TCT Asia Pacific 2023

OPENING THE BLACK BOX OF THE MICROCIRCULATION:

Absolute Flow And Resistance Measurement

Seoul, May 8 th, 2023

CATHARINA-ZIEKENHUIS

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Potential conflicts of interest

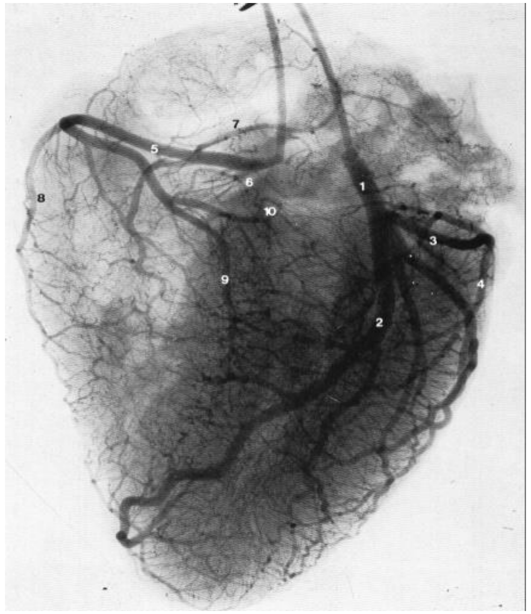
I have the following potential conflicts of interest to report:

- Research contracts : *Abbott*
- Consulting: *Abbott, Heartflow (SAB)*
- Stockholder of a healthcare company: *Philips, GE, ASML, Heartflow*
- Other(s): *patents pending in the fields of coronary microcirculation and aortic valve stenosis*

Opening The Black Box of The Microcirculation

Presently, we have excellent methods to assess epicardial coronary artery disease (FFR, IVUS, OCT)

…. but the coronary microcirculation is still a black box



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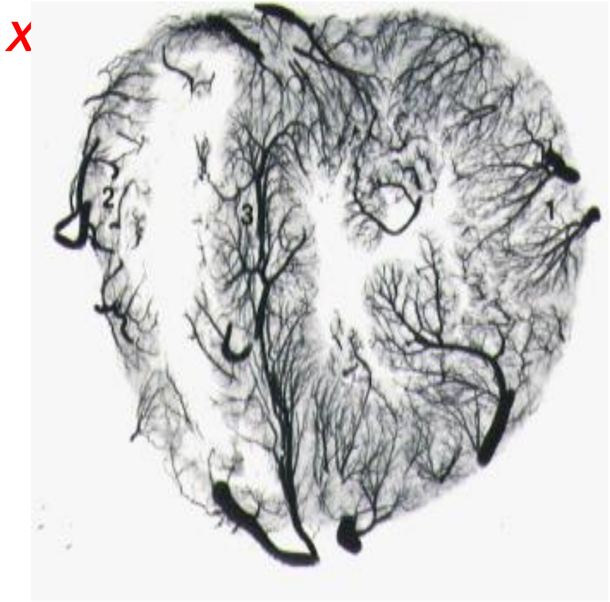

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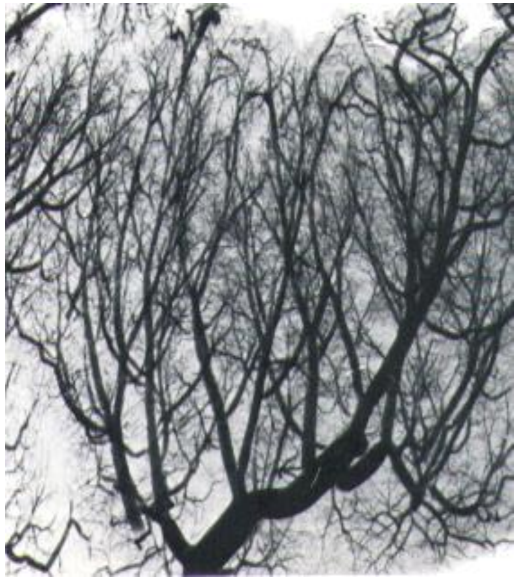
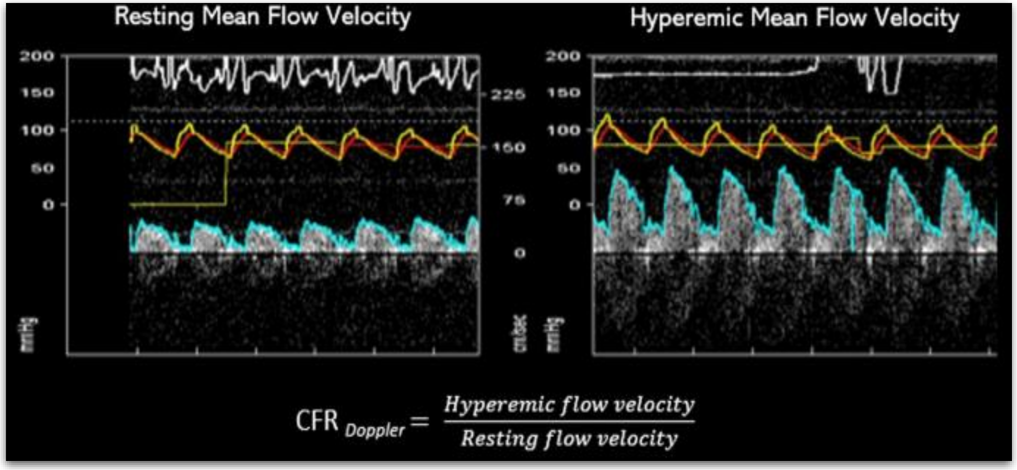
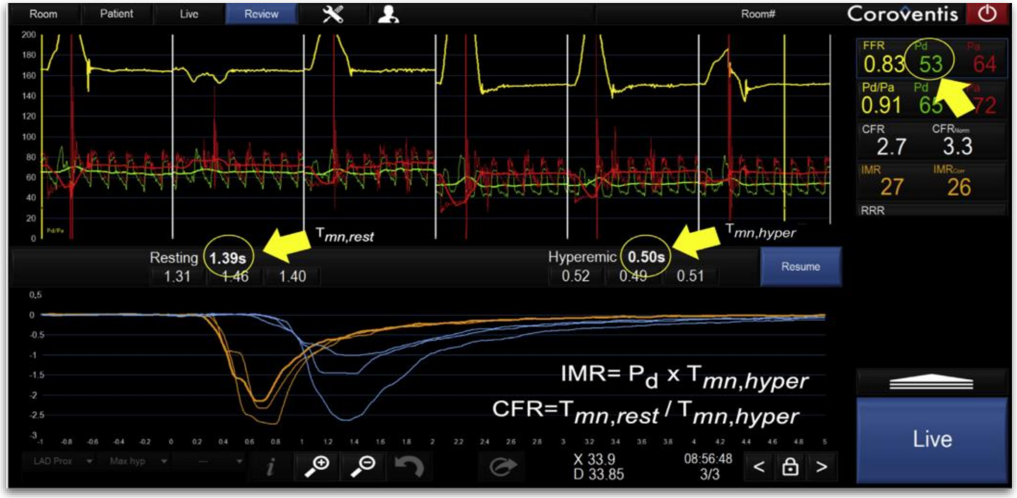


For investigating the microcirculation, we only have surrogates of coronary blood flow (and microvascular resistance)



Doppler flow velocity (cm/s)



Bolus thermodilution T_{mn} (s)

Despite the growing interest in studying the microcirculation of the heart (“ANOCA”, “INOCA”, “MINOCA”) ….

- …*these present* invasive techniques to assess the microcirculation, are crude, inaccurate, and operator-dependent

- **Doppler**: - *not specific for microcirculation*
  - *inaccuracy of measurement ≥ 20%*
  - *no adequate signals in ≥ 30% of patients*
  - *signal extremely operator-dependent*

- **IMR:** - *easier to perform, sometimes quick, sometimes very long*
  - *inaccuracy of ~ 20% (or more in resting “Tmn”)*
  - *operator-dependent, injection technique is important*
  - *CFR unreliable and often overstimated*

Both require infusion of adenosine: not a big deal, but some don’t like it

Consequently, a lot of our knowledge about the microcirculation is limited, often speculative, and open for multiple interpretations

The ideal technique to assess the microcirculation, should be:

- understandable from sound physiology
- easy to perform with standard PCI equipment
- accurate, reproducible, and quantitative
- operator-*independent*

→ ***Measurement of absolute flow and resistance by thermodilution and continuous infusion of saline***

