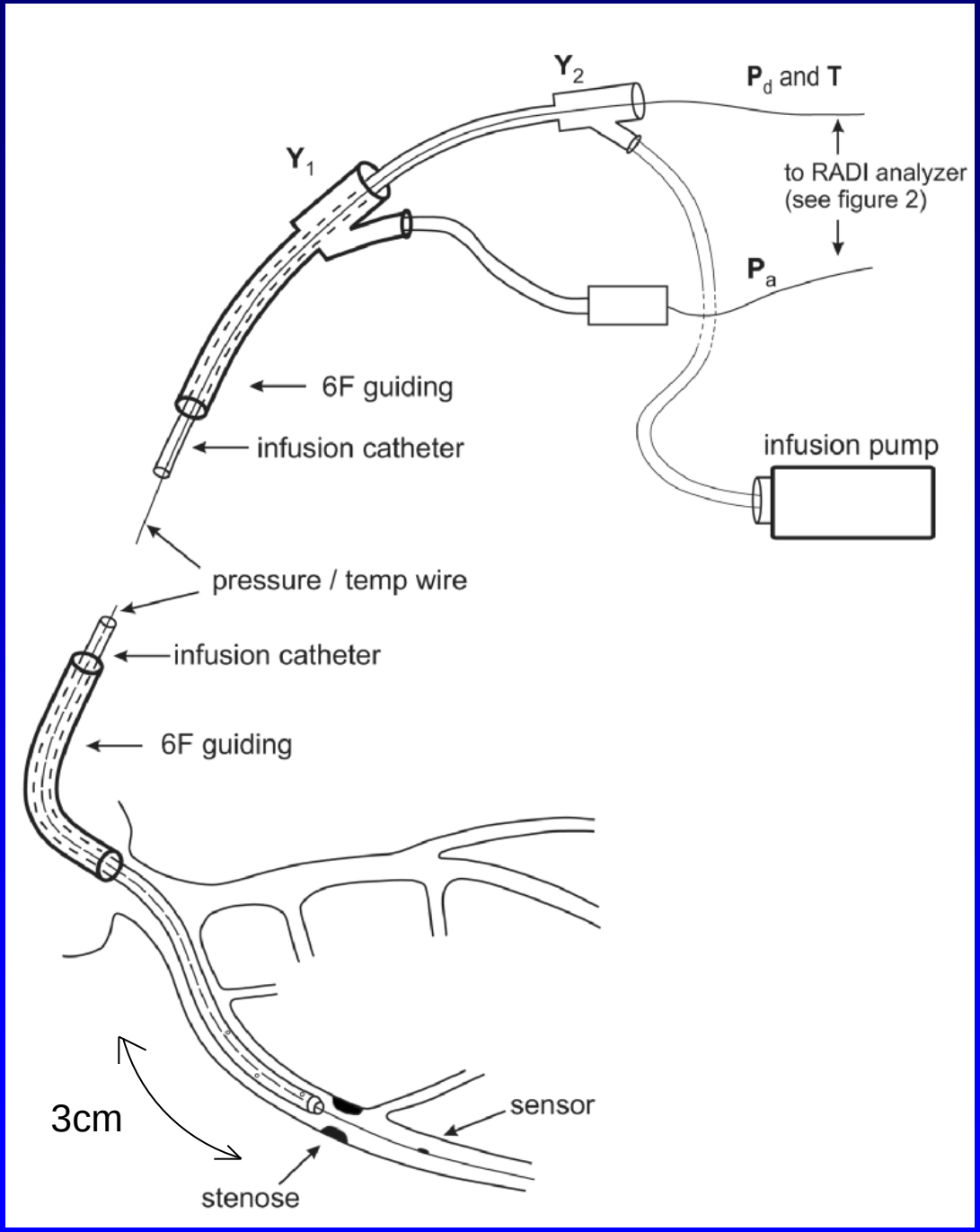
3 cm 6 cm

from tip of infusion catheter

Human validation study

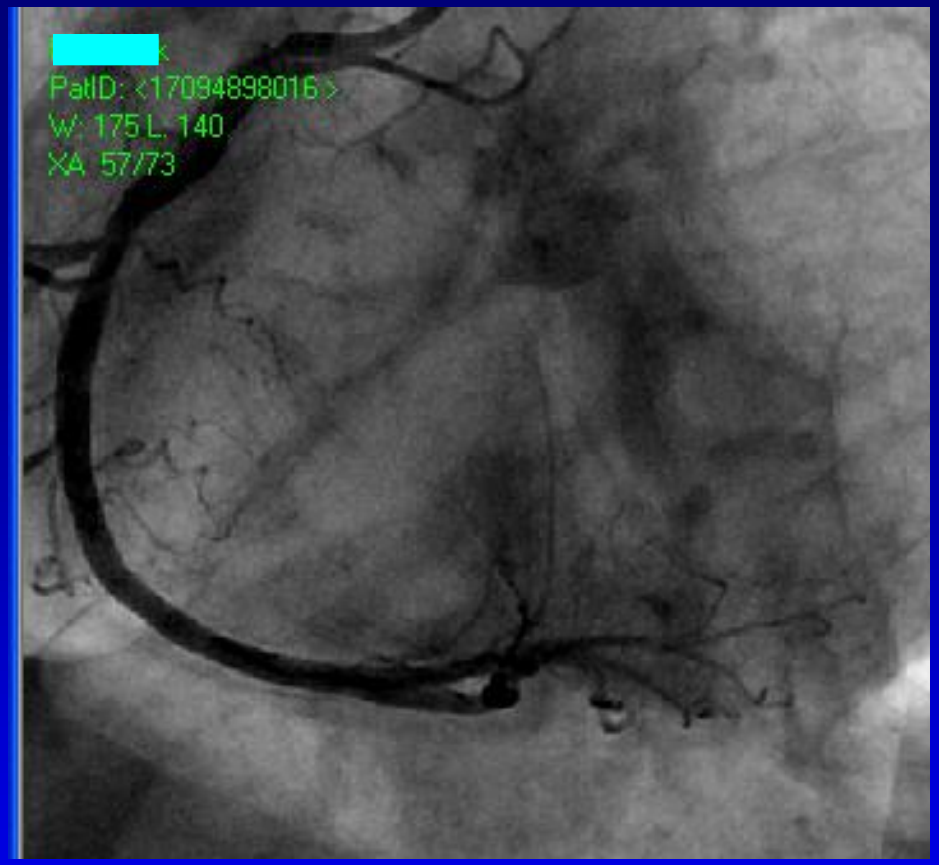
Human study:

instrumentation



Patient # 1:

- normal right coronary artery
- Qi = 25 ml / min saline at room temperature
- sensor located 7 cm from tip of infusion catheter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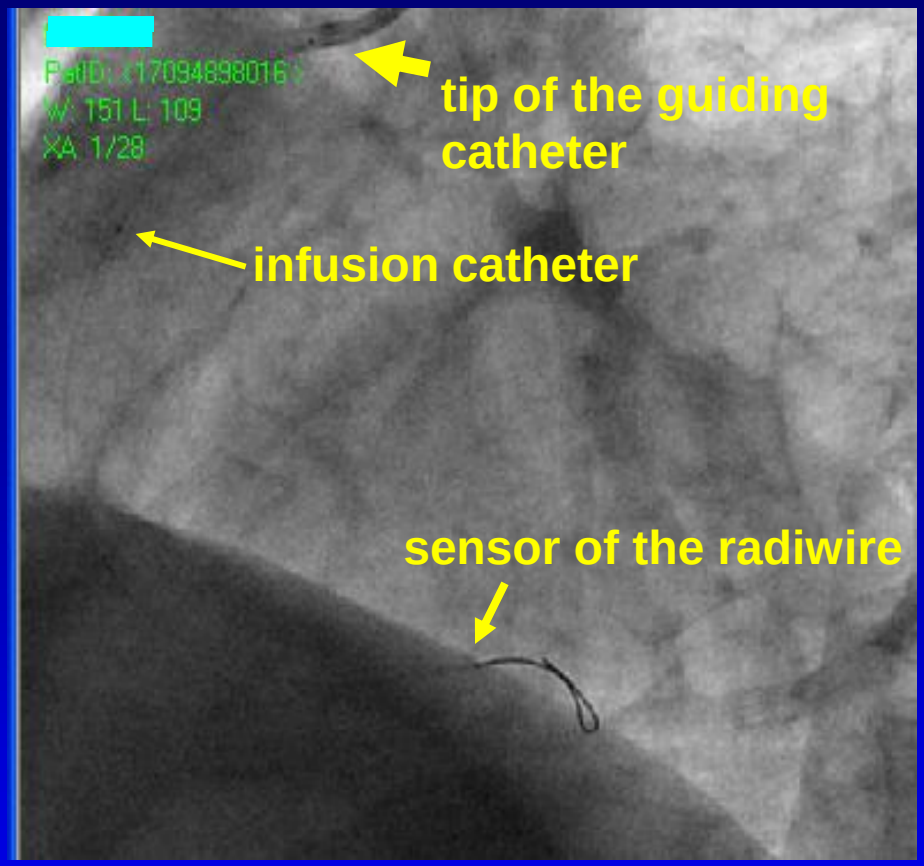
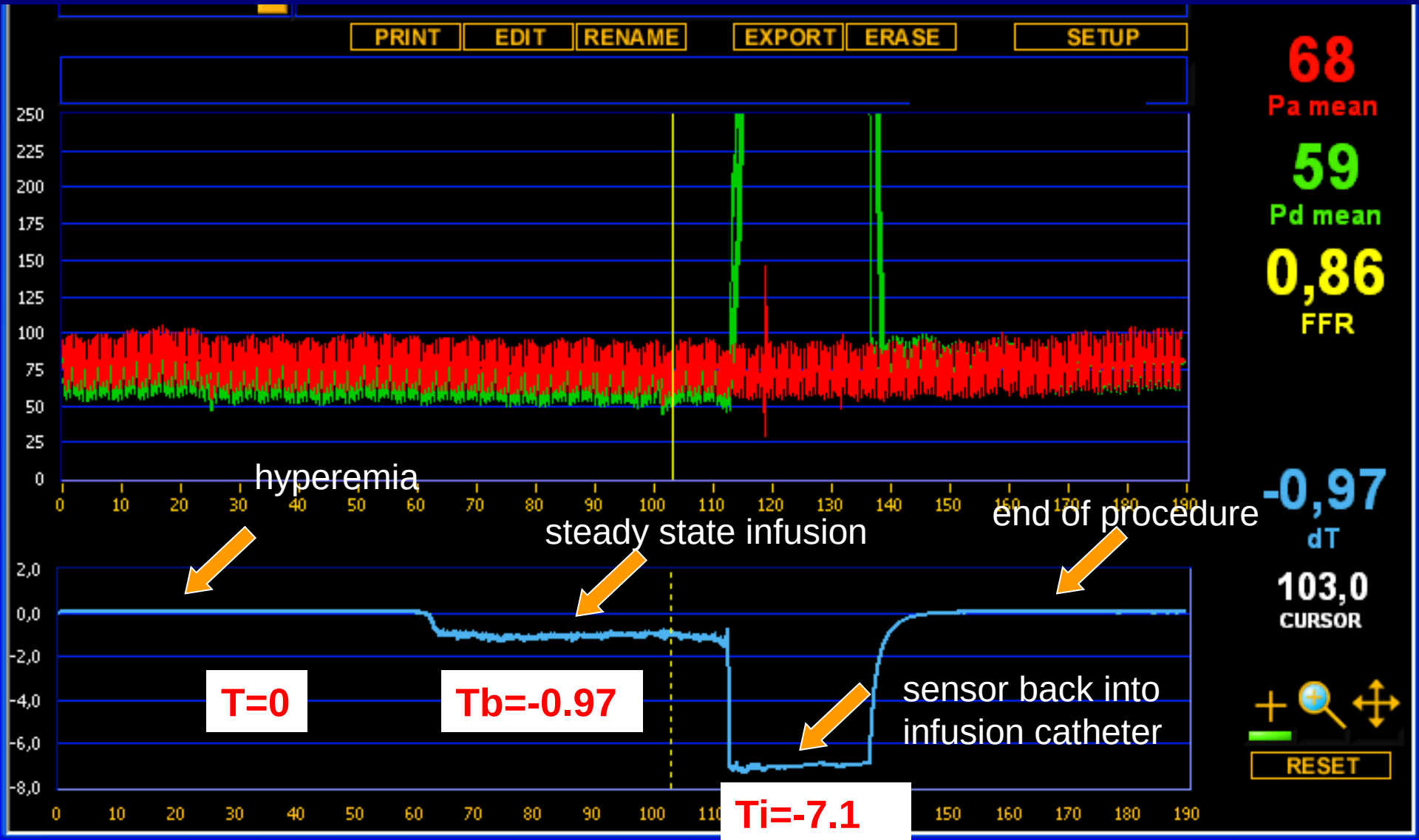
XA 57/73


PatID: <17094898016>
W: 151 L: 109
XA 1/28
tip of the guiding catheter
infusion catheter
sensor of the radiwire

continuous infusion during 3 minutes



Qb= 25 x (7.1 / 0.97) x 1.08 = 198 ml/min

(and normal max flow in this artery is 100/86 x 198 = 230 ml/min)

Patient # 3:

Before intervention

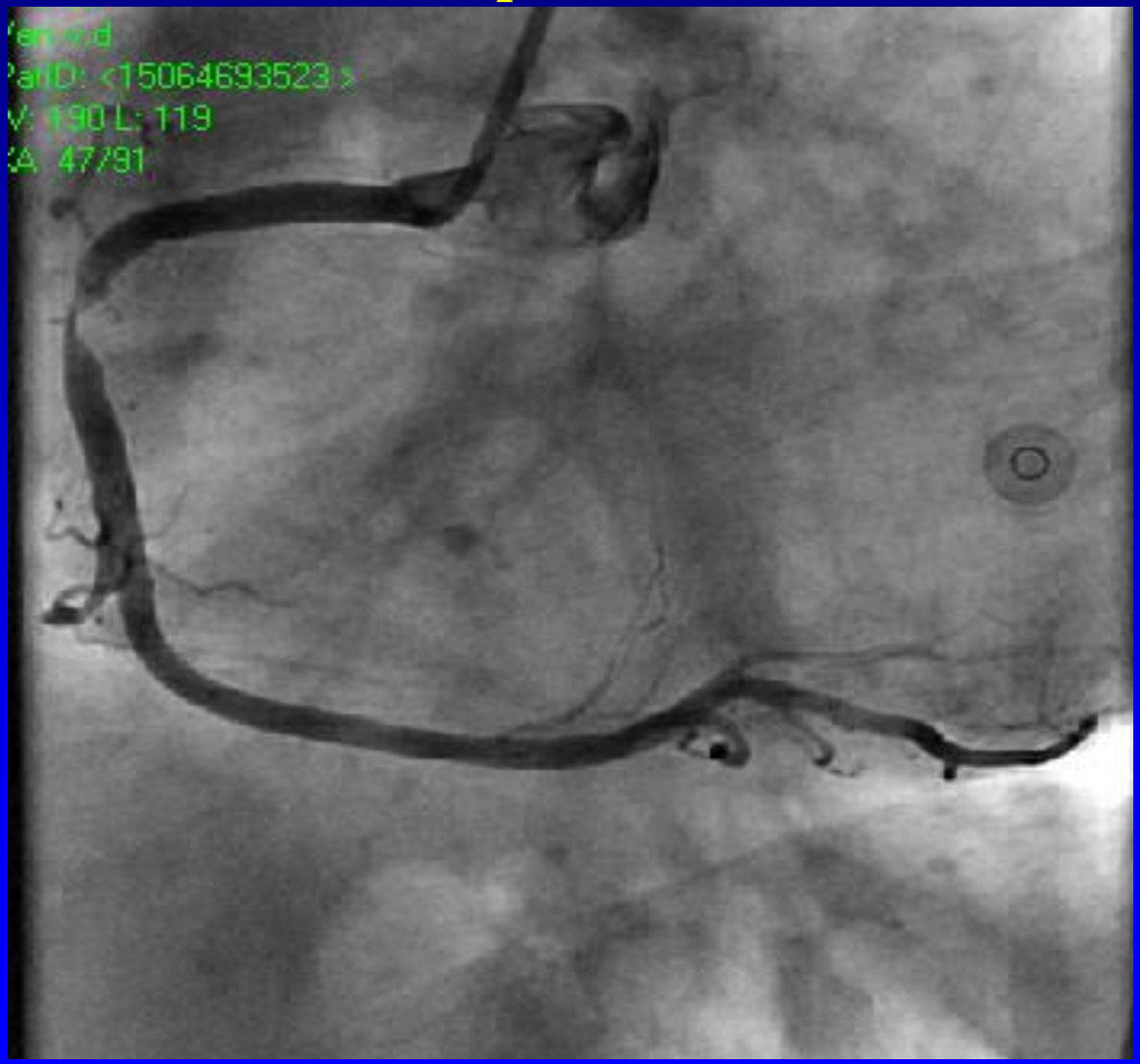
- stenotic right coronary artery
- Qi = 15 ml / min saline at room temperature
- distance 7 cm

After successful stenting:

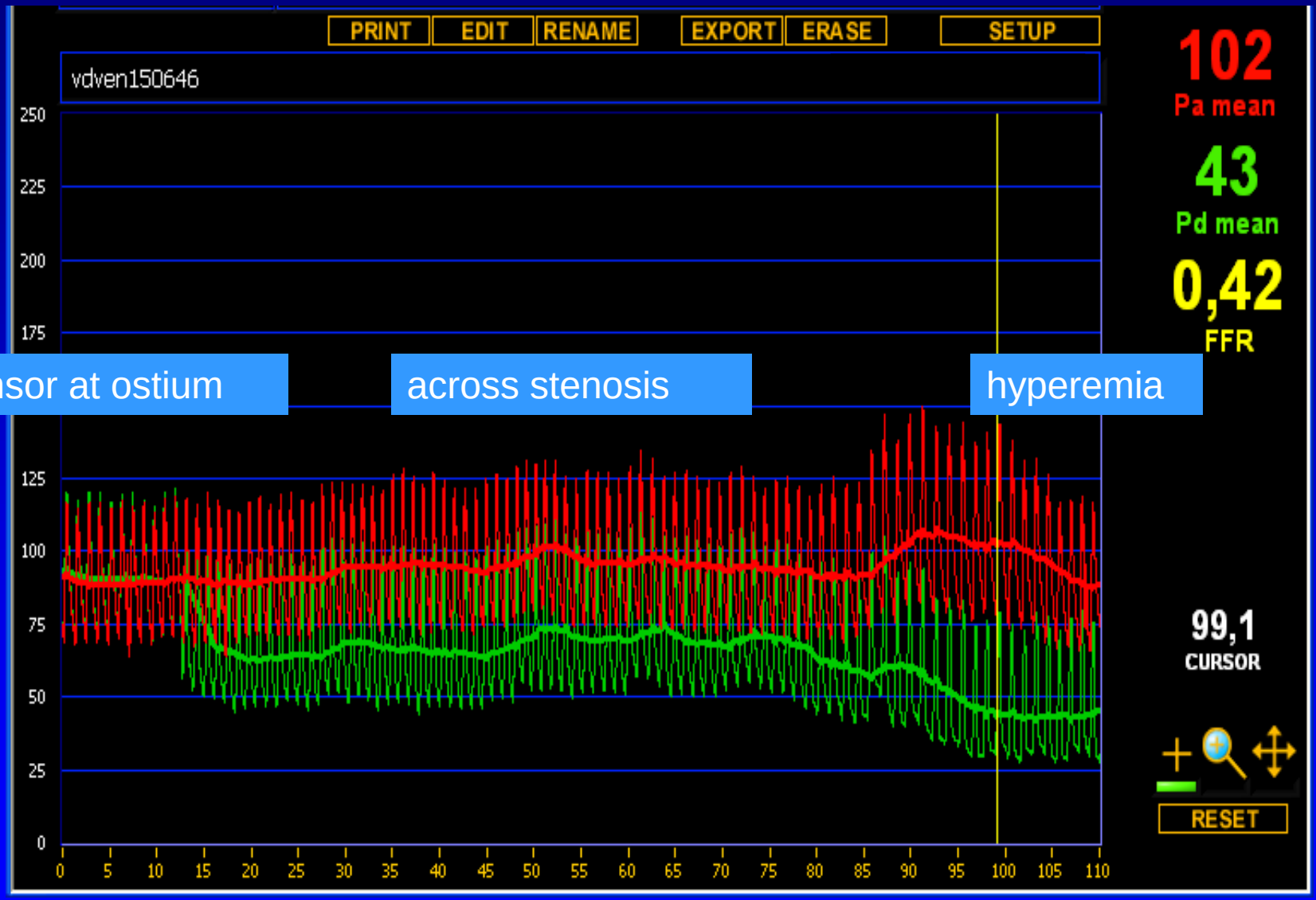
- Qi = 15 ml/min
- Qi is 20 ml/min

Male 58-y-old

Stenose proximale RCA

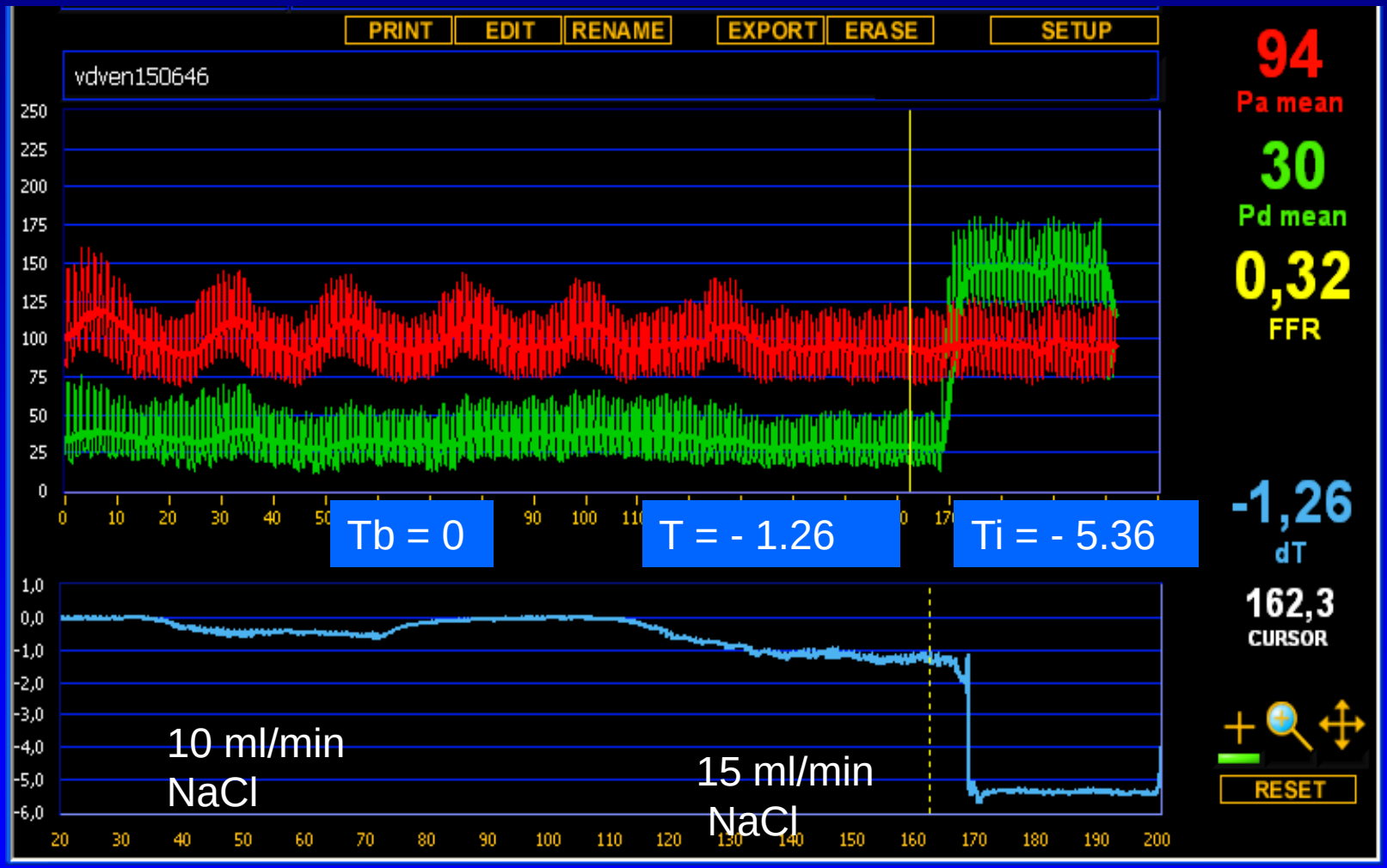


FFR RCA= 0,42


PRINT
EDIT
RENAME
EXPORT
ERASE
SETUP
vdven150646
102
Pa mean
43
Pd mean
0,42
FFR
sensor at ostium
across stenosis
hyperemia
99,1
CURSOR
RESET
250
225
200
175
125
100
75
50
25
0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110

Infusion in RCA

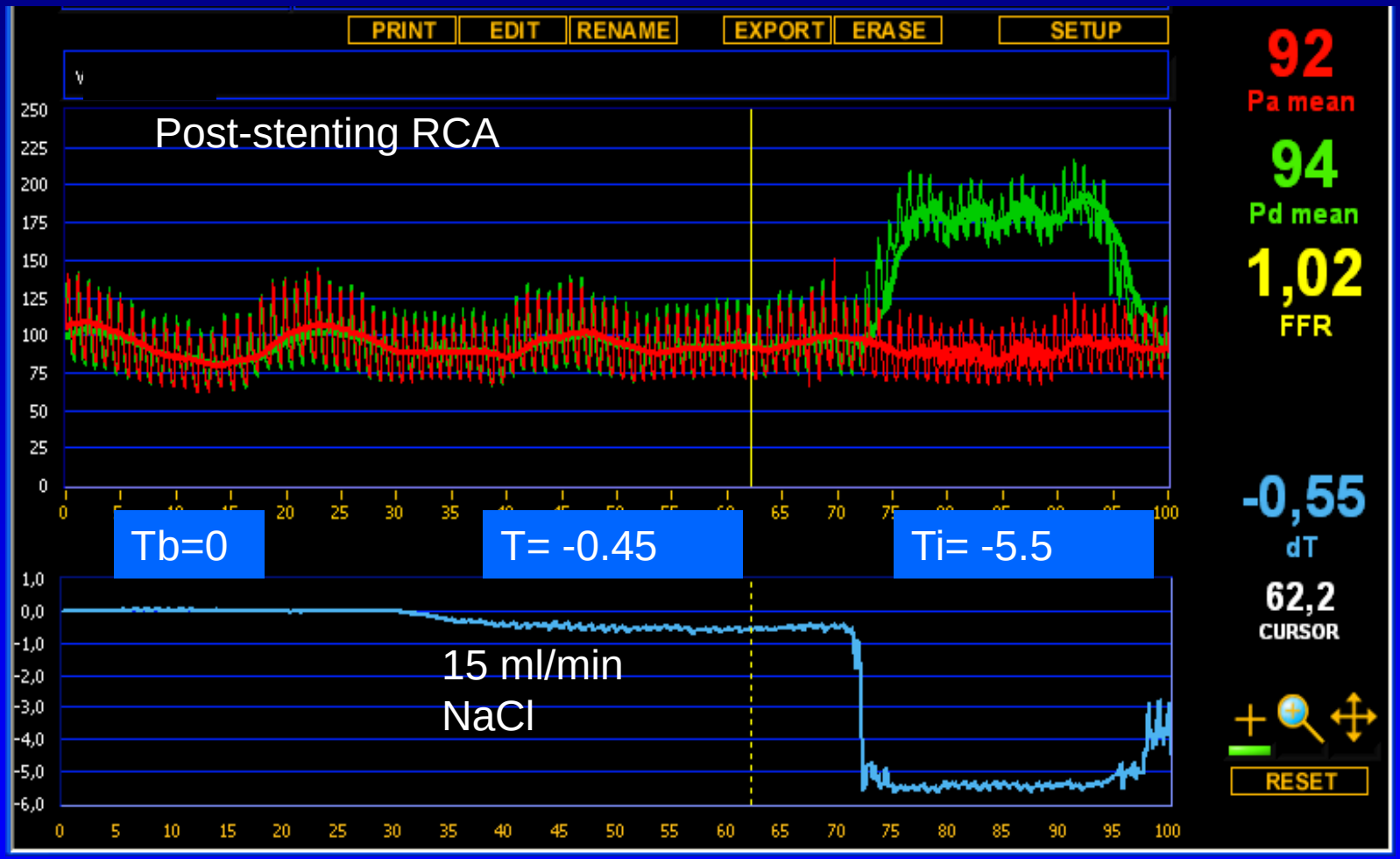
At first, Qi=10ml/min, next infusion interrupted and restarted with a rate of Qi=15ml/min.



Qb= 15 x (5.21 /1.31) x 1.08 = 64 ml/min

After stenting of RCA: FFR=0.98

Infusion rate Qi = 15ml/min.