Principle of continuous thermodilution for absolute Q & R measurements

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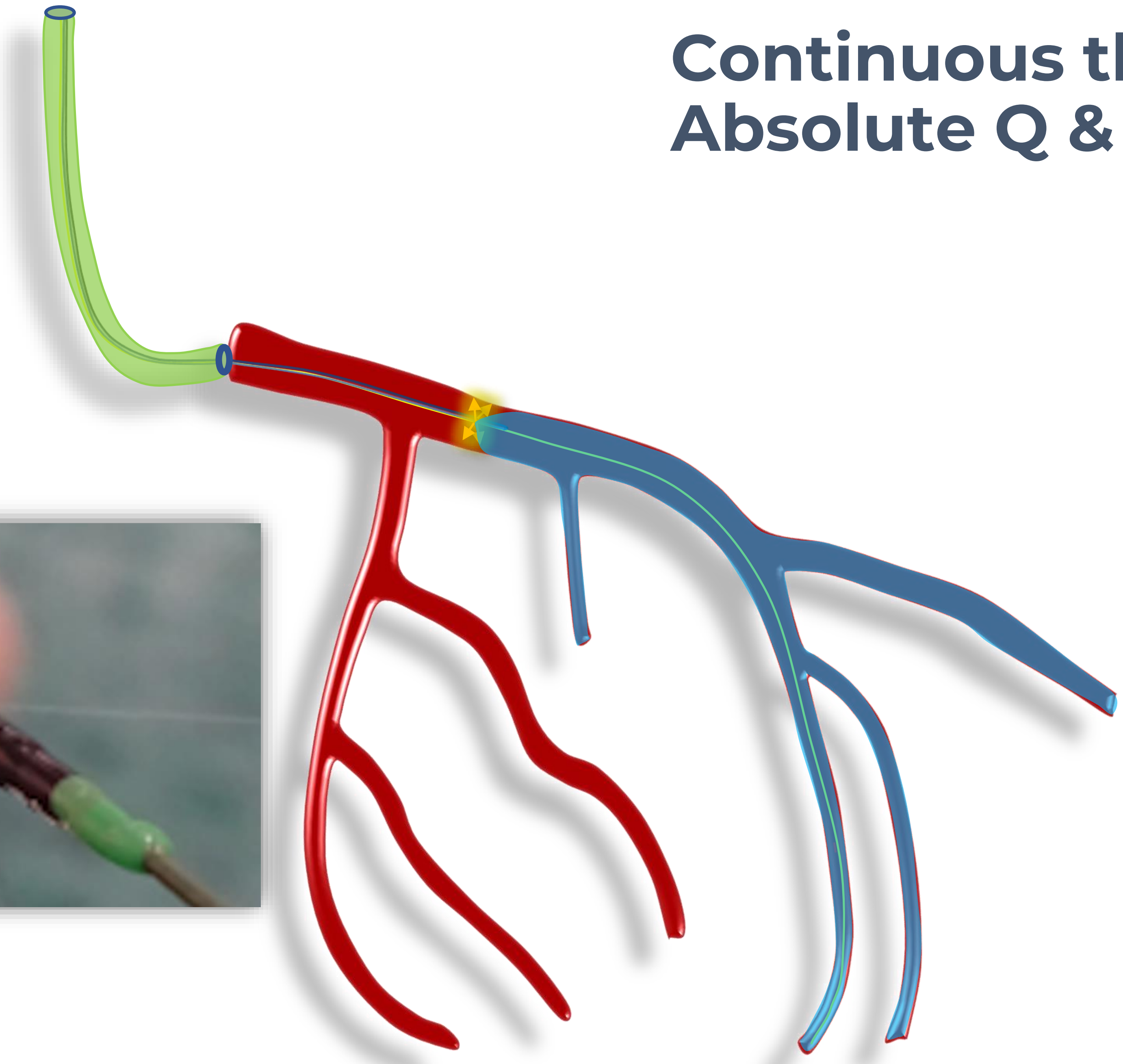
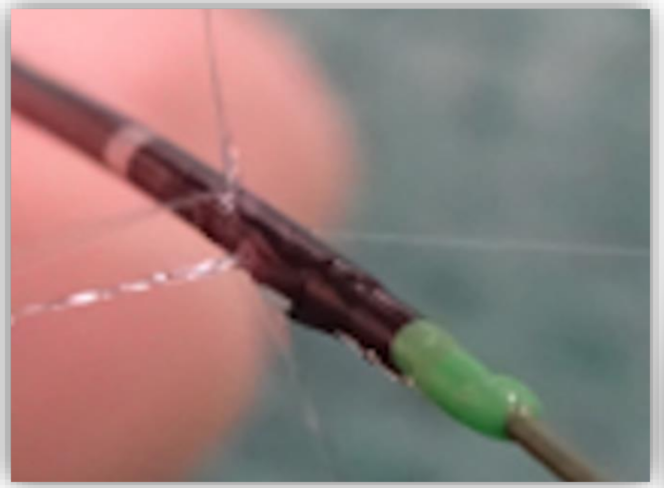
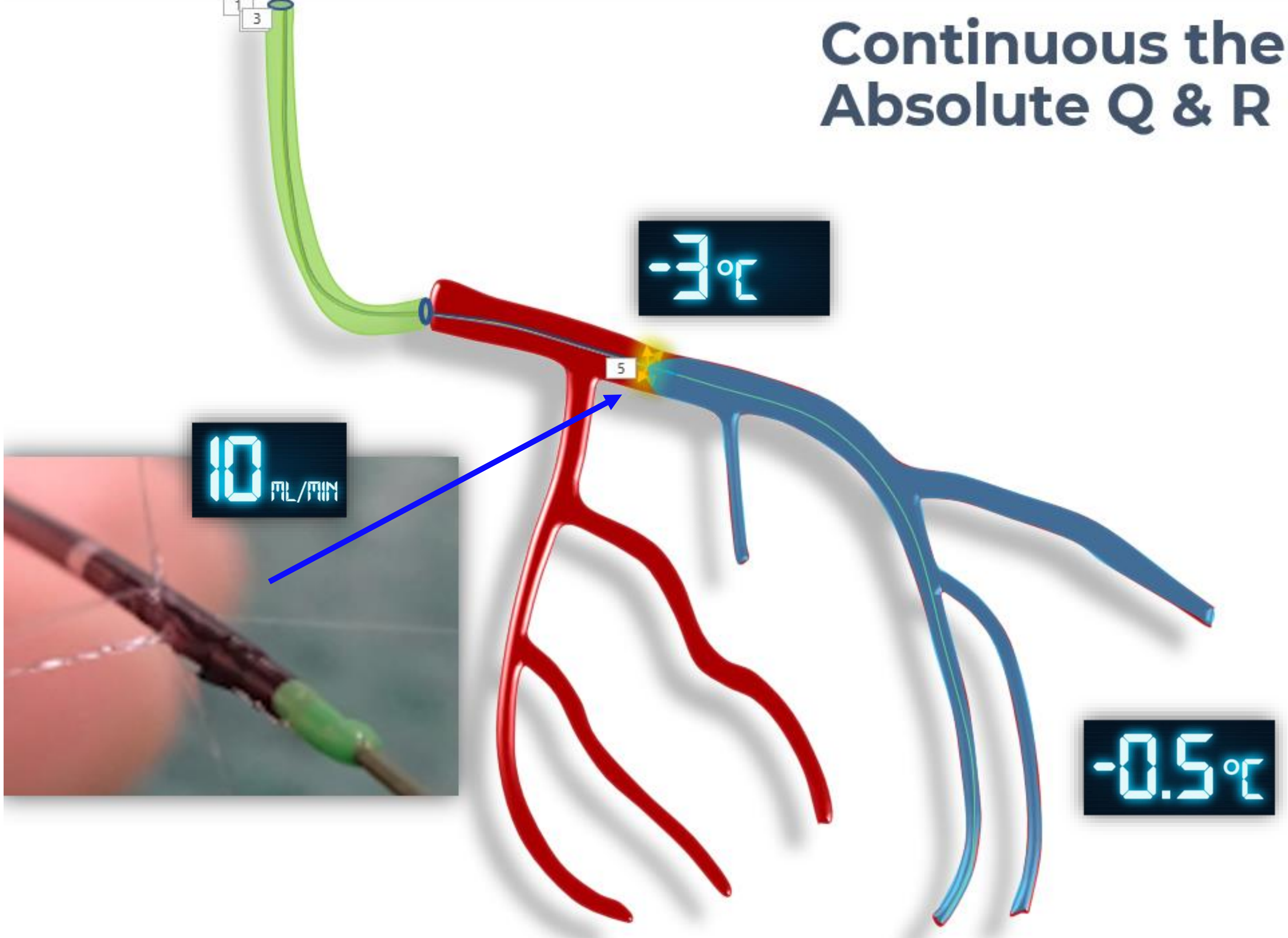
CoreAalst | OPTIMA

Continuous thermodilution for Absolute Q & R measurements

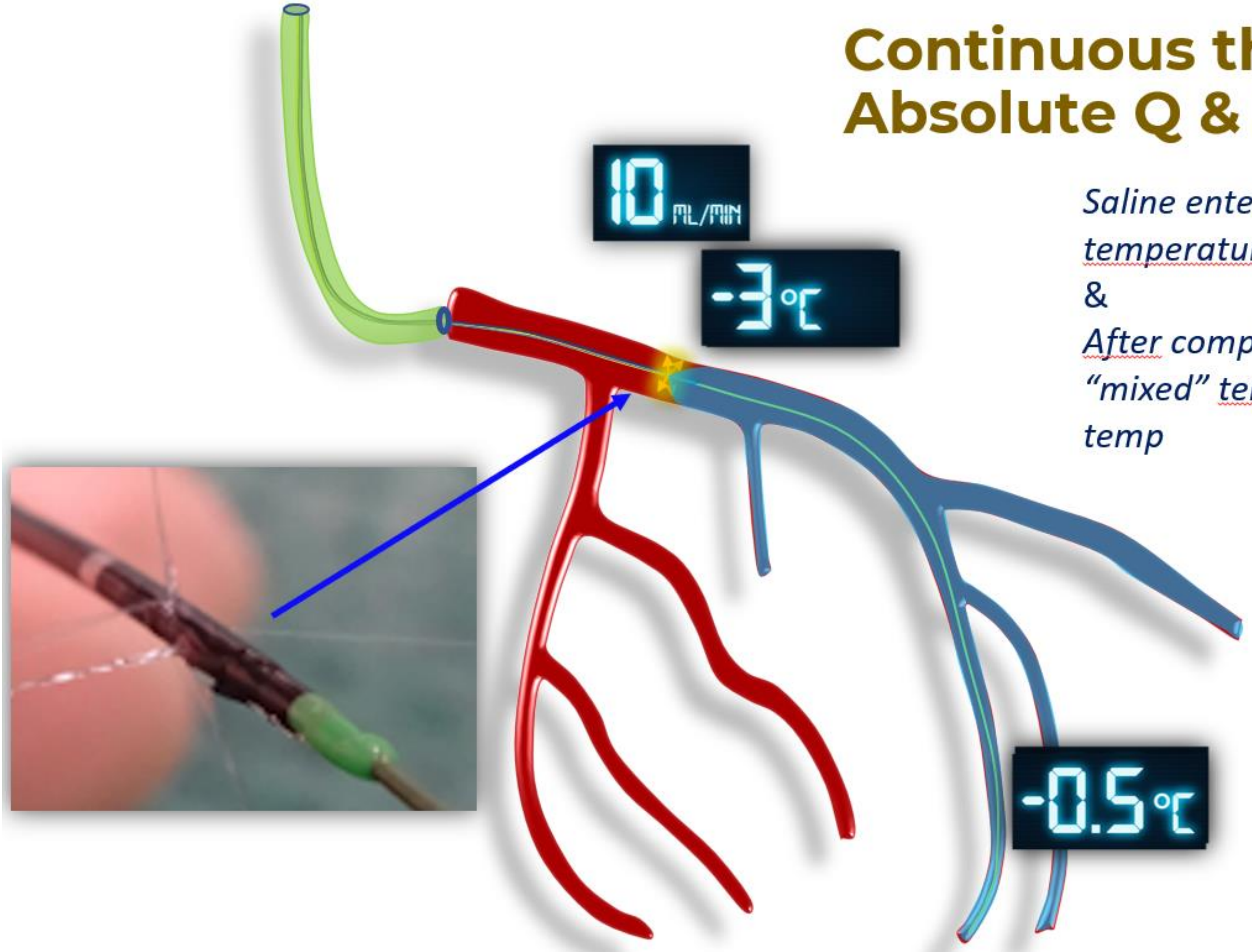




Continuous thermodilution for Absolute Q & R measurements



Continuous thermodilution for Absolute Q & R measurements



Saline enters the proximal coronary artery at a temperature of 3°C below blood temperature

&

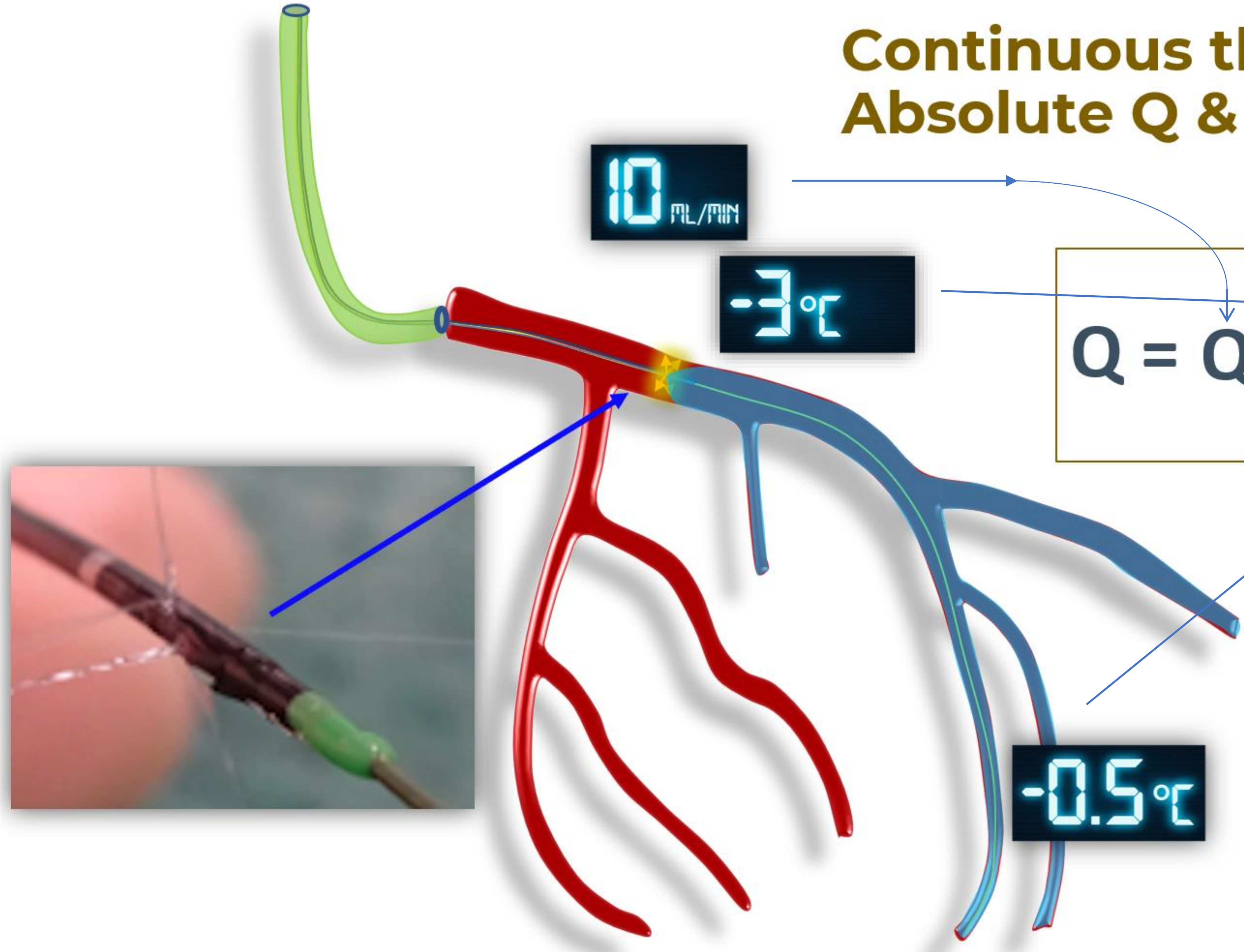
After complete mixing of blood and saline, the "mixed" temperature equals 0.5 °C below blood temp

↓

Blood flow must be 6 x infusion flow of saline

60 ml/min

Continuous thermodilution for Absolute Q & R measurements



$$Q = Q_{saline} \times \frac{T_{saline}}{T_{mixture}} \times 1.08$$

Q_{saline} is known infusion rate of saline (mL/min)

T_{saline} , T_{mix} are the **difference** vs body temperature (°C)

1.08 accounts for difference in **specific heats** of saline and blood

Continuous thermodilution for absolute Q & R measurements

$$Q = Q_{saline} \times \frac{T_{saline}}{T_{mixture}} \times 1.08$$

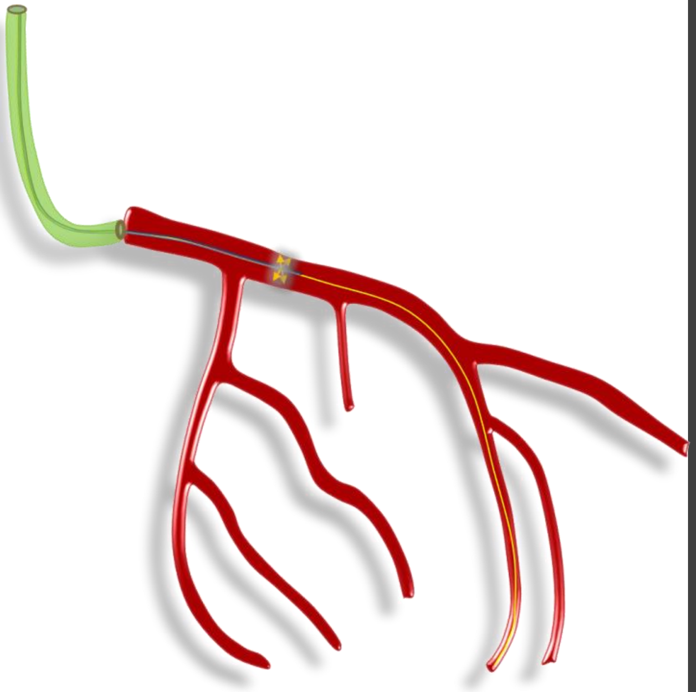
Q_{saline}	is known infusion rate of saline (mL/min)
T_{saline} , T_{mix}	are the **differences** vs body temperature (°C)
1.08	accounts for **specific heats** of saline and blood

- Coronary Pressure and Temperature can be measured very accurately (up to 2 mmHg and 0.01 °C) using the Abbott PressureWire®

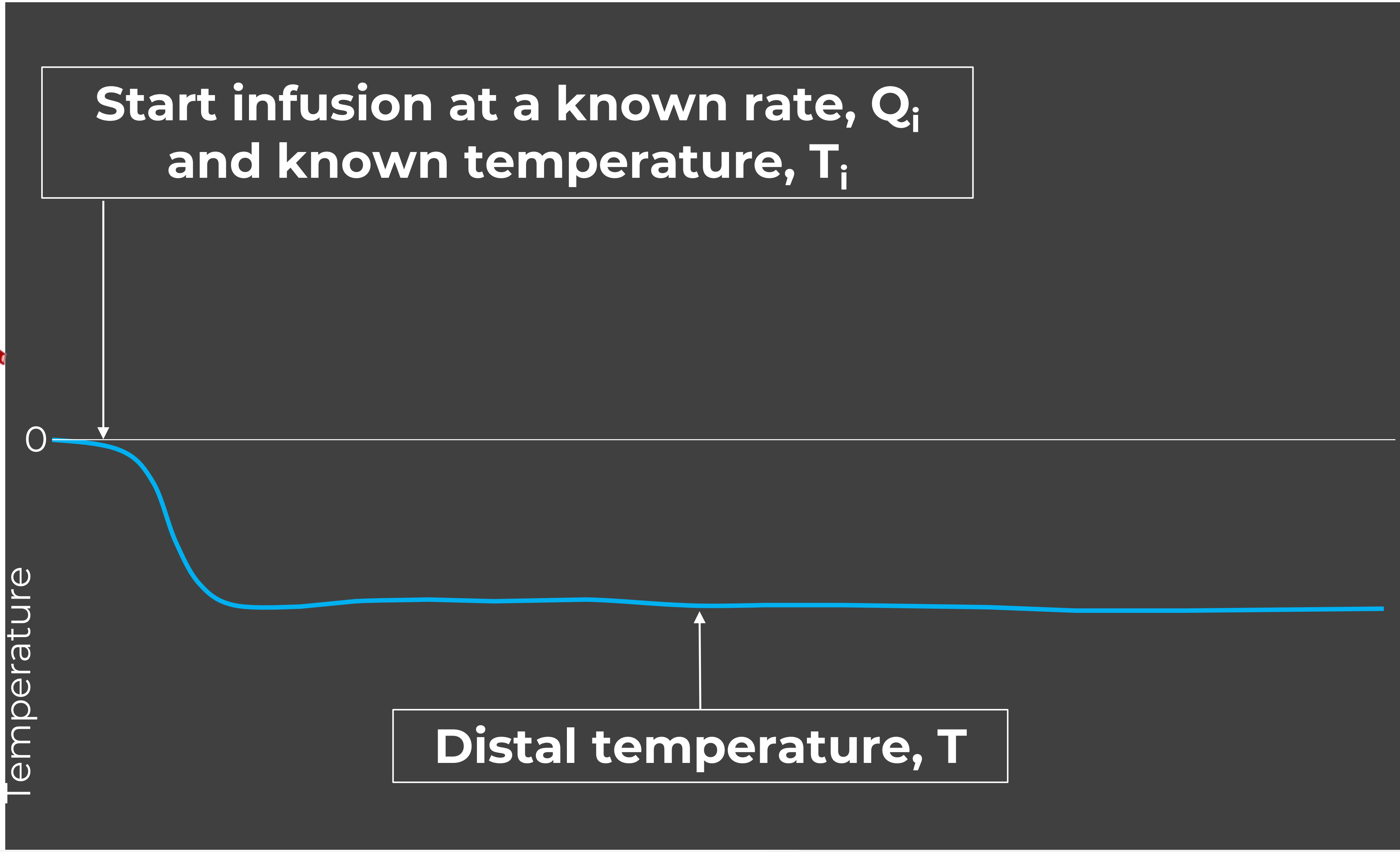
- Microvascular Resistance (R_{μ}) equals pressure divided by flow

→ If Myocardial Flow is calculated in ml/min , also Microvascular Resistance (R_{μ}) can be measured accurately in mmHg/l/min or Wood Units (WU)