Qb= 15 x (5.5 / 0.45) x 1.08 = 196 ml/min

Human Study: Selected Patients

- 35 patients referred for PCI or FFR measurement

- single stenosis in segment without major sidebranches (24 RCA, 10 LAD, 1 LCX)

- FFR ≤ 0.75 in 14 patients → stenting
- in these patients thermo measurement before and after PCI with saline at room temperature, for indirect quantitative validation

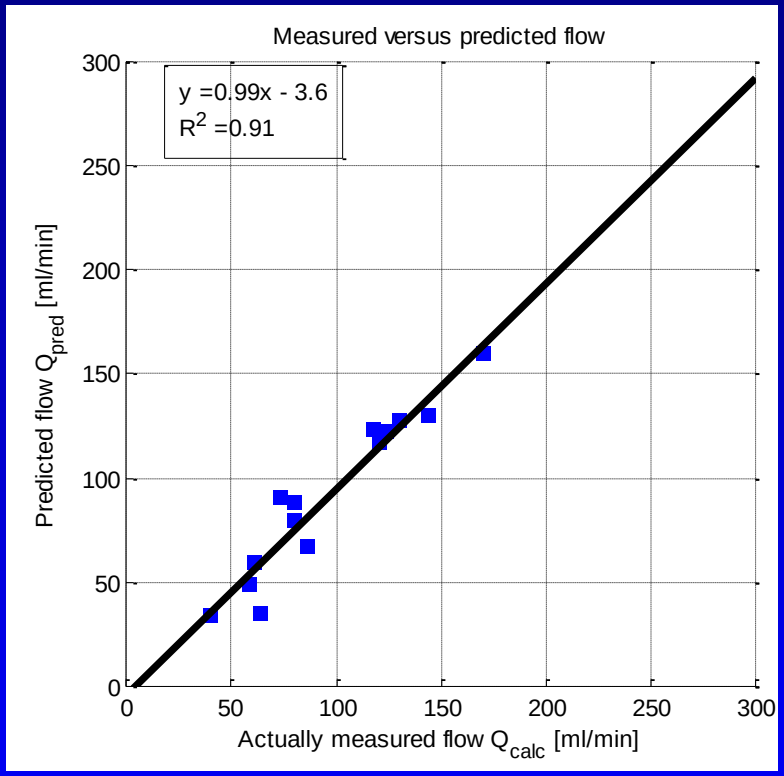
- in 10 patients 2 different infusion rates of saline (10-15 and 15-25 ml/min)

- in 11 patients 2 different sensor positions (3-4 and 6-8 cm distal to the tip of the infusion catheter

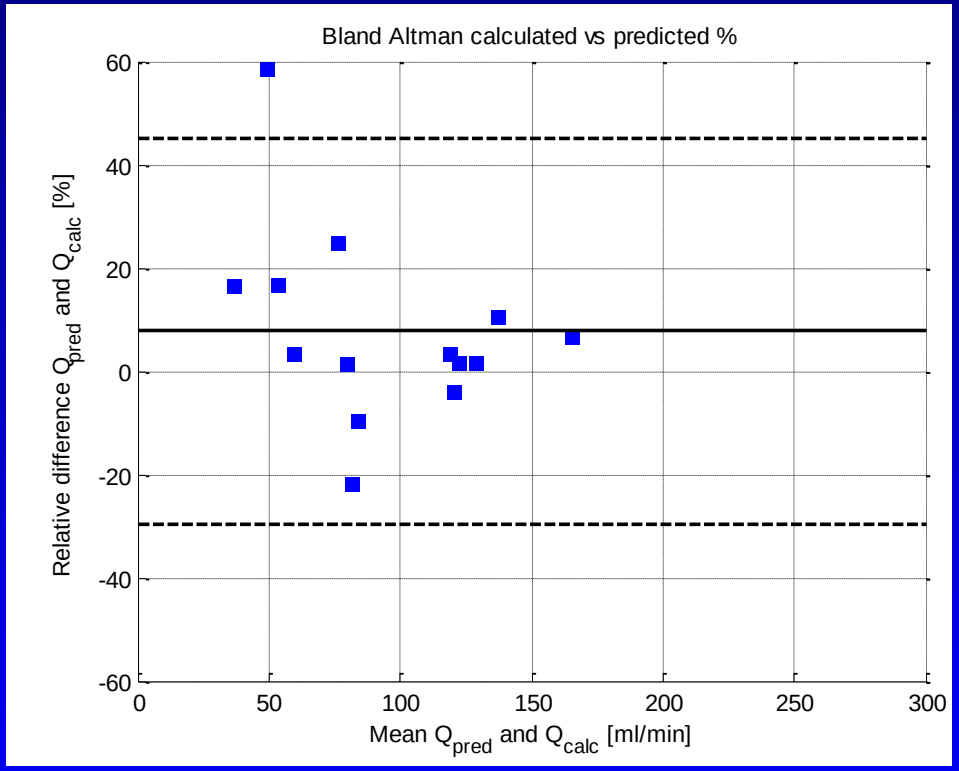
- all measurement in duplo with 2-min interval in between

Human study: quantitative validation

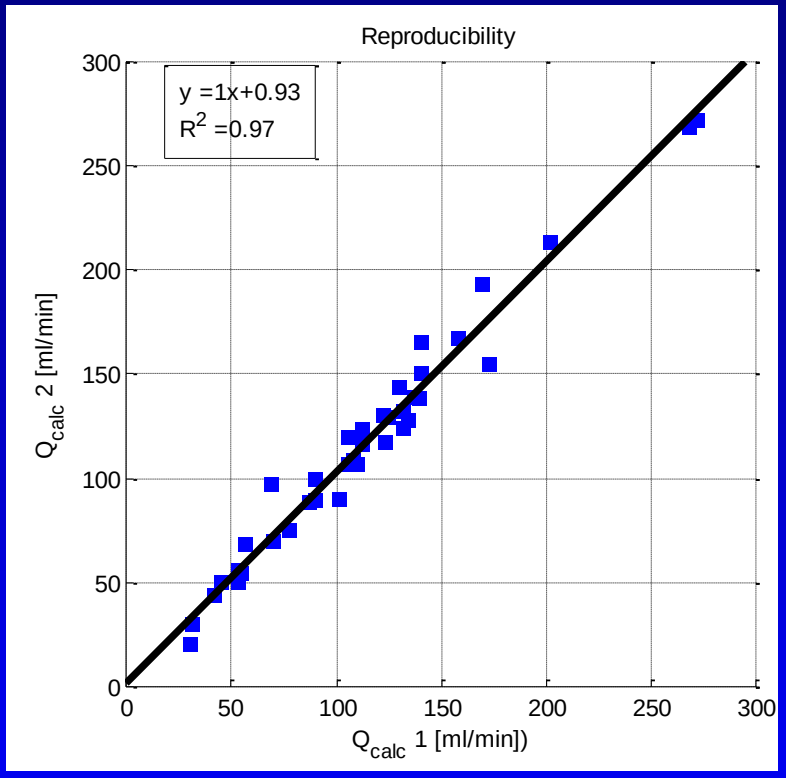
predicted flow

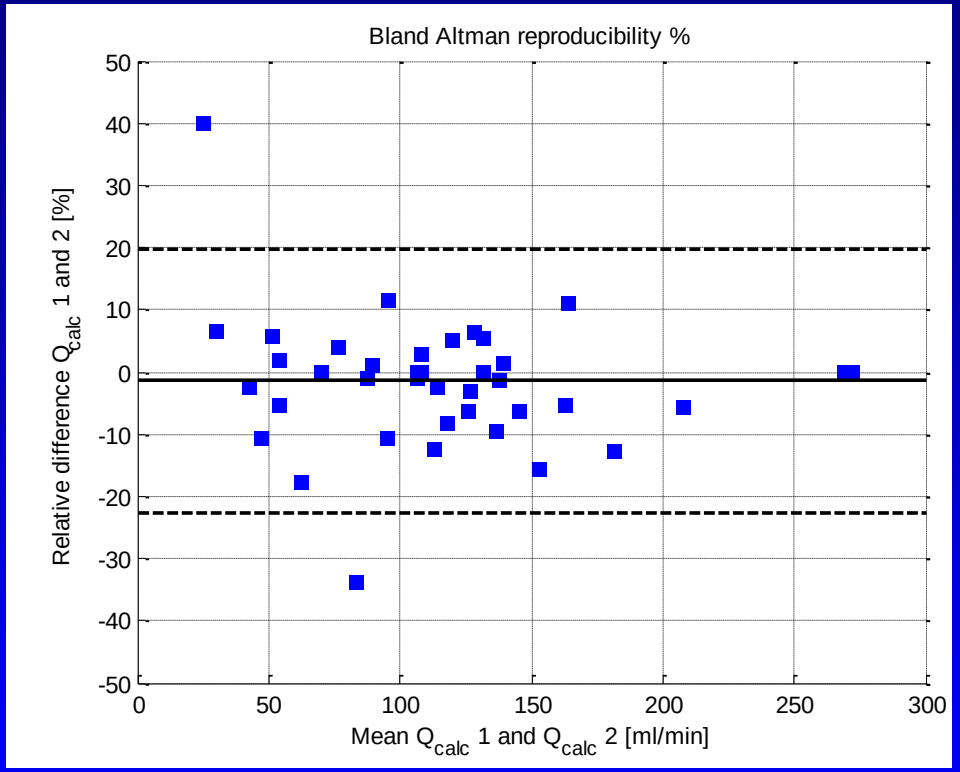


measured flow



Human study: reproducibility





Clinical application:

Absolute Myocardial Flow and Microvascular Resistance in Acute Myocardial Infarction and at Follow-up

Wijnbergen et al, submitted

absolute flow in the infarct area (ml/min/g)

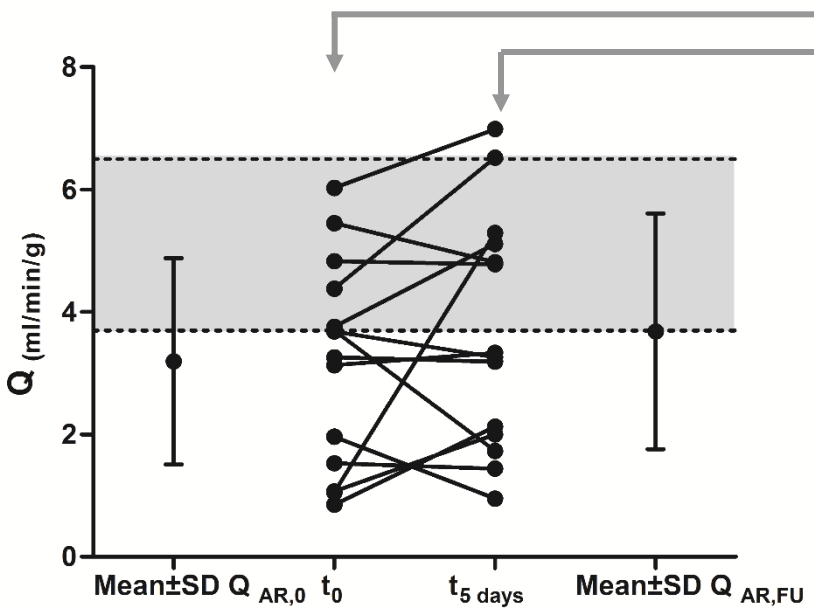


Figure 4a

absolute resistance in the infarct Area (dyn.s.cm^{-5})