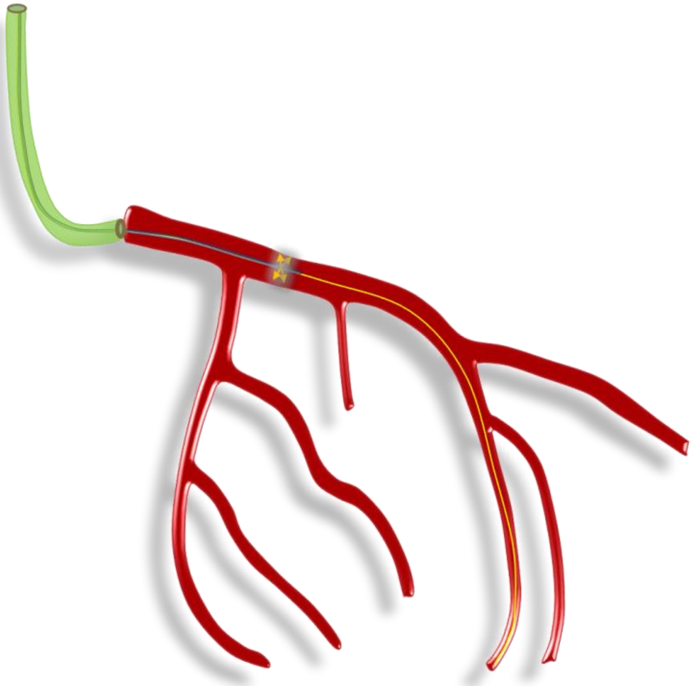
Continuous thermodilution for absolute Q & R measurements



$$Q = Q_i \times \frac{T_i}{T} \times 1.08$$

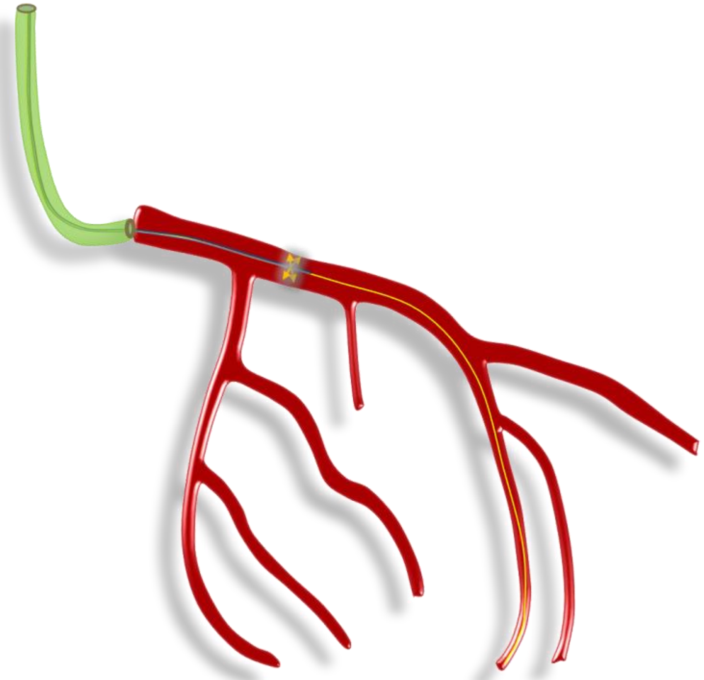


Continuous thermodilution for absolute Q & R measurements



$$Q = Q_i \times \frac{T_i}{T} \times 1.08$$

Continuous thermodilution for absolute Q & R measurements



$$Q = Q_i \times \frac{T_i}{T} \times 1.08$$

Practicalities

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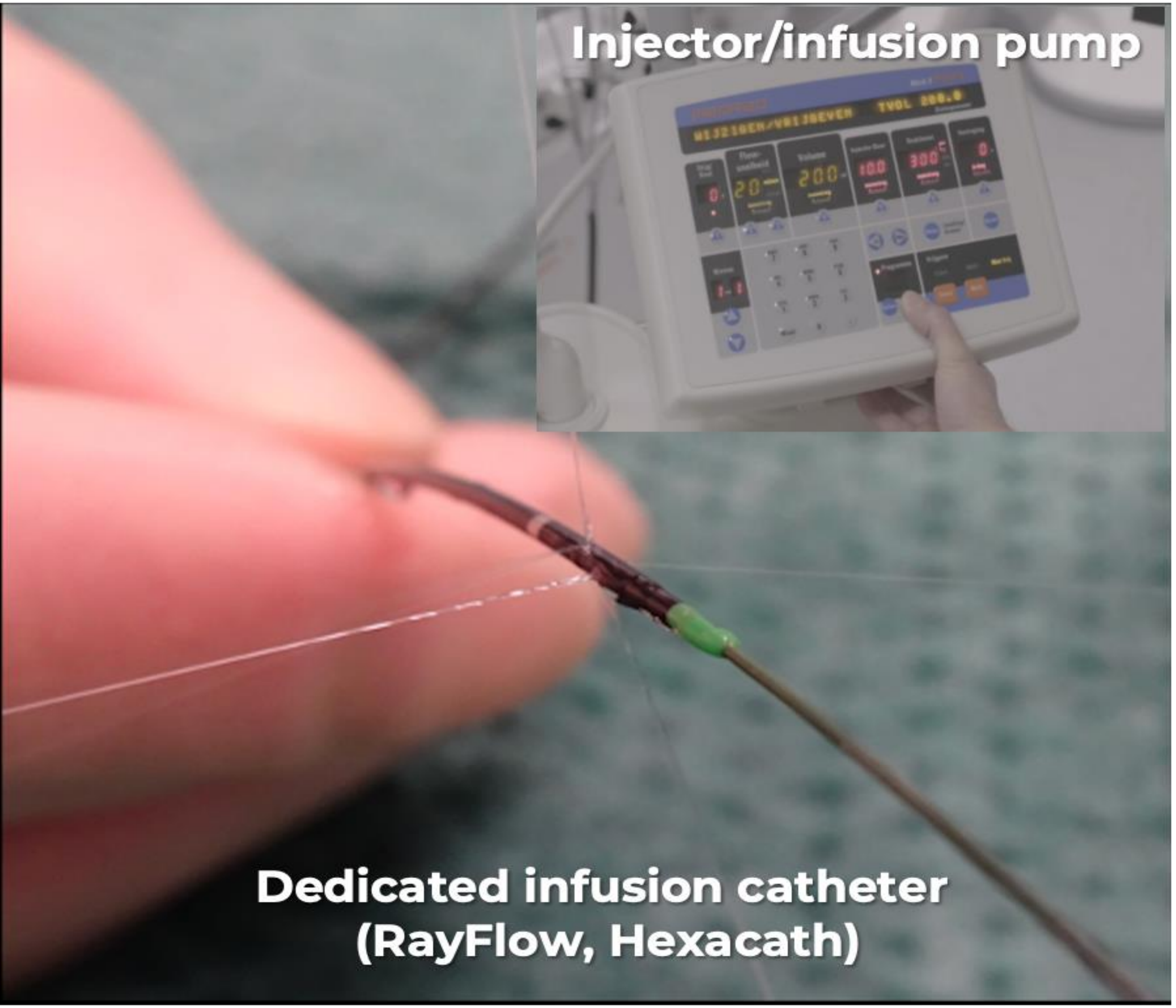
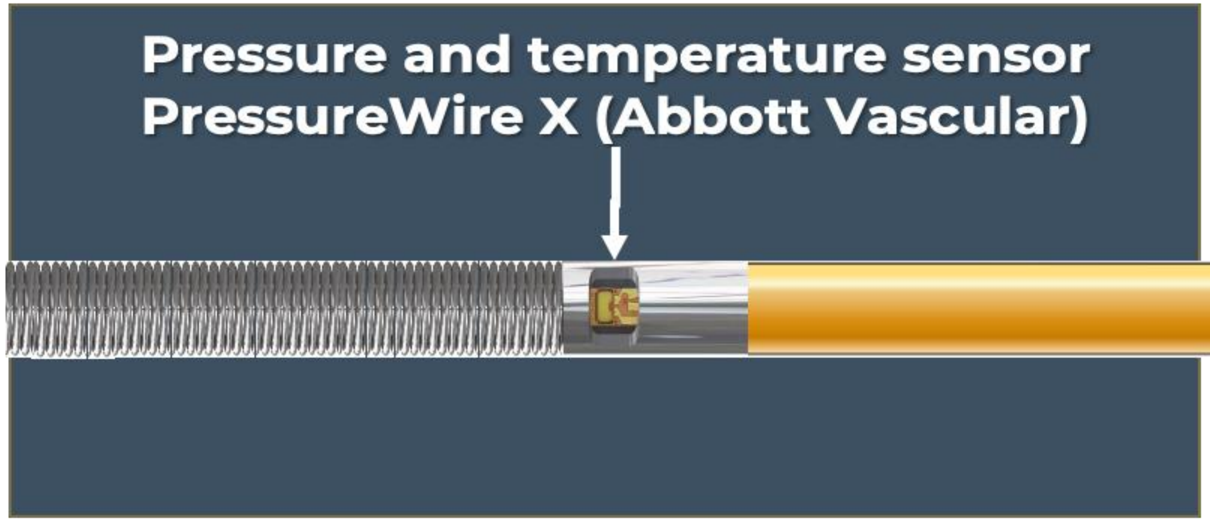
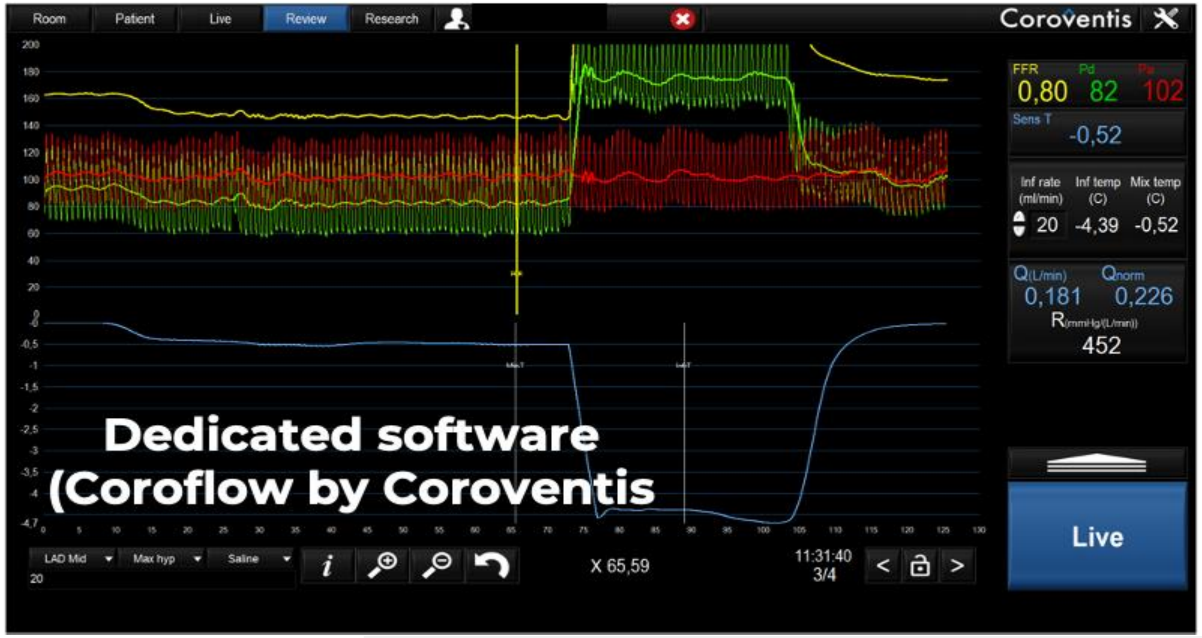
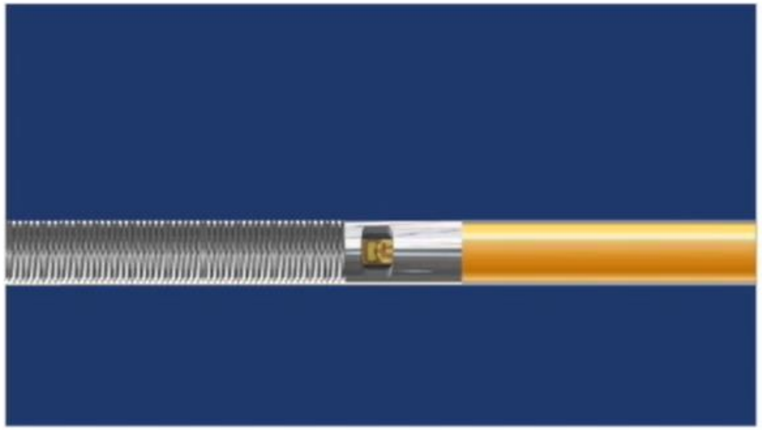
EQUIPMENT for Continuous thermodilution for absolute Q & R measurements