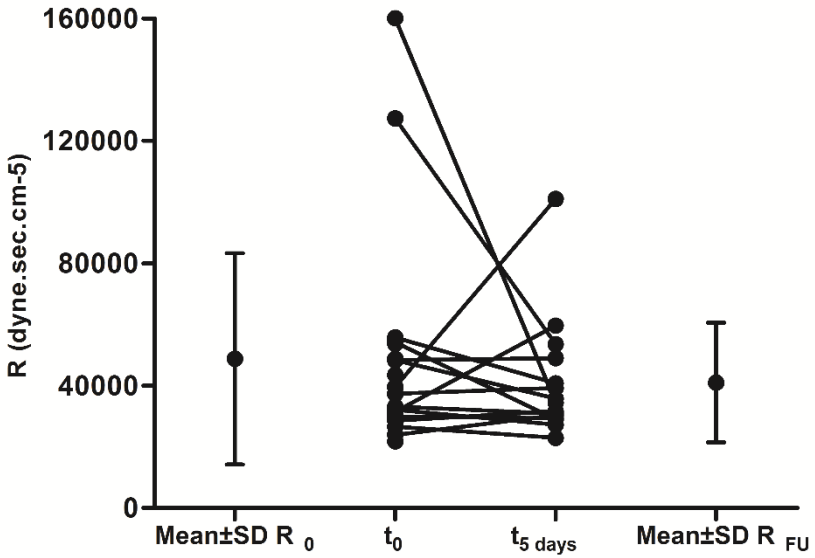


Figure 4b

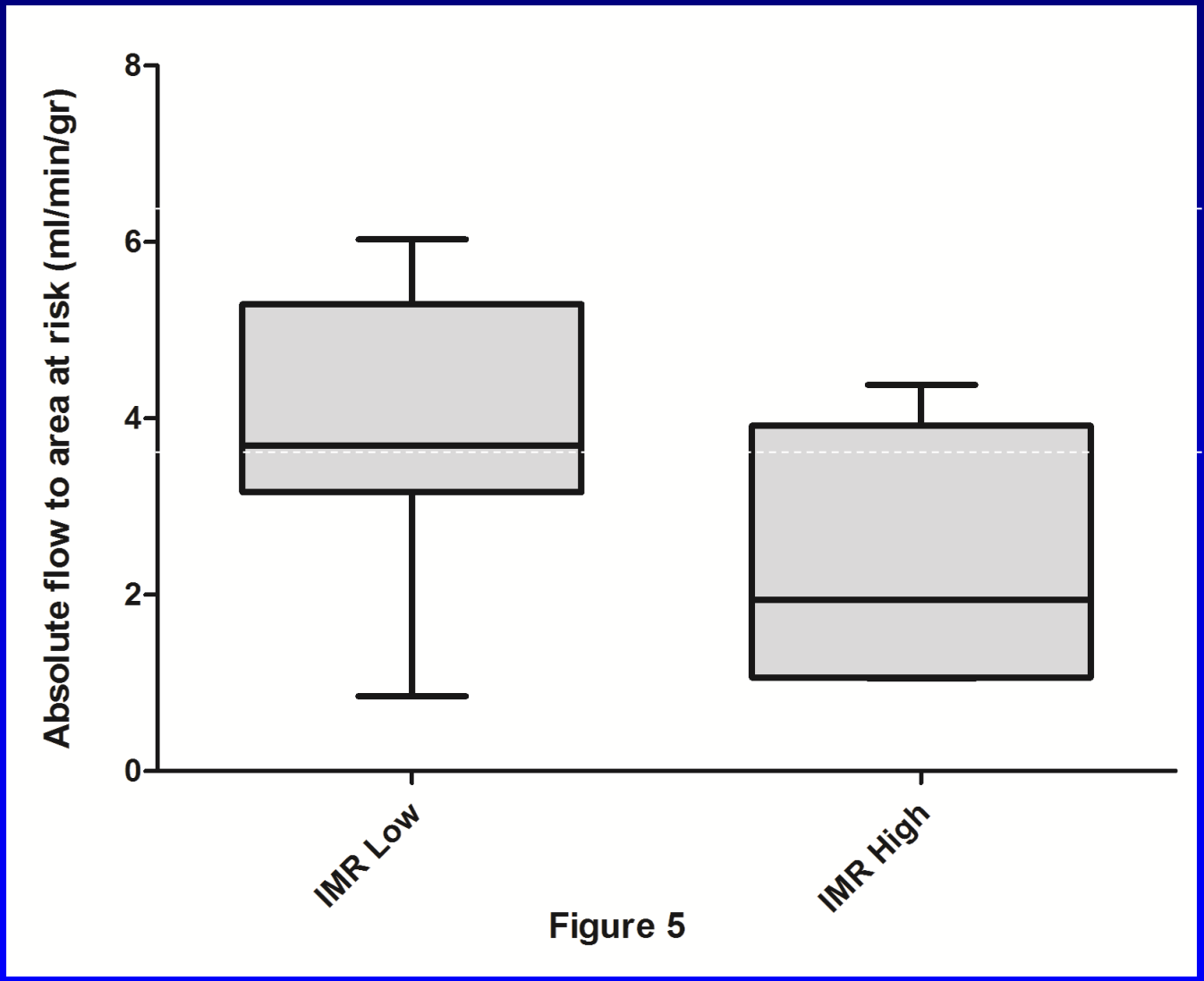
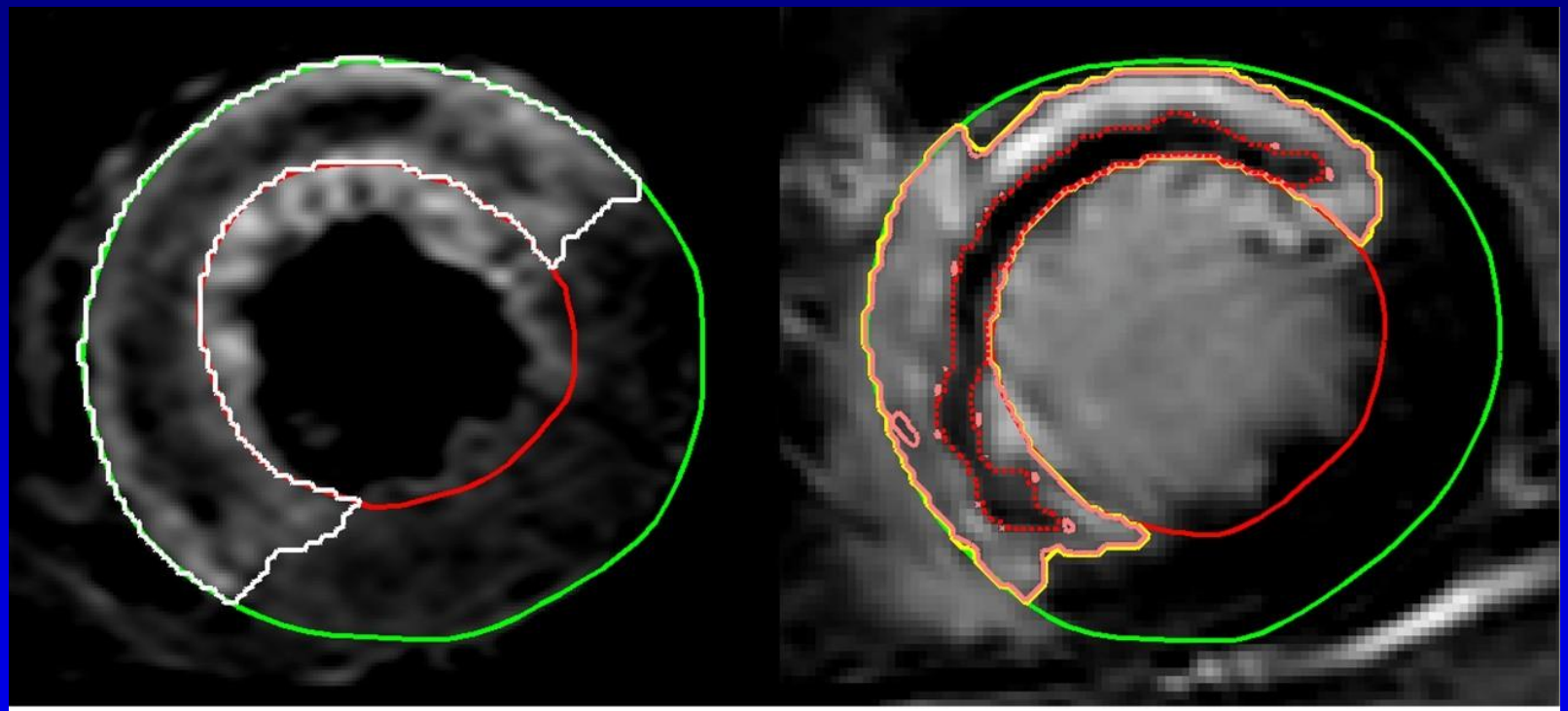
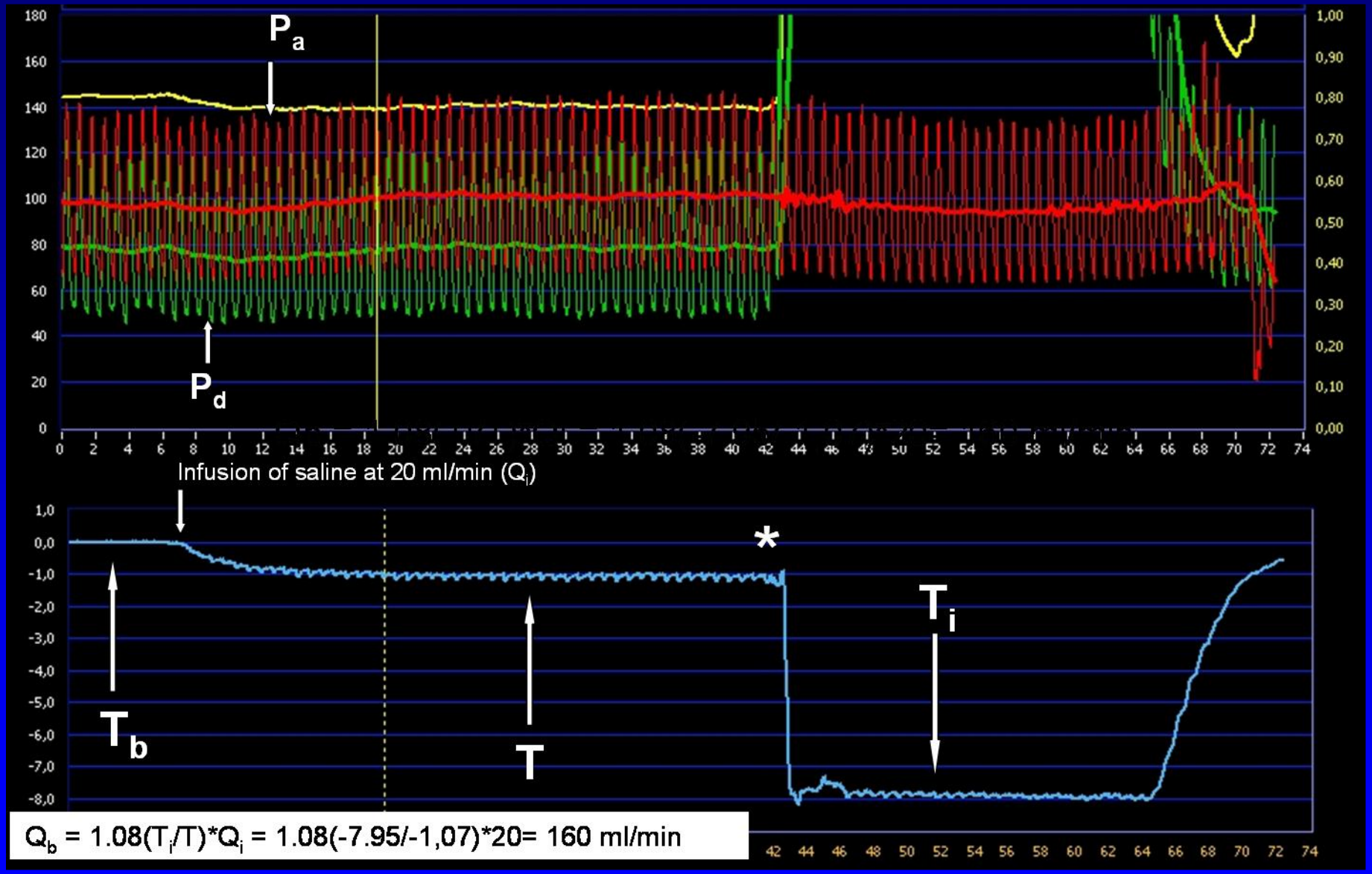


Figure 5


T2-Weighted CMR
LGE-CMR


P_a
P_d
Infusion of saline at 20 ml/min (Q_i)
*
T_b
T
T_i
$Q_b = 1.08(T_i/T)*Q_i = 1.08(-7.95/-1,07)*20= 160$ ml/min

HUMAN STUDY: CONCLUSIONS (1)

- Using this technique of continuous low rate saline infusion, *direct measurement of absolute coronary blood flow is possible*
- Within reasonable limits, the measurements are independent of infusion rate and sensor position
- Use of a *specific infusion catheter (Hexacath, Inc, Paris)* ensuring complete mixing, is paramount
- Because pressure is measured simultaneously, also coronary resistance can be calculated quantitatively
- *When Pw is also measured (and FFR_{myo}, FFR_{cor}, and FFR_{coll} are known) also absolute microvascular flow and resistance and absolute collateral flow and resistance can be calculated*

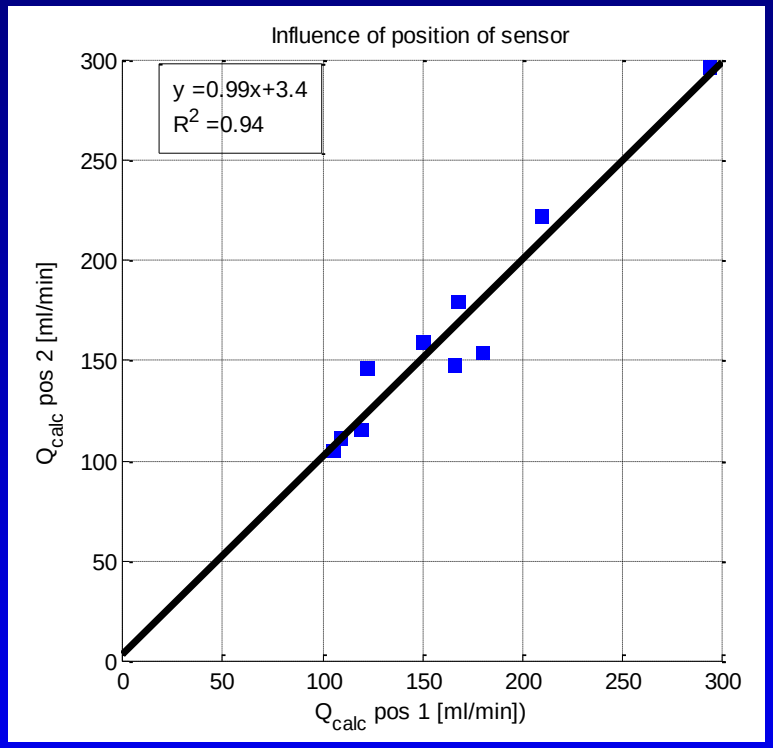
NOTES:

- Very reproducible, not difficult, some patience required
- Instrumentation (introduction and connection of the infusion catheter) is not trivial and needs to be done carefully
- The infusion catheter is not commercially available yet; monorail infusion catheter is underway *(hexacath, Paris)*
- In my view, the method is useful for scientific purposes and very specific categories of patients, (post-HTX, syndrome X, microvascular disfunction, AMI) and can be used by dedicated interventionalists in the cathlab

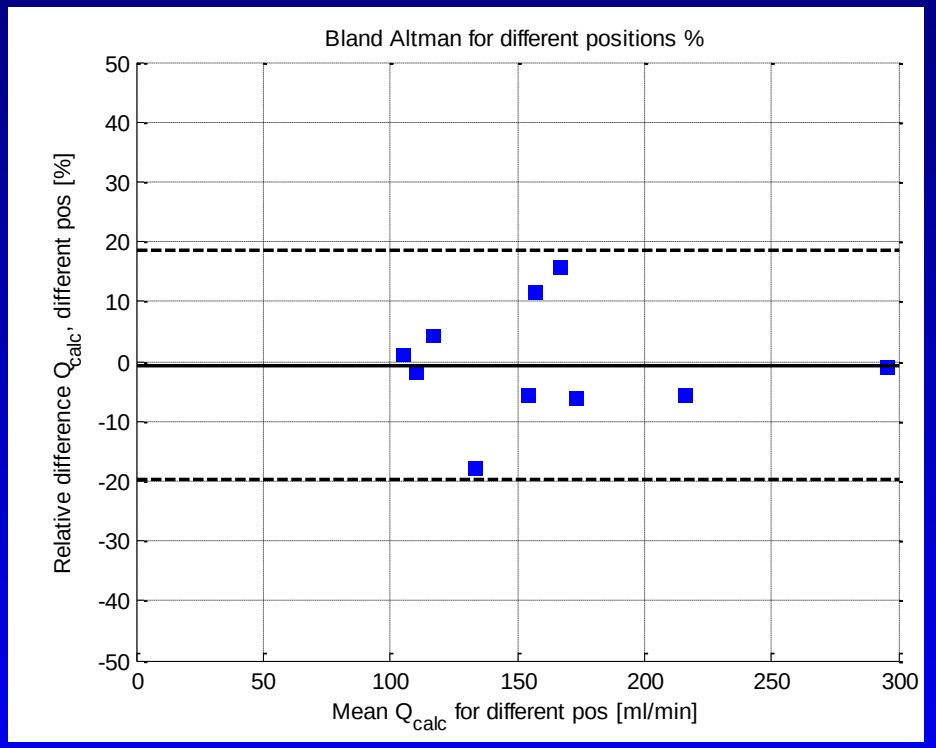
EINDE

Human study: proximal vs distal sensor position

distal position (6-8 cm)

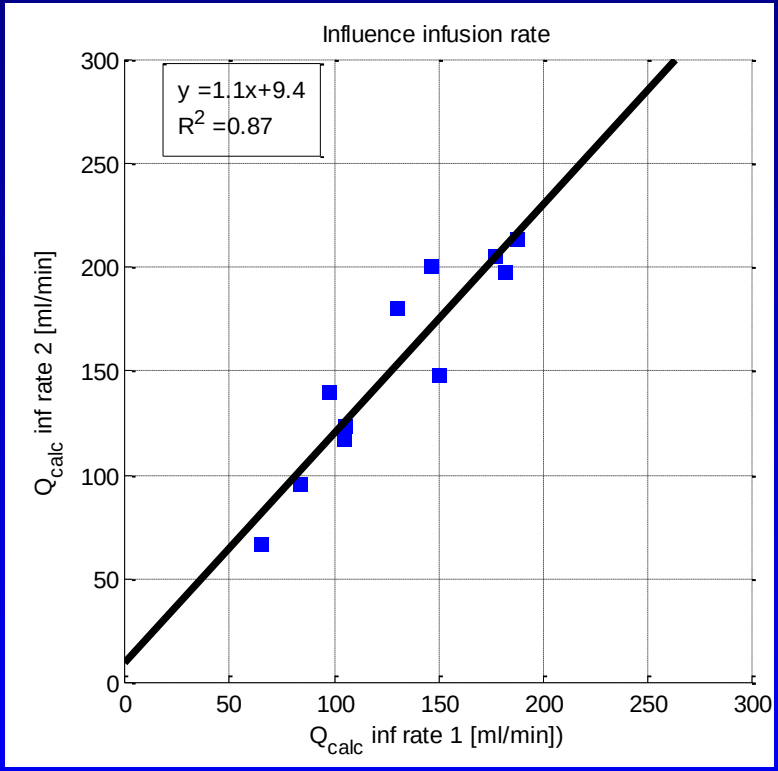


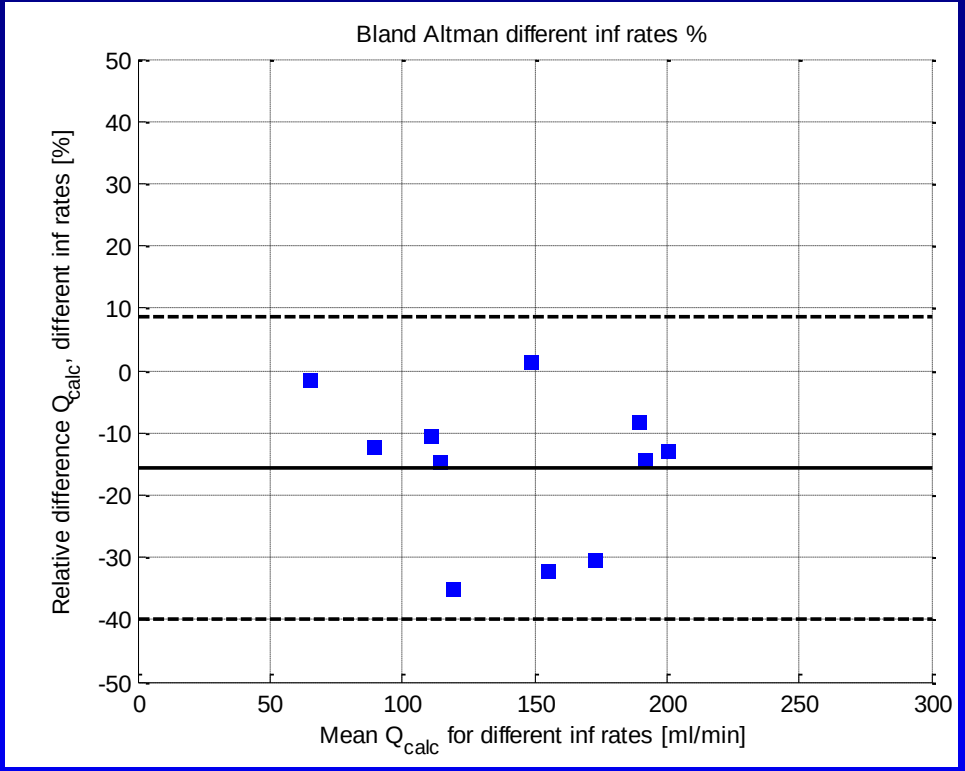
proximal position (3-4 cm)



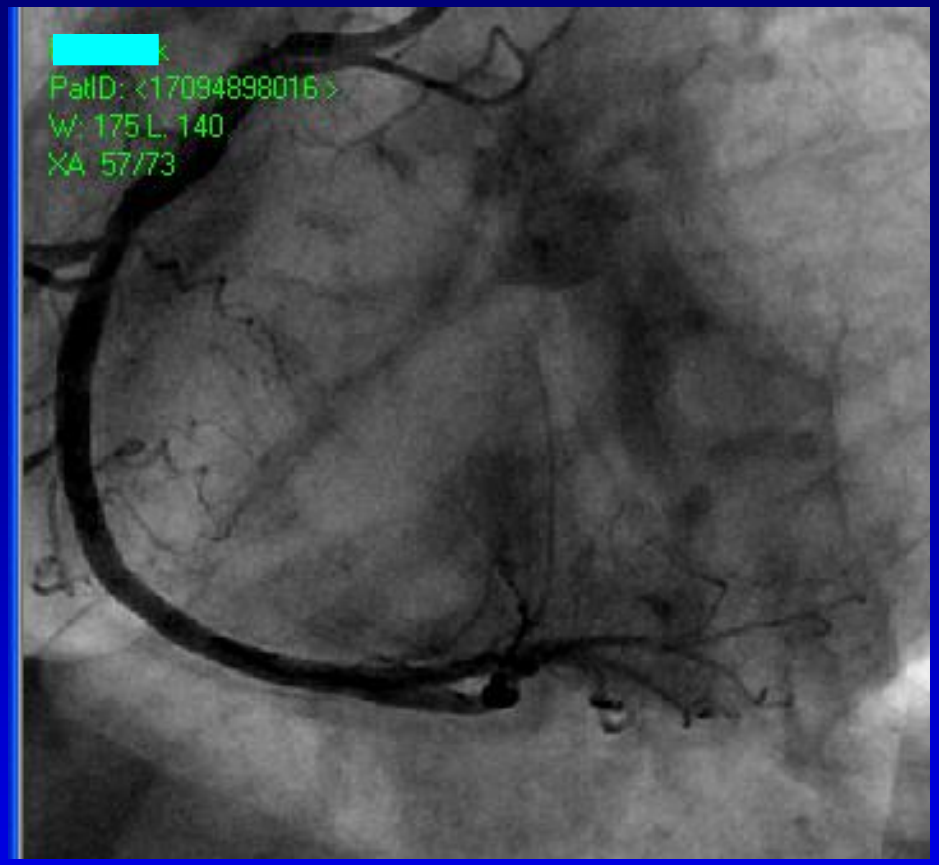
Human study: low vs high infusion rate

high infusion rate 15- 25 ml/min





low infusion rate 10-15 ml/min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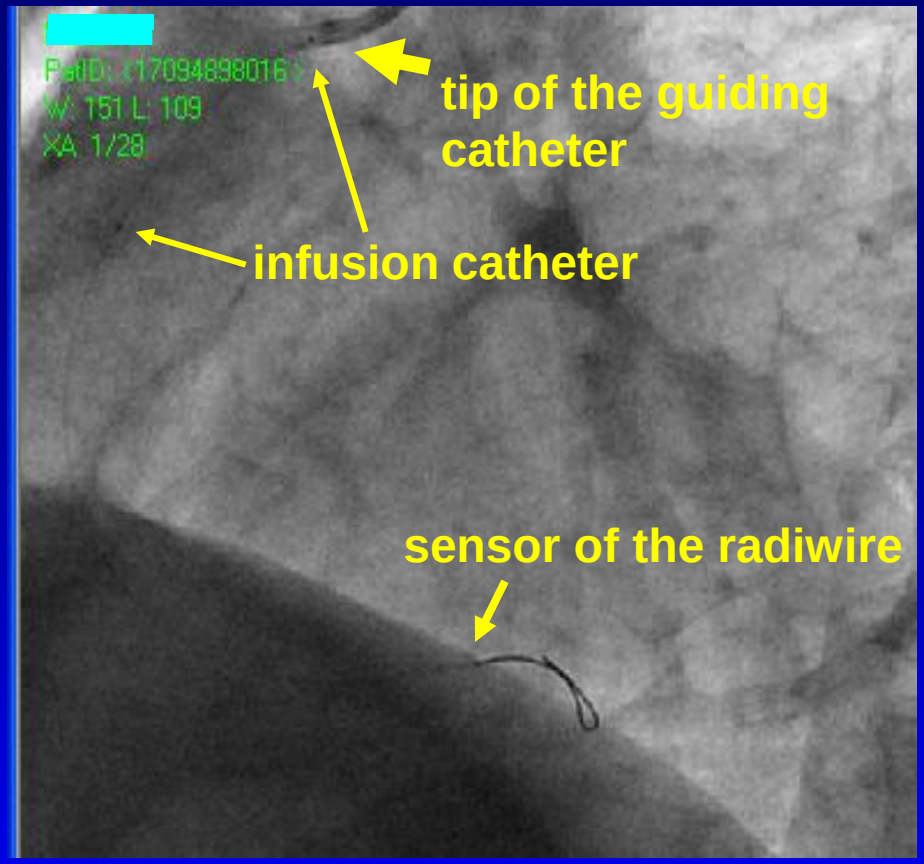
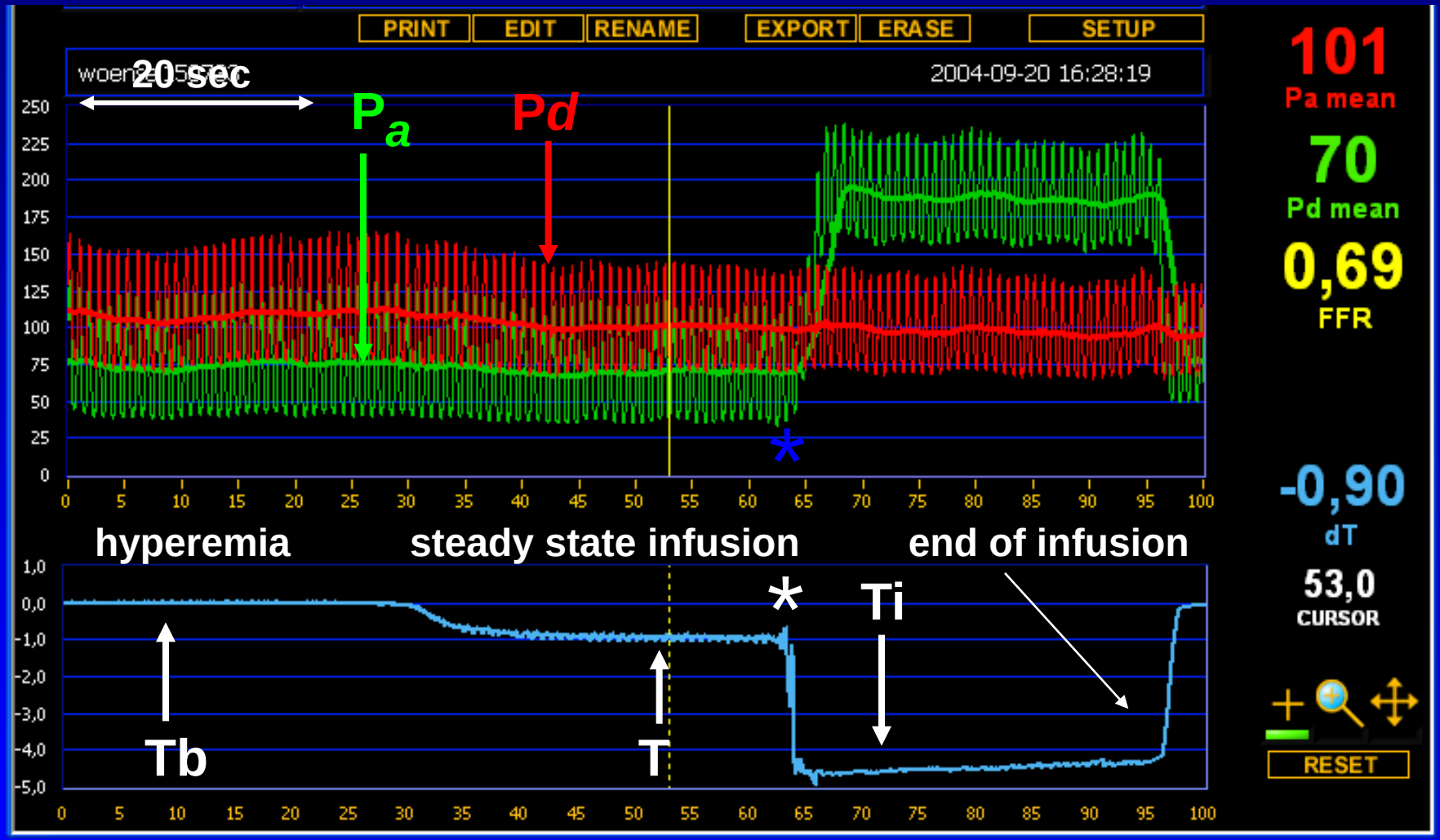
XA 57/73