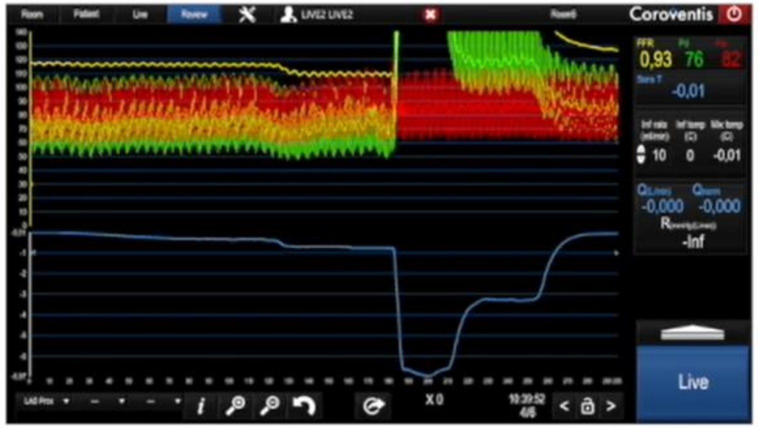




Equipment to perform Continuous Thermodilution



PRESSURE/TEMPERATURE WIRE (Abbott)



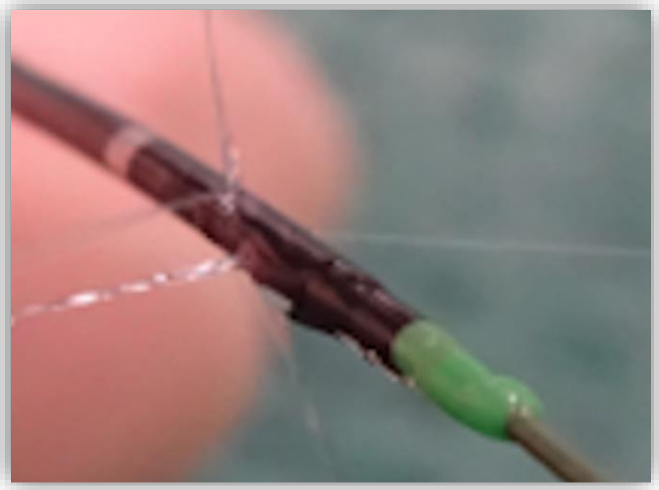
COROVENTIS

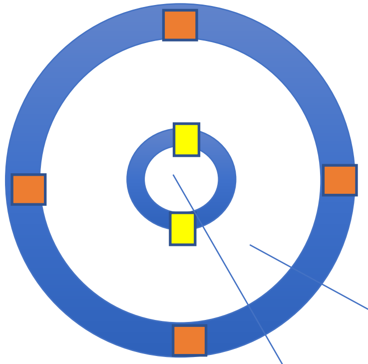
RAYFLOW CATHETER (HEXACATH)

INFUSION PUMP (POWER INJECTOR)

Some important practicalities (1)

1. To apply this method, homogeneous ***complete mixing*** of saline and blood is mandatory.
   This can ***not*** be achieved be a regular infusion catheter, but only by the so-called monorail RayFlow® infusion catheter *(Hexacath, Paris)*



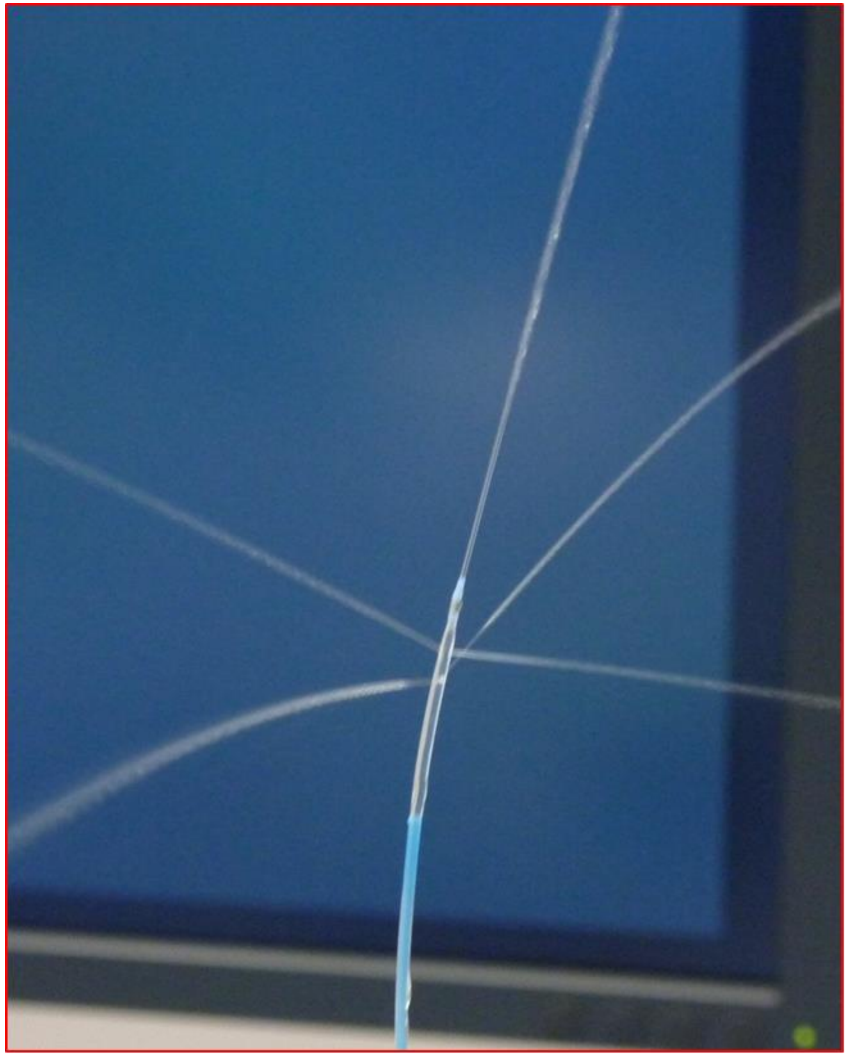


Cross-section close to tip

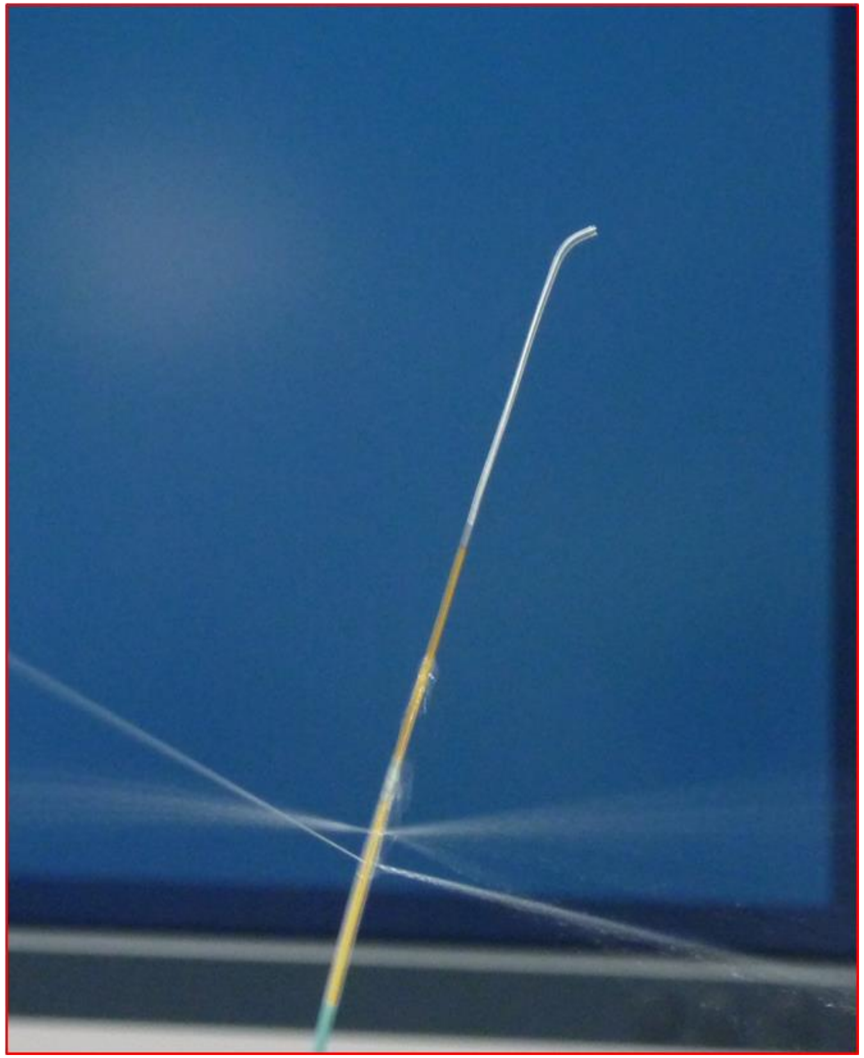
- monorail catheter 2.2 F
- 4 outer sideholes for saline infusion
- 2 inner sideholes for measuring infusion temperature, when pressure/temp sensor is pulled back

Infusion Catheter For Thermodilution (RayFlow ®)