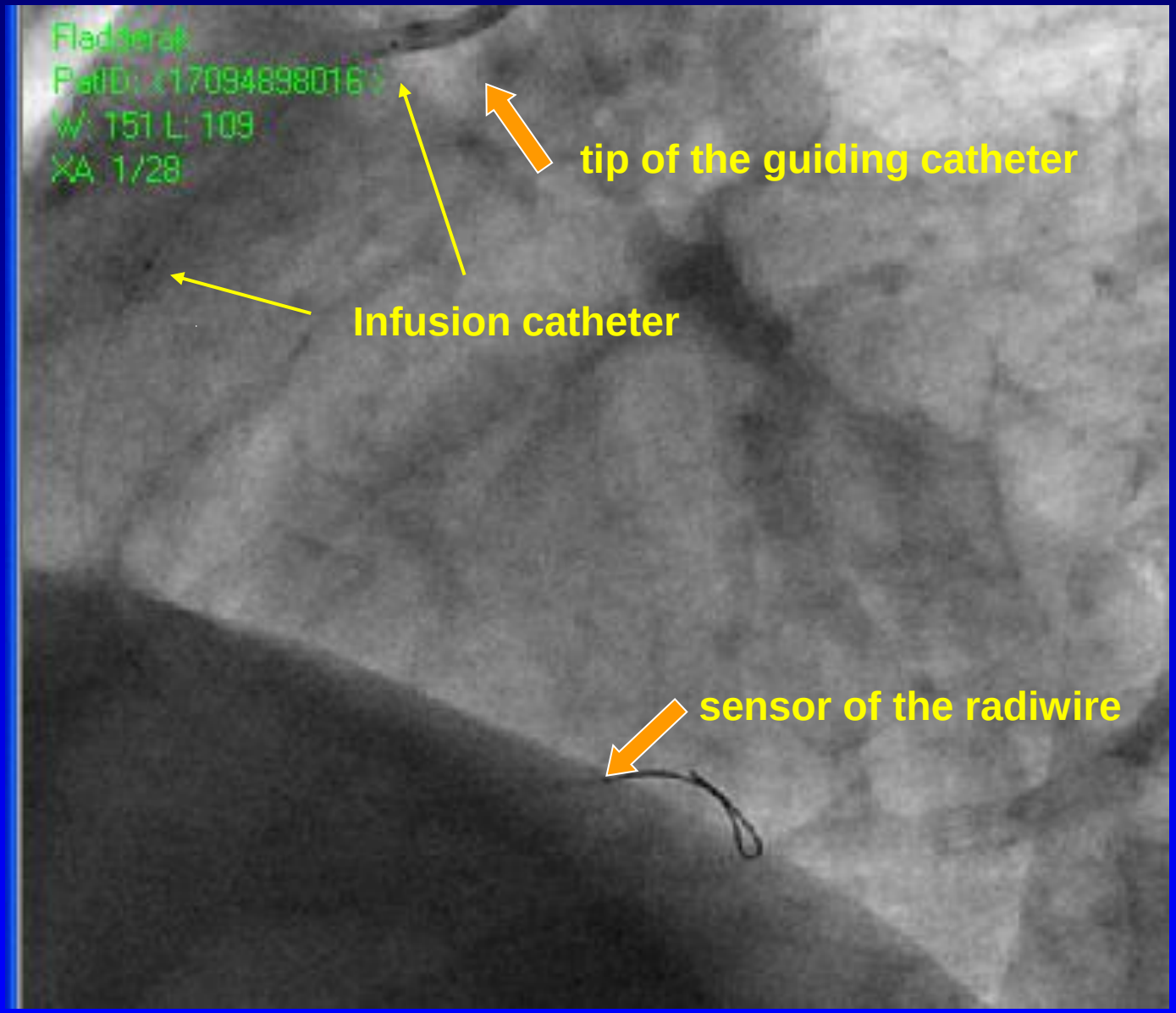

PatID: <17094898016>
W: 151 L: 109
XA 1/28
tip of the guiding catheter
infusion catheter
sensor of the radiwire

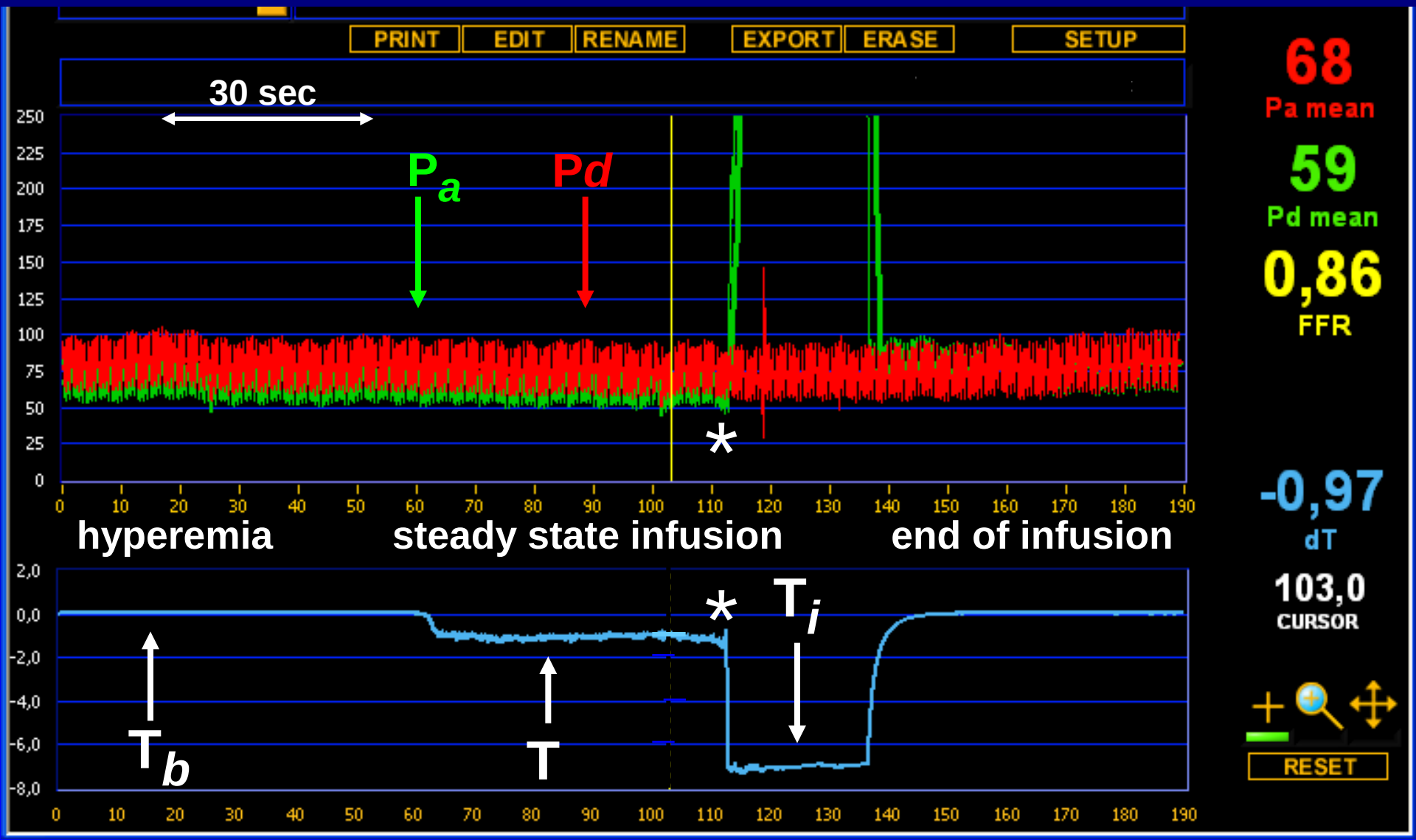
Stenotic LAD artery, FFR = 0.69



Qb = 4.5/0.9 * 15 * 1.08 = 81 ml/min

Male, 56-y-old


tip of the guiding catheter
Infusion catheter
sensor of the radiwire



Qb= 25 x (-7.1 / -0.97) x 1.08 = 198 ml/min

The dream of every cardio-scientist would be to know

- **coronary, myocardial, and collateral blood flow quantitatively**

and

- **to be able to relate such values to the normal values for that individual patient !!**

Together with distal coronary pressure measurement, this would also enable the calculation of

- **true (absolute) microvascular resistance**

enabling studying microvascular disorders, evaluation of stem-cell therapy, and many others

Or vice-versa:

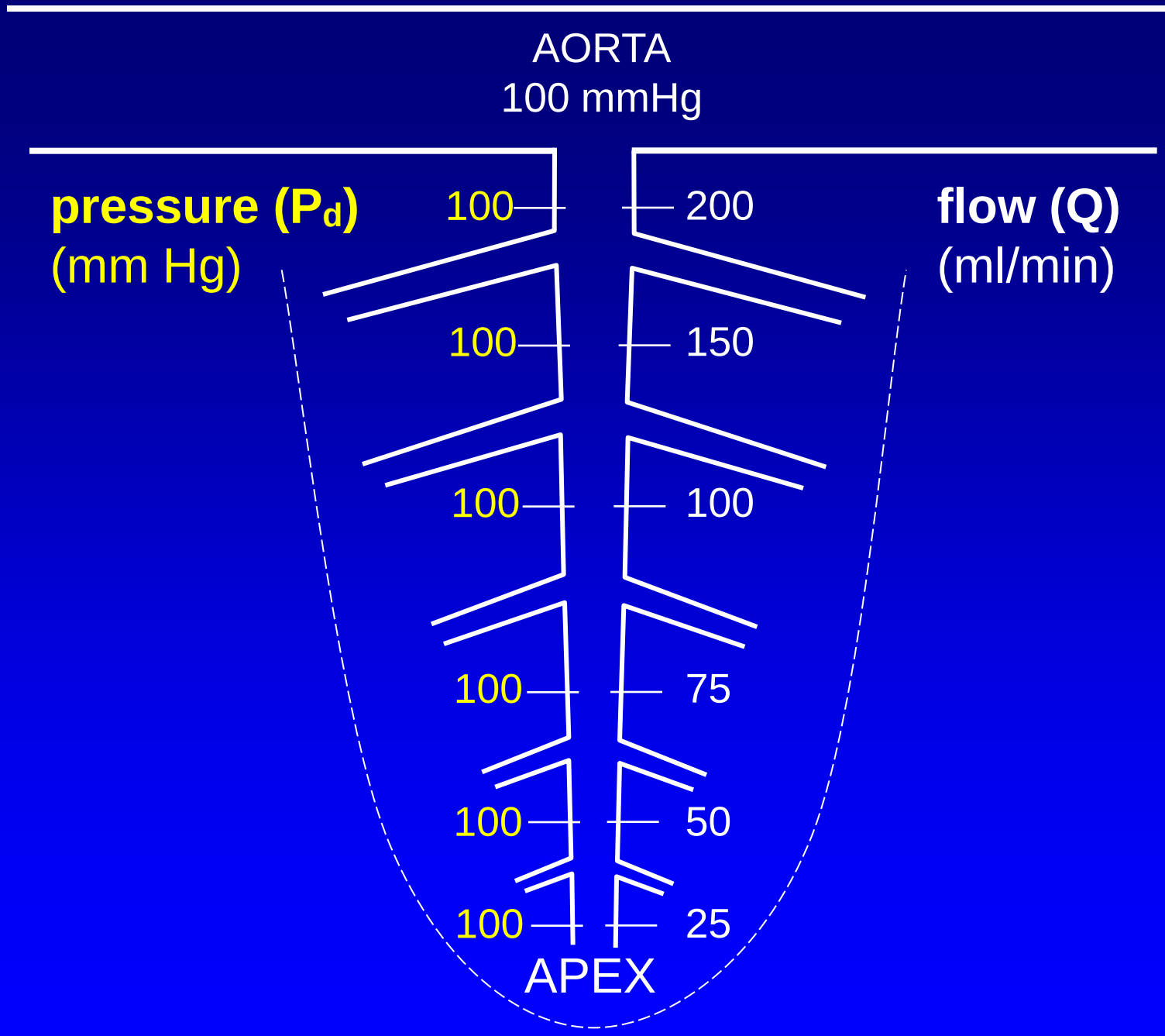
- FFR after stenting is 0.98 = 160ml/min

- 160ml/min = 98%
- 164ml/min = 100%

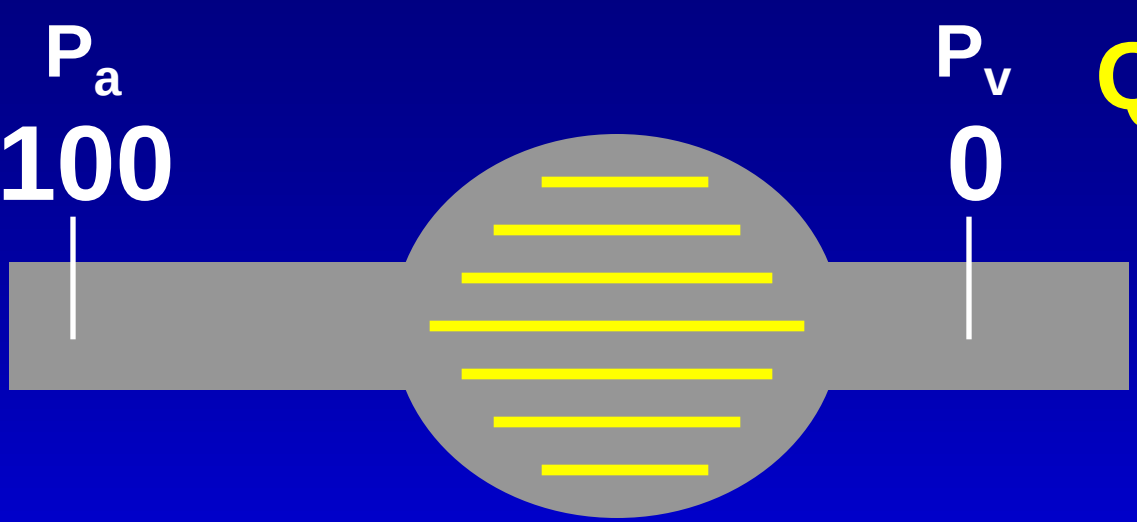
- FFR before stenting was 42%
- This correlates with 164 x 42% = 69 ml/min, whereas we found 69 ml/min by the first “direct” measurement

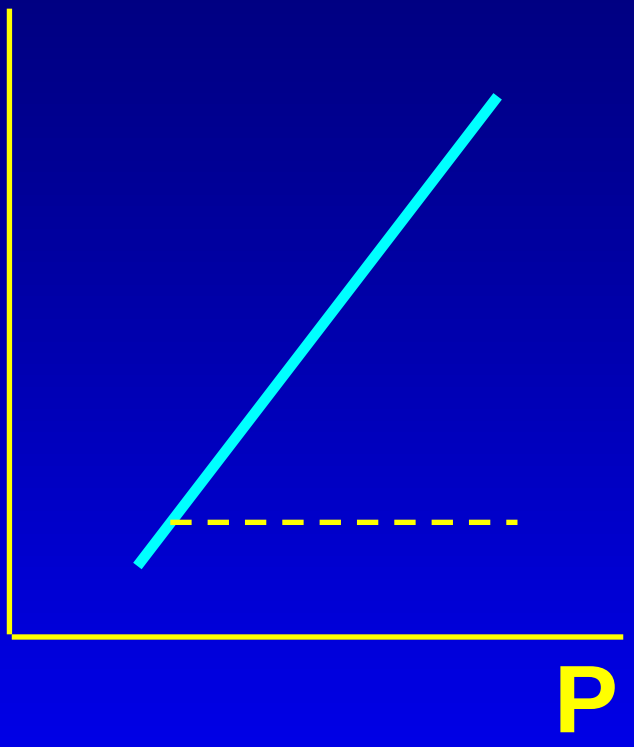
So, for clinical decision making in the cathlab, absolute flow has little value.