(complete mixing of blood and saline)



without guidewire

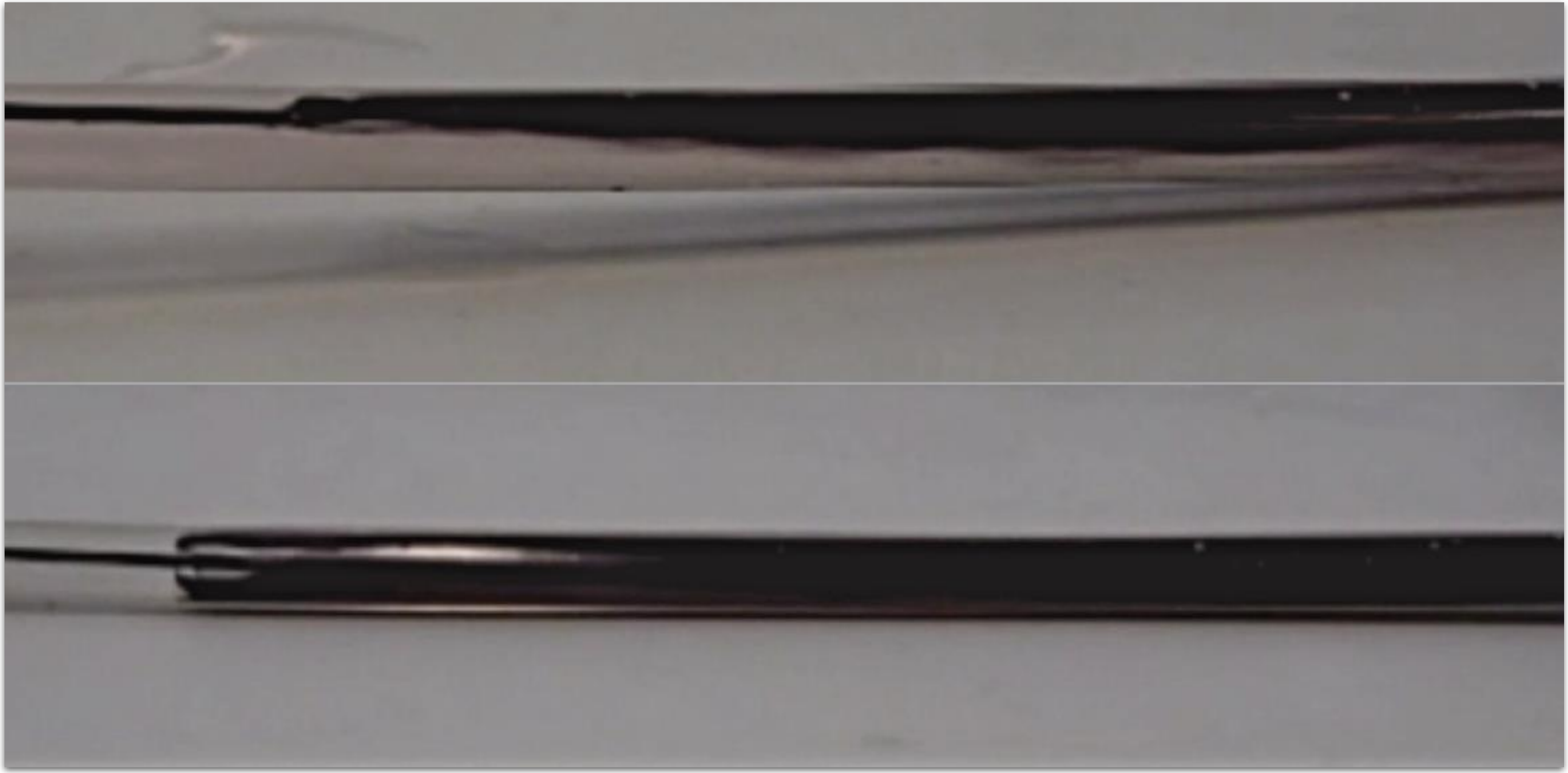


with guidewire

Continuous thermodilution for absolute Q & R measurements

End-hole catheter

RayFlow[R] Catheter



van 'tVeer M, Toth G et al EuroInterv 2016;12:701-707

RayFlow ® monorail infusion catheter:

- Manufactured by Hexacath, Paris, France
- CE approved (Europe) since 2017
- FDA approved (USA) on April 12th, 2023
- PDMA approval (Japan) expected Q2-2023
- Approved in Korea in 2022

Some important practicalities (2): rest and hyperemia

In suspected microvascular disease, ANOCA, MINOCA, NOCAD, etc, the index artery to investigate is generally the LAD

Resting Measurements: ***10 ml/min of saline in LAD***

Hyperemic measurements: ***20 ml/min of saline in LAD***

NO separate hyperemic drug necessary; 20 ml/min of saline induces maximum hyperemia
(Gallinoro et al, EuroIntervention 2021;17:e671-e679 De Bruyne et al, JACC 2021;78:1541-1549)

Large LCX or Large RCA: 10 ml/min (rest) and 20 ml/min (hyperemia)
Small or middle-sizes RCA or LCX: 8 ml/min (rest) and 15 ml/min (hyperemia)

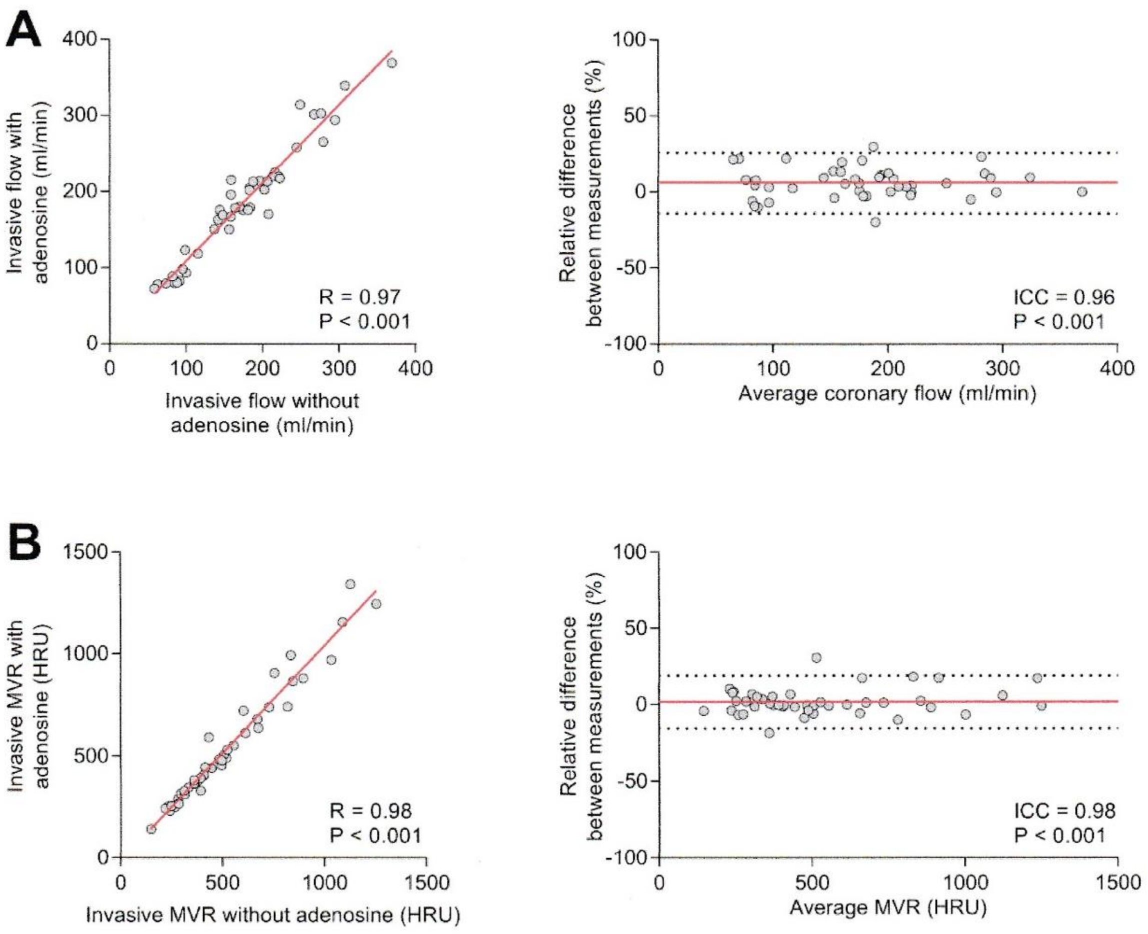
Saline infusion at 20 ml/min induces true maximum hyperemia:

Flow

(saline + adeno vs saline alone)

Resistance

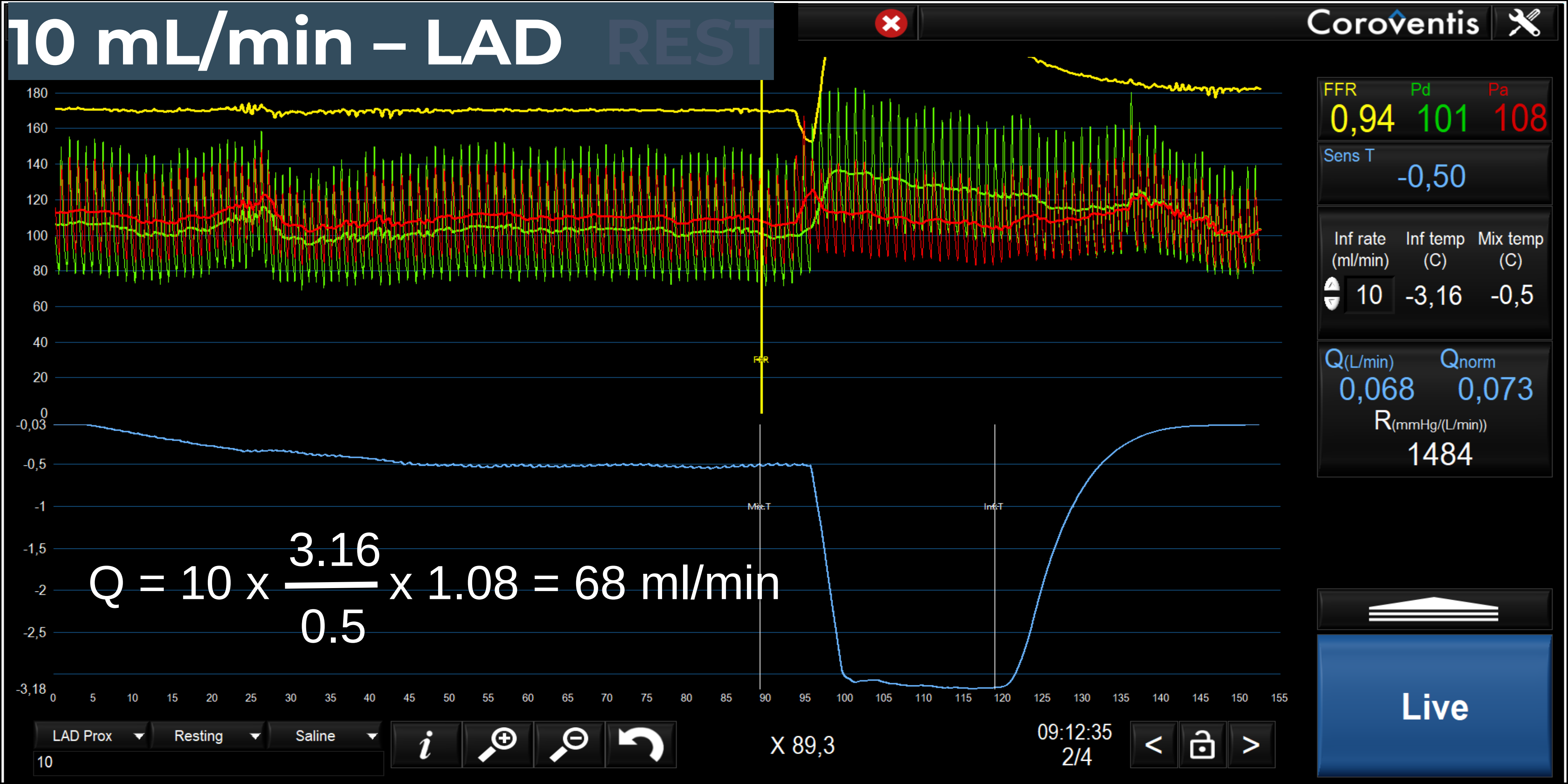
(saline + adeno vs saline alone)