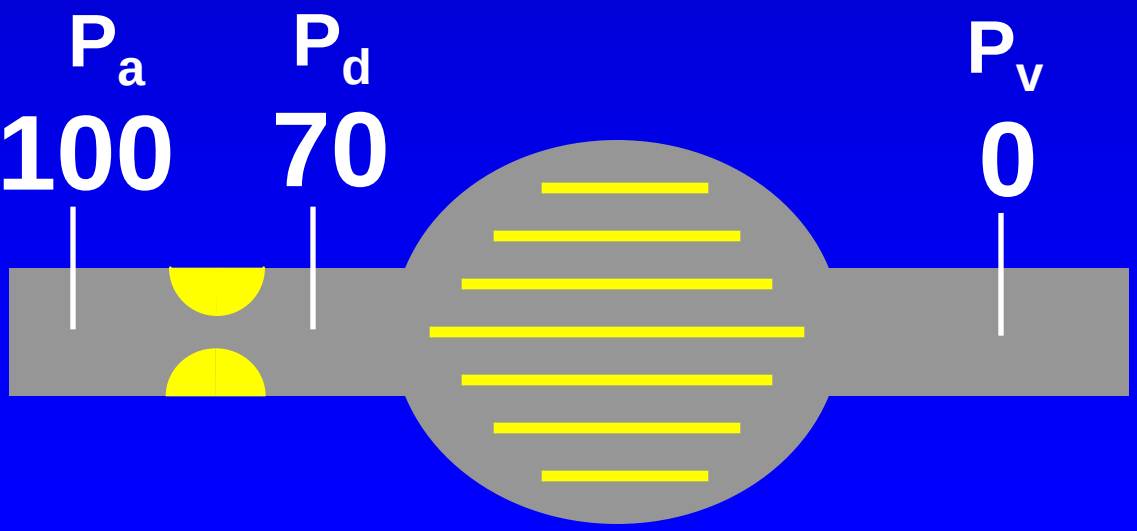
Besides that, it has been impossible so far to measure absolute coronary or myocardial flow invasively


AORTA
100 mmHg
pressure (P_d)
(mm Hg)
flow (Q)
(ml/min)
100
200
100
150
100
100
100
75
100
50
100
25
APEX

During Maximal Vasodilatation







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

$$= 0.70$$

Pressure-flow equations:

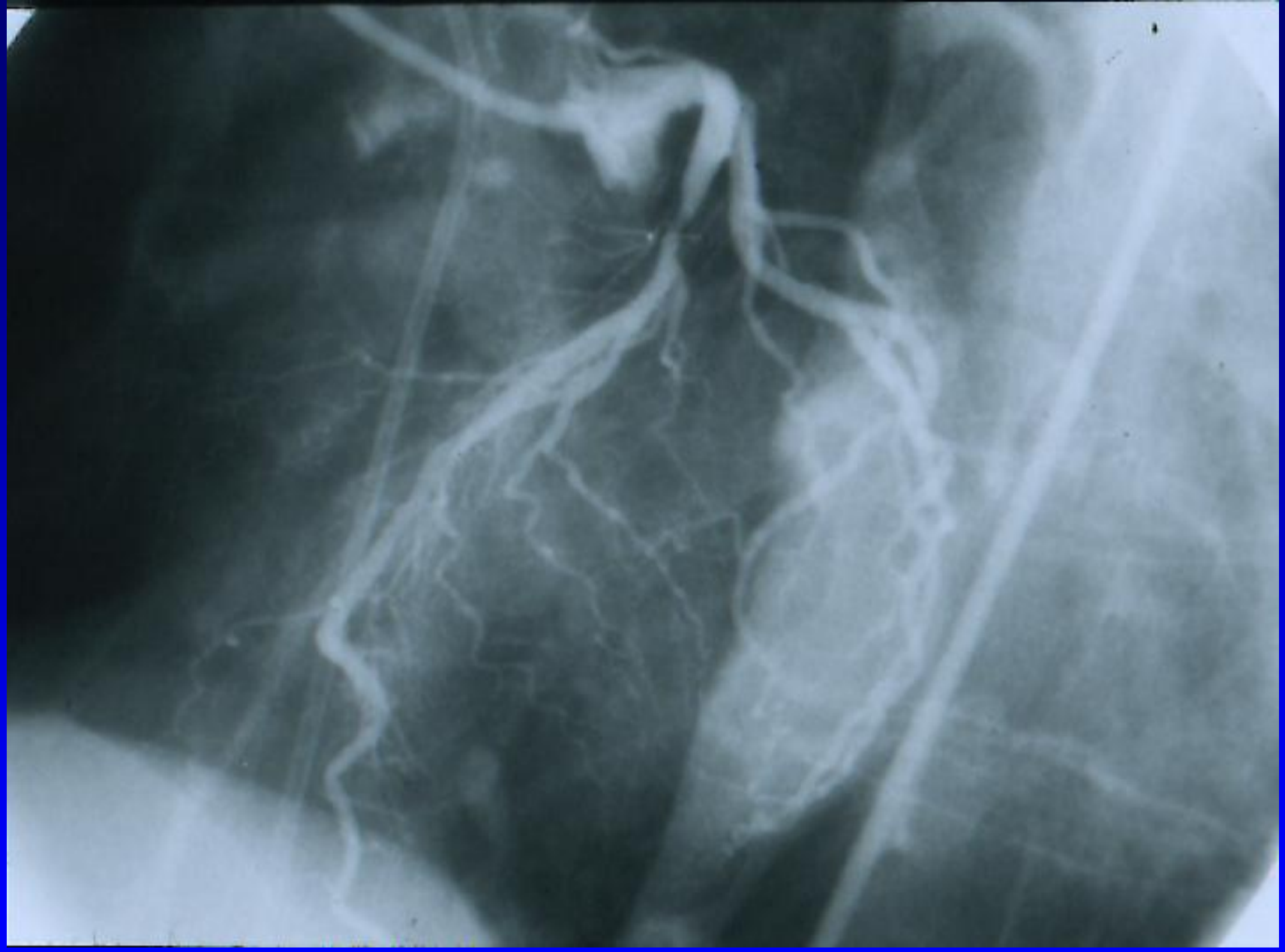
1. Fract. Myocardial Flow Res. $(FFR_{myo}) = \frac{P_d - P_v}{P_a - P_v}$

2. Fract. Coronary Flow Res. $(FFR_{cor}) = \frac{P_d - P_w}{P_a - P_w}$

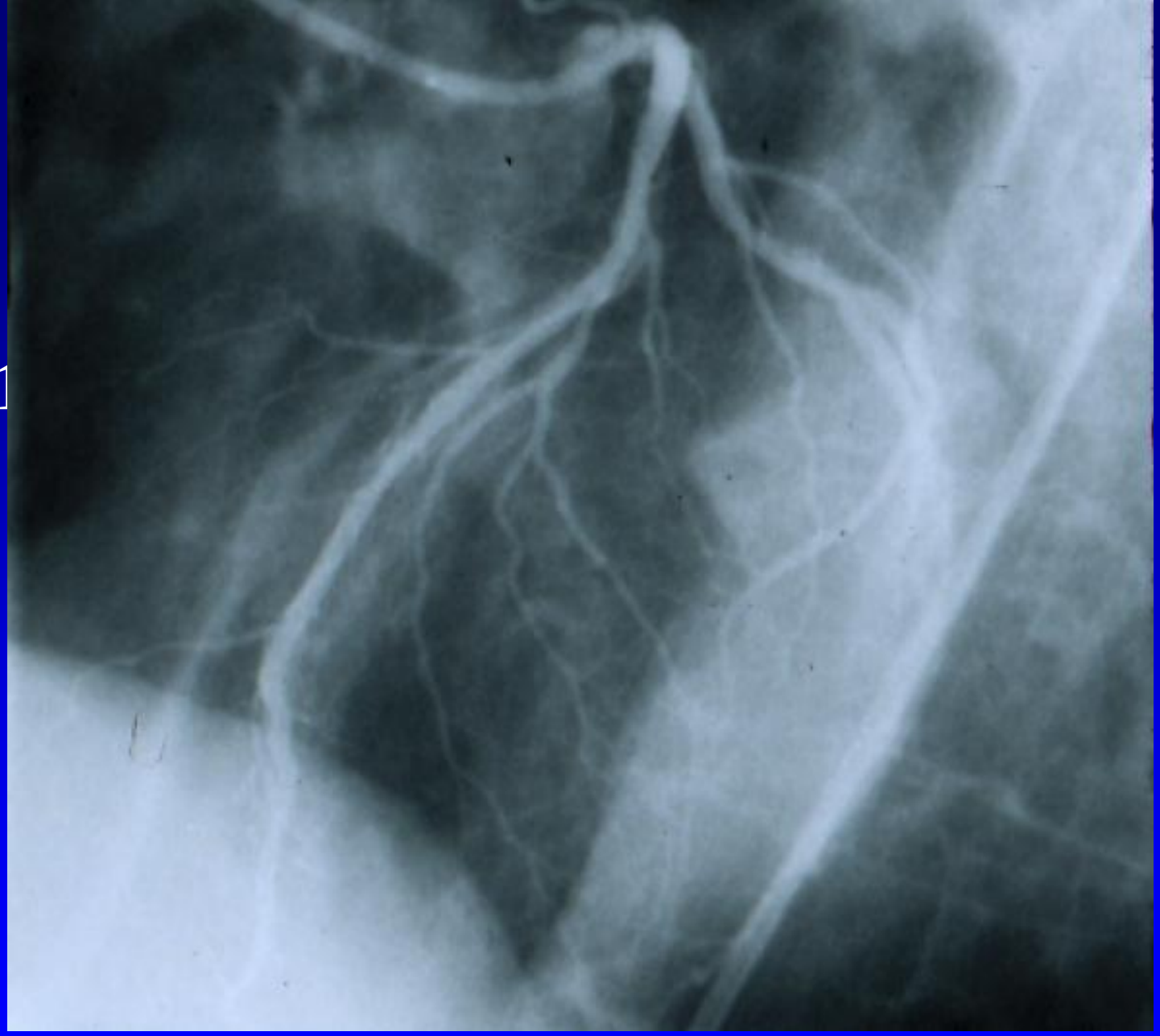
3. Fractional Collateral Flow $= (FFR_{myo} - FFR_{cor})$

Pa = mean aortic pressure at maximum hyperemia
Pv = mean central venous pressure at maximum hyperemia
Pd = mean distal coronary pressure at maximum hyperemia
Pw = coronary wedge pressure at balloon inflation

Circulation 1993;87:1354-1367



10 vb5-PTCA - de Wit-Stek (1)



Example (1)

	before PTCA	occlusion	after PTCA
Pa	90	90	90
Pd	40	-	80
Pv	0	0	0
Pw	-	20	-

$$FFRmyo = \frac{40-0}{90-0} \qquad \frac{80-0}{90-0}$$

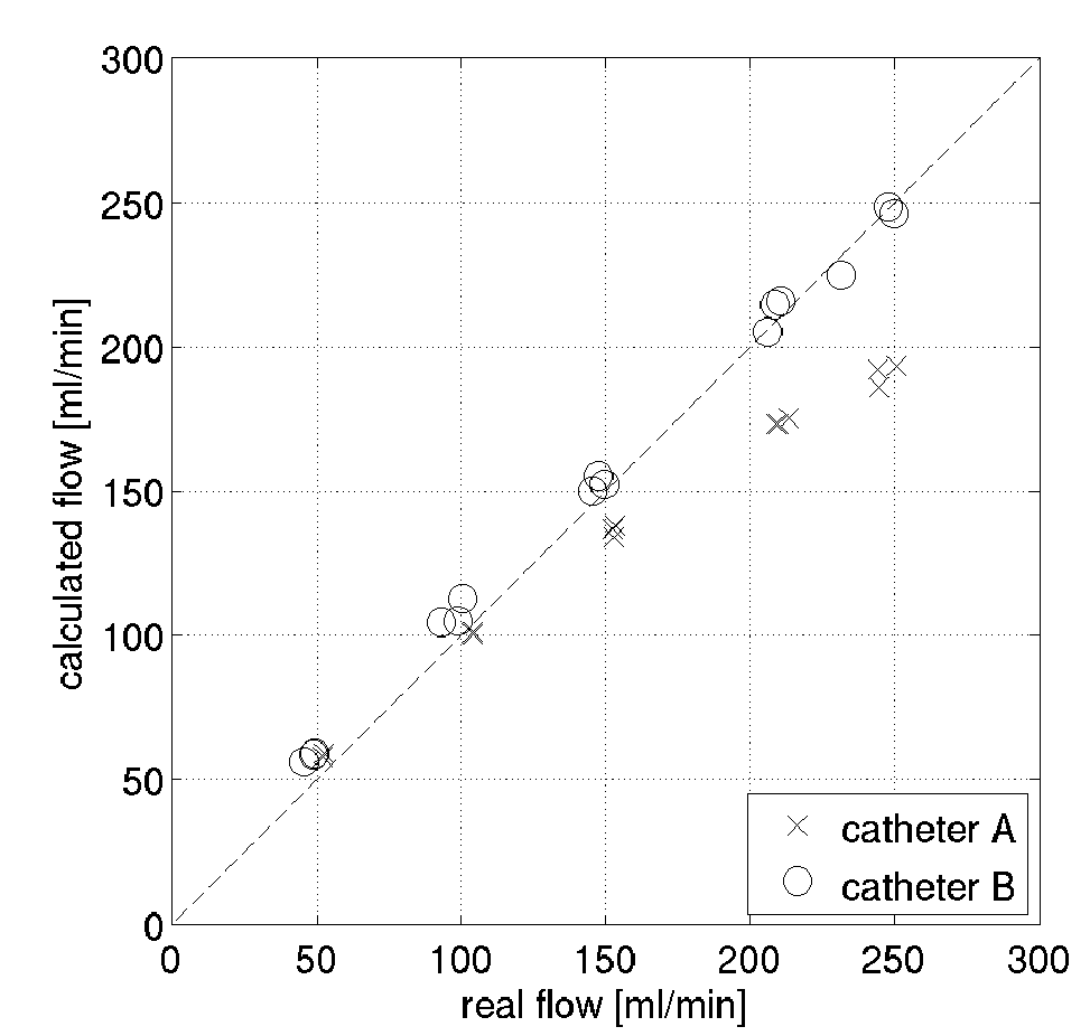
$$FFRcor = \frac{40-20}{90-20} \qquad \frac{80-20}{90-20}$$

$$\text{collateral flow at occlusion} = \frac{20-0}{90-0} = 0.22$$

Example (1)

	before PTCA	occlusion	after PTCA
fract. myoc. flow res.	0.44	0.22	0.89
fract. coron. flow res.	0.29	-	0.86
fract. collat. flow	0.15	0.22	0.03

….and it would even be more attractive if absolute flow and resistance could be related to a normal value for an individual patient and individual heart rate, blood presssure, etc !