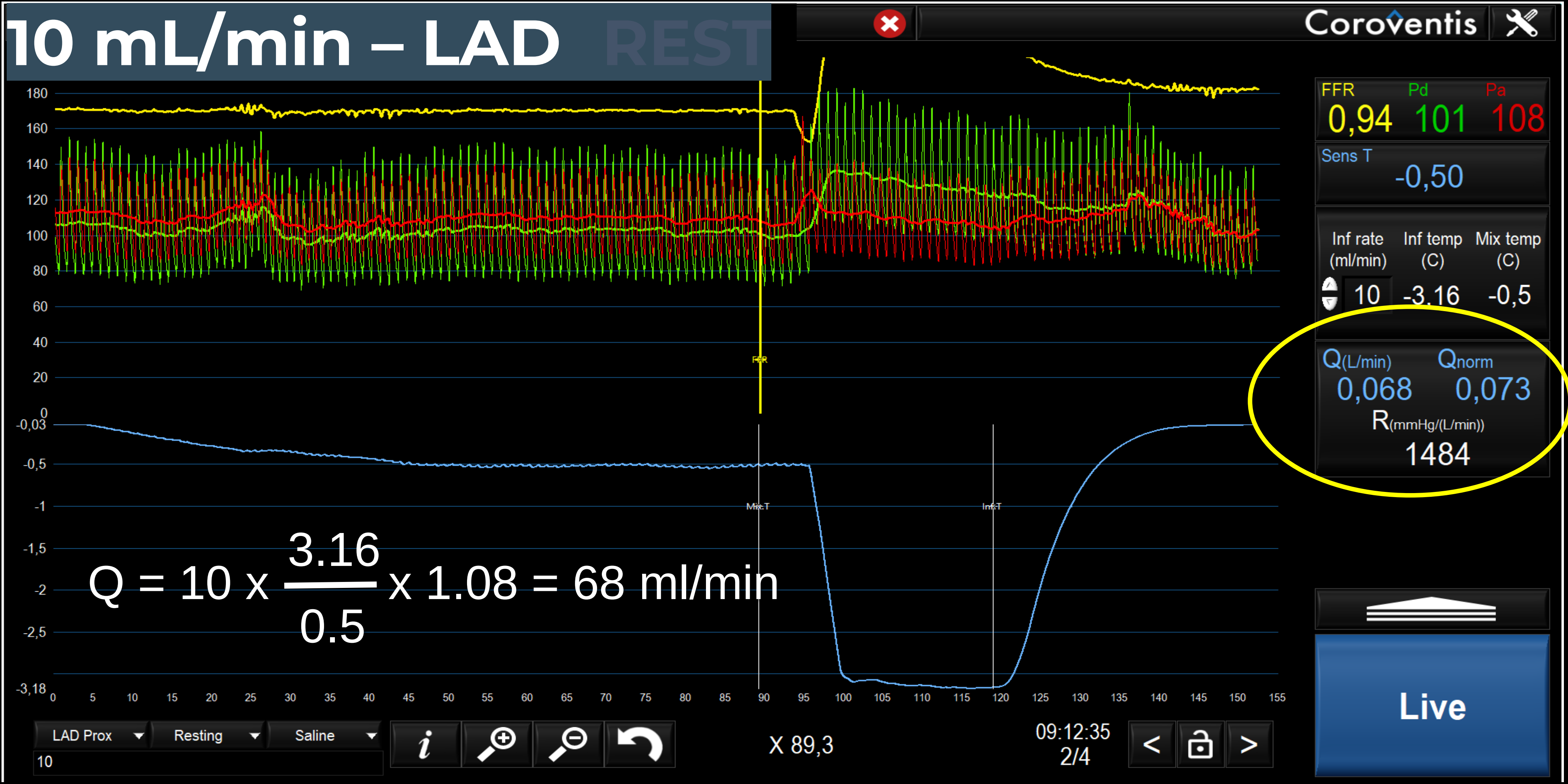
Scatterplots and corresponding Bland-Altman plots comparing invasive measurements of absolute hyperemic flow (**A**) and microvascular resistance (**B**) with and without adenosine. Abbreviations as in figure 3.

Everaars et al, Europ Heart J, 2019;40:2350-2359

Resting conditions

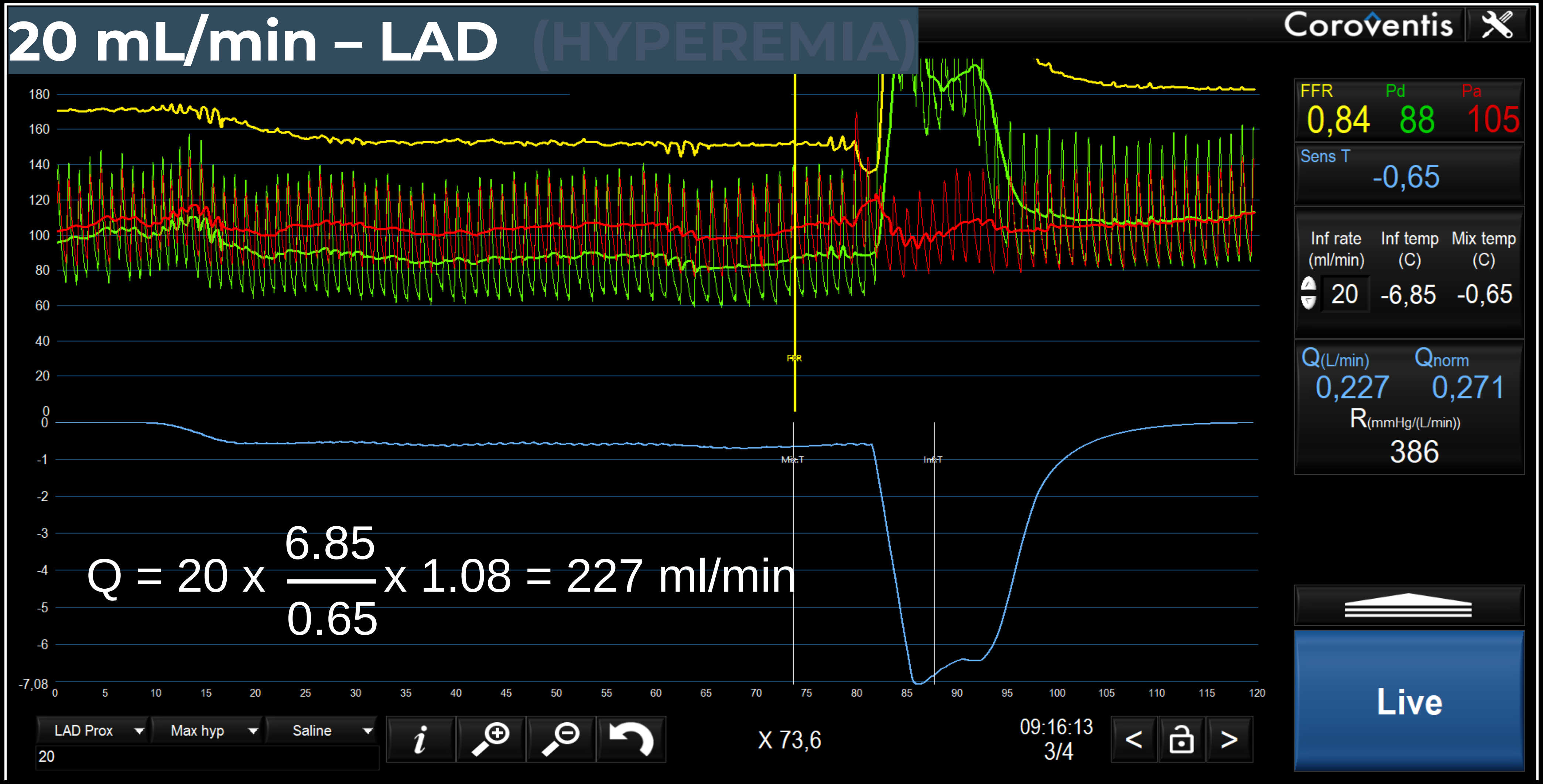


Resting conditions

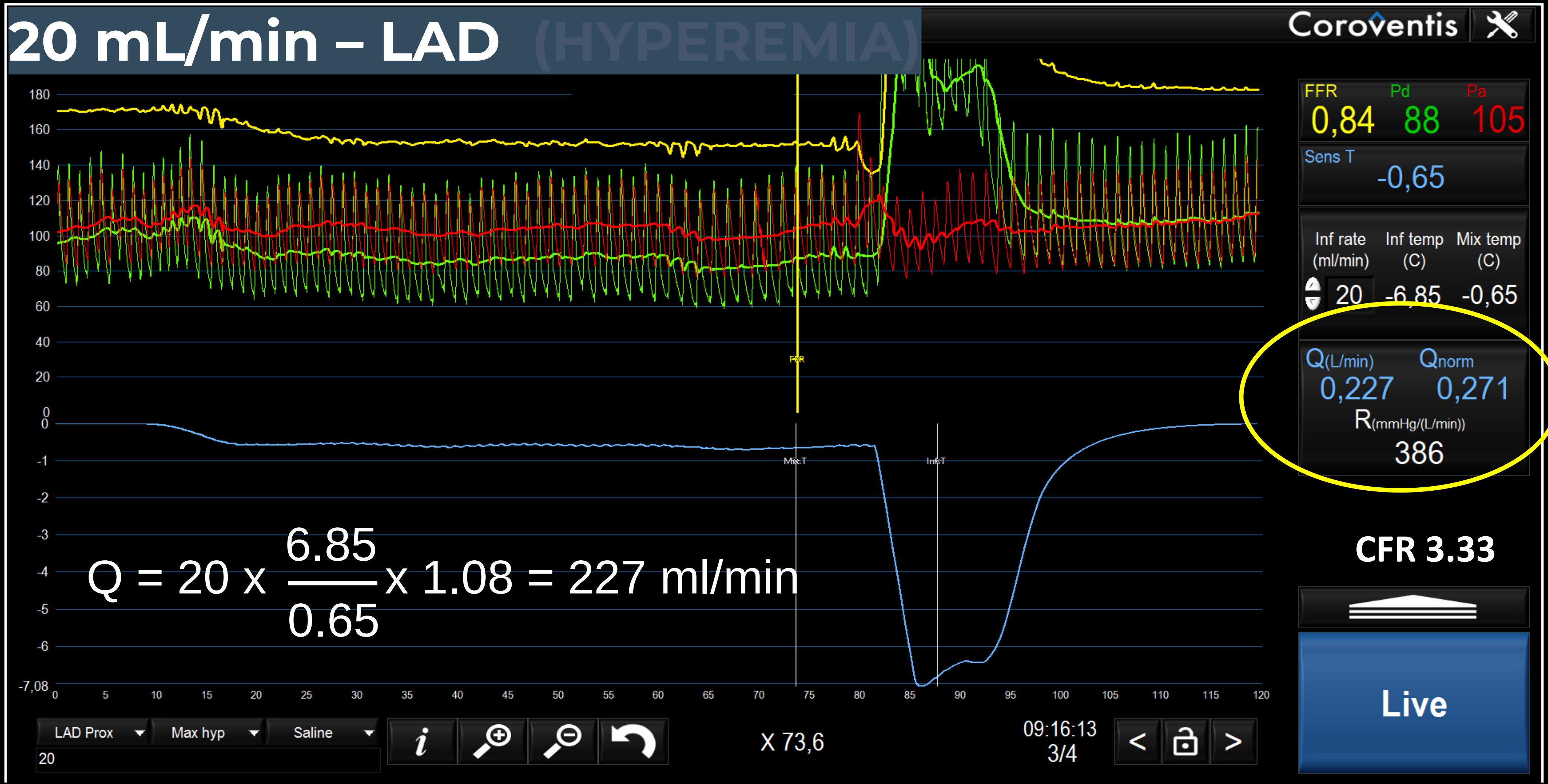


Resting R_{μ} of the anterior wall = 1484 WU

Maximum hyperemia (= minimal microvascular resistance)