In-vitro tests: *o = BS modified & OCCAM-2 infusion catheter*

x = standard infusion catheter

incomplete mixing ⟶ underestimation of flow

ANIMAL STUDY: CONCLUSIONS

- Using this technique of continuous low rate saline infusion, direct measurement of absolute coronary blood flow is possible
- Within reasonable limits, the measurements are independent of infusion rate and sensor position
- Use of a specific infusion catheter ensuring complete mixing, is paramount
- Because pressure is measured simultaneously, also resistance can be calculated quantitatively
- The method can be extrapolated to man without major modifications

FFR before stenting = 0.42

Qb before stenting = 69 ml/min

→***Expected normal max flow*** =

100/42 x 69 ***= 163 ml/min***

FFR before stenting = 0.42
Qb before stenting = 69 ml/min

→Expected normal max flow = 100/42 x 69 = 163 ml/min

FFR after stenting = 0.98
Qb after stenting = 160 ml/min

→"true" normal max flow = 100/98 x 160 = 164 ml/min

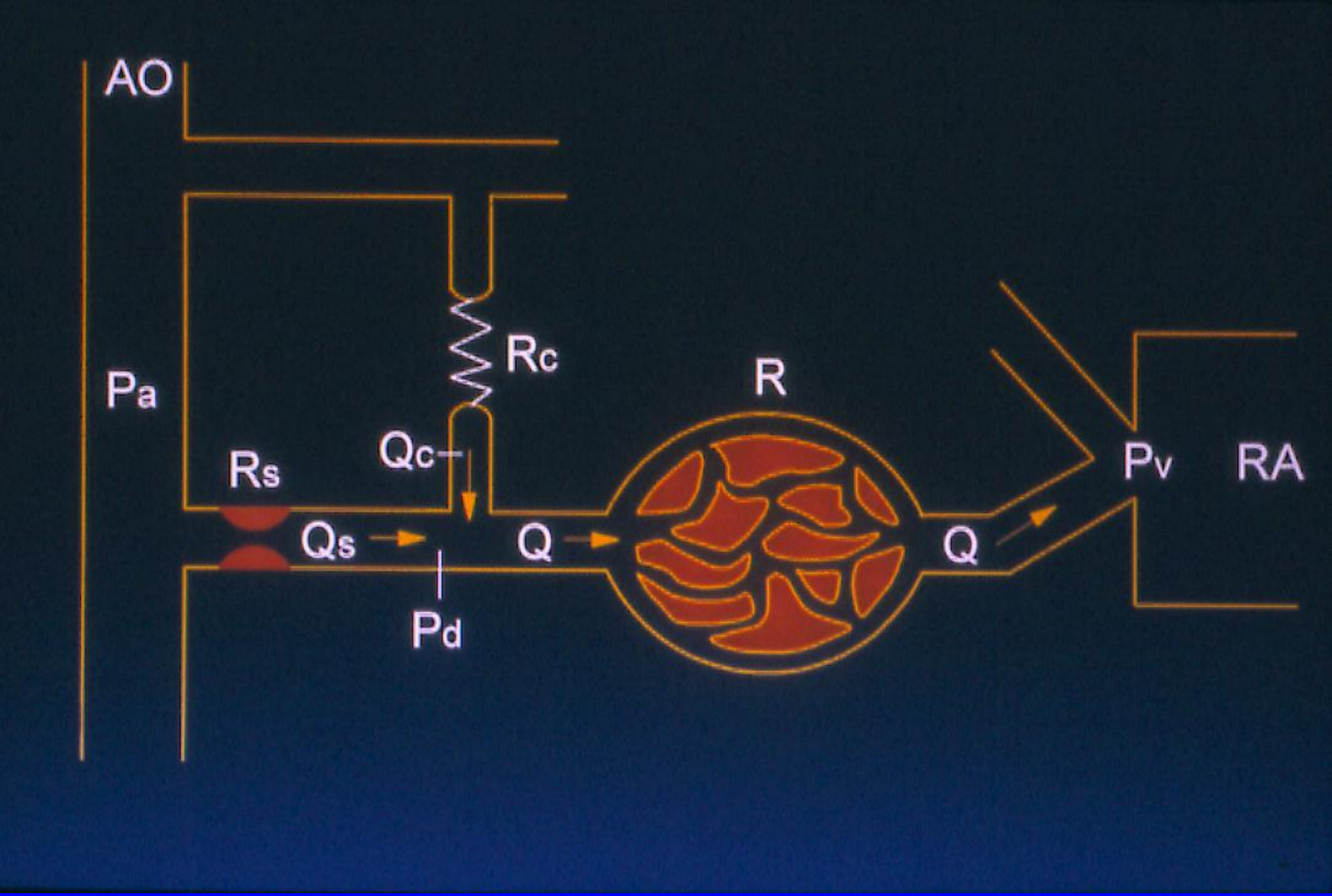
Traditional coronary sinus thermodilution:

- disappointing results, not suitable for clinical use
- not specific for one coronary artery or branch
- could not be related to a normal value
- **grossly inaccurate due to *incomplete mixing:***

  - design of infusion catheter
  - venous vs pulsatile arterial flow
  - entangling of saline along catheter

Human Study: Measurement protocol

- introduction of pressure wire
- hyperemia by i.v. adenosine 140 µg/kg/min
- measurement of **FFR**, stop adenosine
- introduction of infusion catheter over PW
- connection of infusion catheter to infusion pump by second Y-connector
- induction of steady state hyperemia by i.v. adenosine 140 µg/kg/min
- at steady state hyperemia: zeroing of blood temperature
- start saline infusion (room temp; 10-25 ml /min = Q_i) results in rapid decrease of distal blood temp by 0.5-2.0 °C
- recording of steady state during 20-30 seconds (**T**)
- rapid withdrawal of PW to record infusion temperature (T_i)
- stop adenosine; repeat sequence 2 min later


AO
Pa
Rc
R
Qc
Rs
Pv
RA
Qs
Q
Q
Pd

myocardial blood flow = coronary flow + collateral flow

FFR myo = FFR cor + FFR coll

Before PCI (stenotic artery) : 0.44 = 0.29 + 0.15

After PCI (stented artery) : 0.89 = 0.86 + 0.03

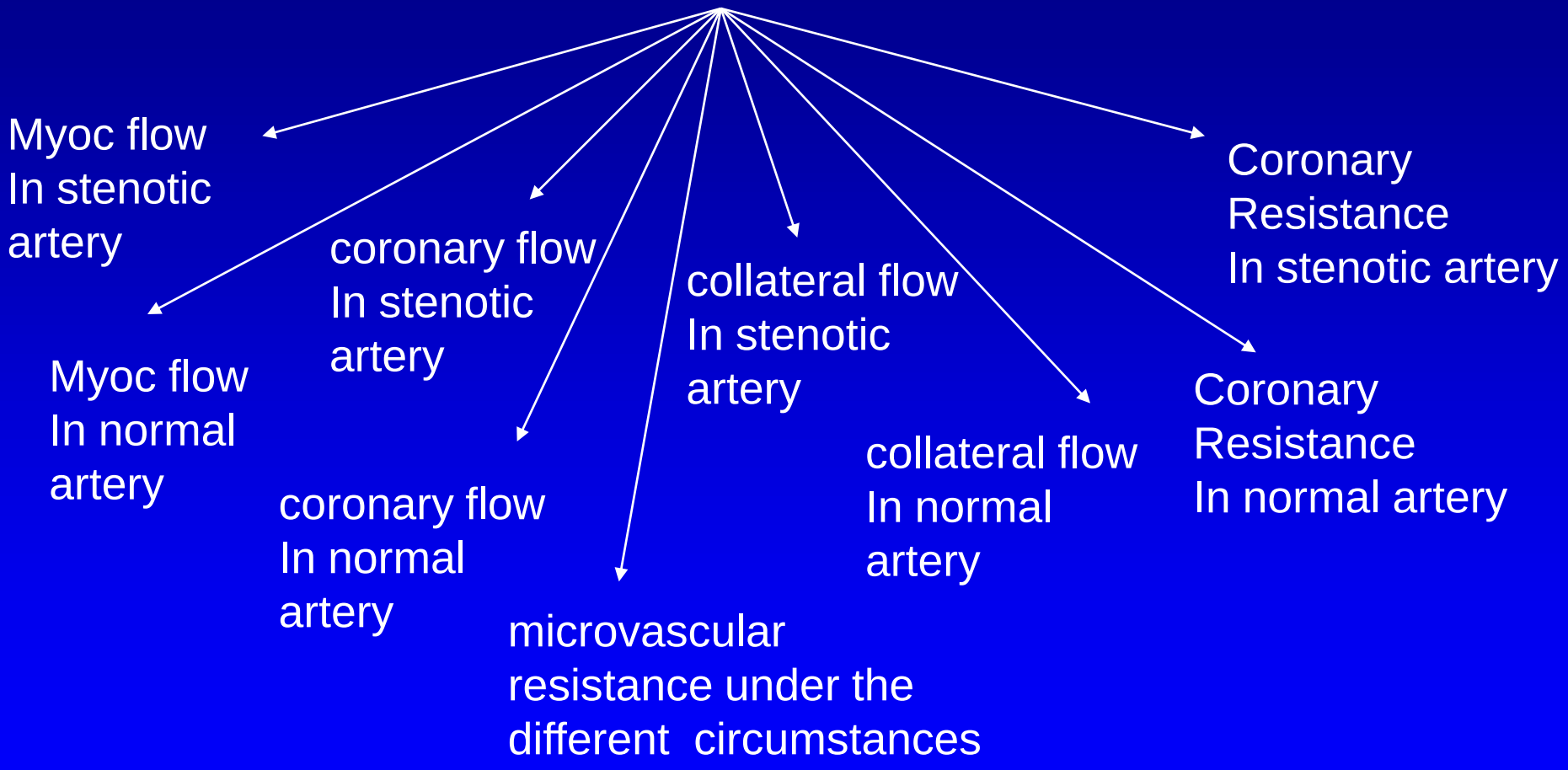
So, myocardial, coronary, and collateral flow both before and after PCI, are all expressed as a fraction of ***normal maximum myocardial blood flow***

→ **If one of these numbers is known quantitatively (ml/min), all the other values are known as well**

→ **And if distal coronary pressure is also measured, microvascular resistance is known as an absolute number**

FFR

describes the mutual relation between



continuous infusion of saline to determine absolute maximum coronary blood flow

$$Qb = Qi \cdot \frac{Ti - Tb}{T - Tb} \cdot 1.08$$

***And if all temperatures are expressed relative to the Temperature of the blood (zero-ed*) :**

$$Qb = Qi \cdot \frac{Ti}{T} \cdot 1.08$$

Absolute max coronary blood flow

temp of infusion at tip of guiding catheter

temp of blood at sensor position

infusion flow

OCCAM/AMT infusion catheter design:

- 2.8 F outer diameter
- 4 sideholes in last 8 mm
- almost no infusion through tip
- maximum infusion 40 ml/min

continuous infusion of saline to determine absolute maximum coronary blood flow: theory

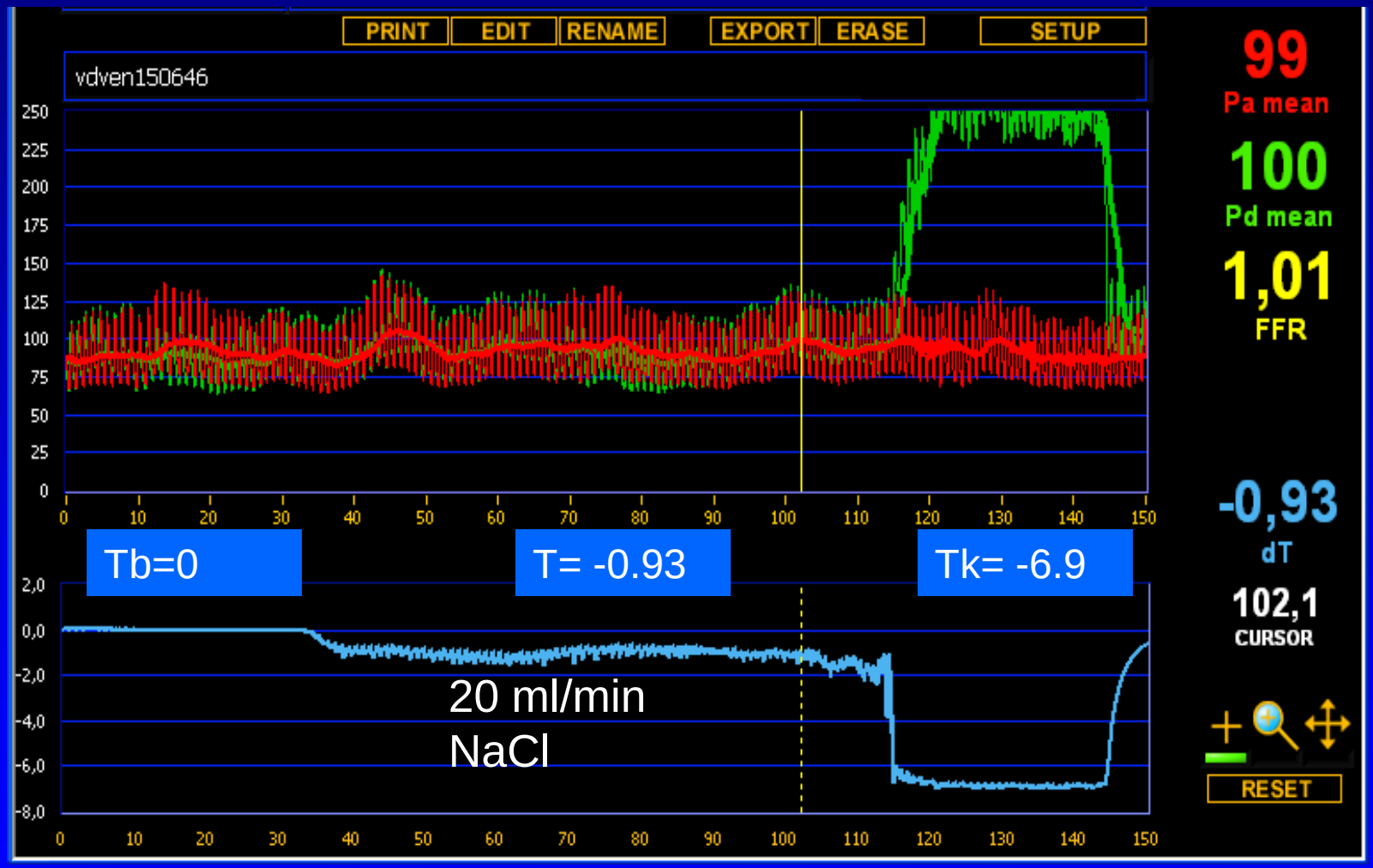
- Temperature sensor somewhere in the distal part of the coronary artery
- Induction of steady state hyperemia (i.v. adenosine)
- Measurement of blood temperature (**Tb**)
- Infusion of saline with known infusion rate (**Qi**) and known temperature (**Ti**)
- Measurement of temperature of sensor (**T**) after mixing of blood and infused saline
- Calculation of maximum absolute flow (**Qb**) by :

$$Qb = Qi \cdot \frac{Ti - Tb}{T - Tb} \cdot 1.08$$

Zierler, 1954
Ganz, 1971

After stenting of RCA: FFR=0.98

Infusion with Qi = 20 ml/min.



Qb= 20 x (6.9 / 0.83) x 1.08 = 160 ml/min