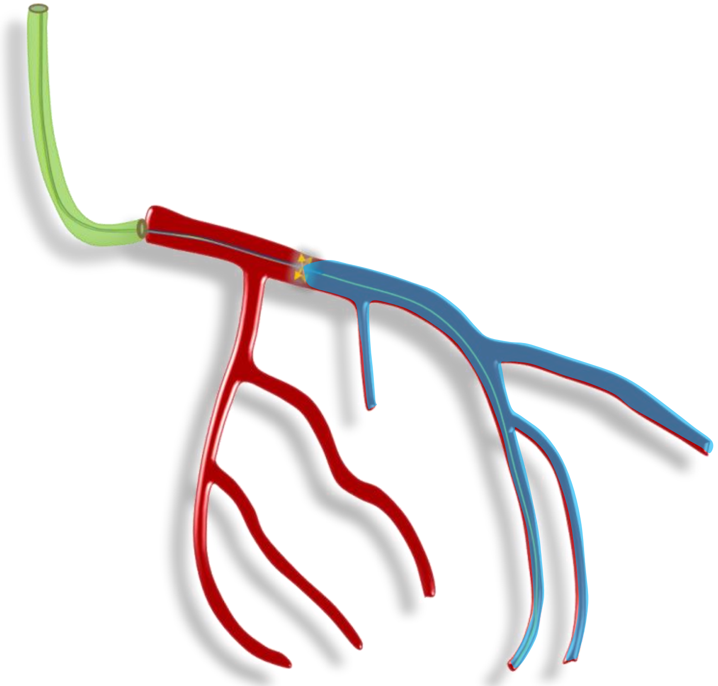
Maximum hyperemia (= minimal microvascular resistance)



Hyperemic (= minimal) R_{μ} of the anterior wall = 386 WU

Absolute CFR = 227/68 = 3.4

Some important practicalities (3):



FLOW (**Q**) which is measured is total flow distal to the tip of the infusion catheter

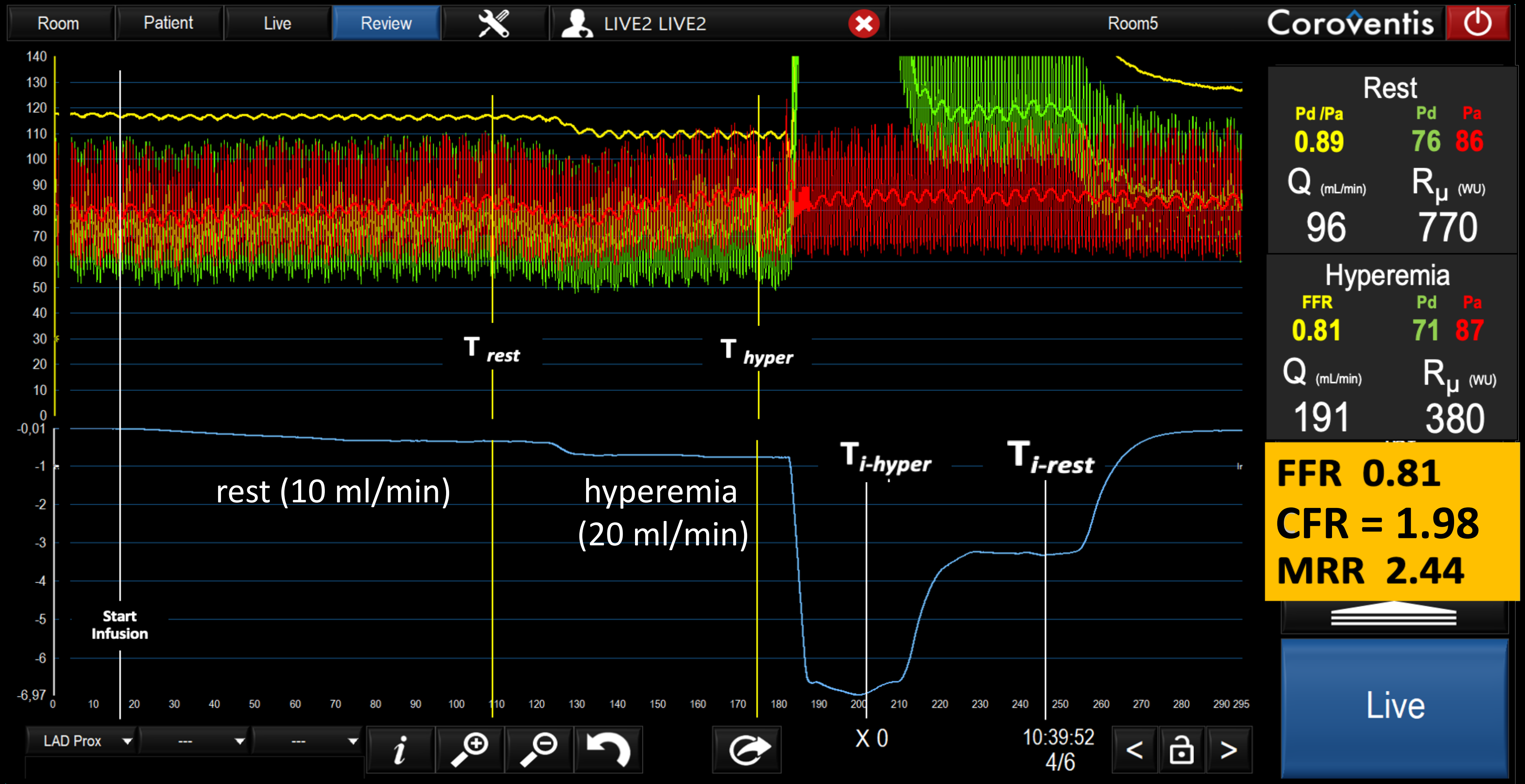
MICROVASCULAR RESISTANCE ($\mathbf{R}_{\mu}$) is the resistance of the myocardium distal to the tip of the infusion catheter

$$Q = Q_i \times \frac{T_i}{T} \times 1.08$$

In case of INOCA, MINOCA, etc you will place the tip in the Proximal coronary artery (generally the LAD).

In case of , for example, measuring flow & resistance in an Infarction area, you will place the tip close to the stent

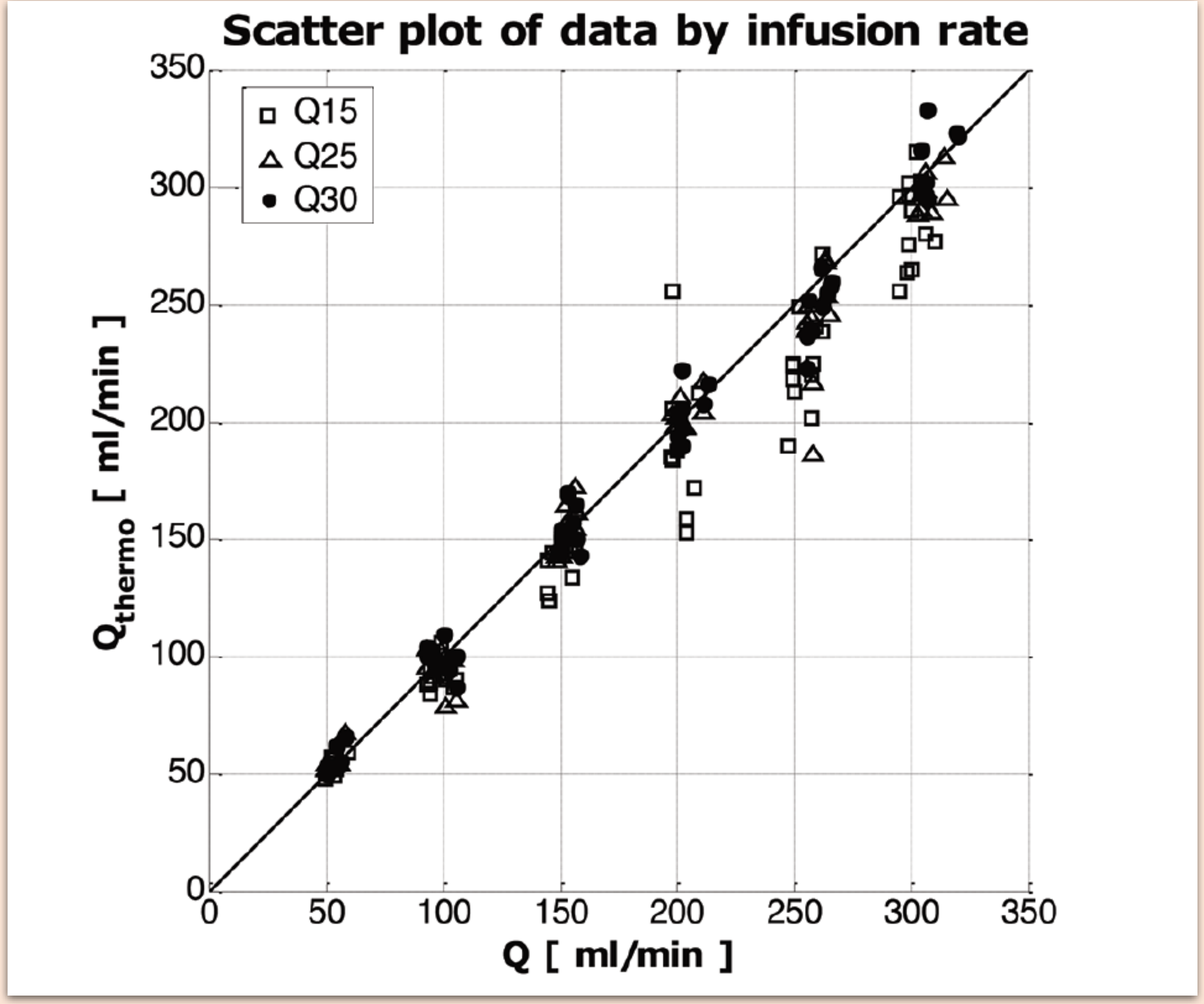
Some important practicalities (4): 2 separate runs or one long run



Validation

Accuracy

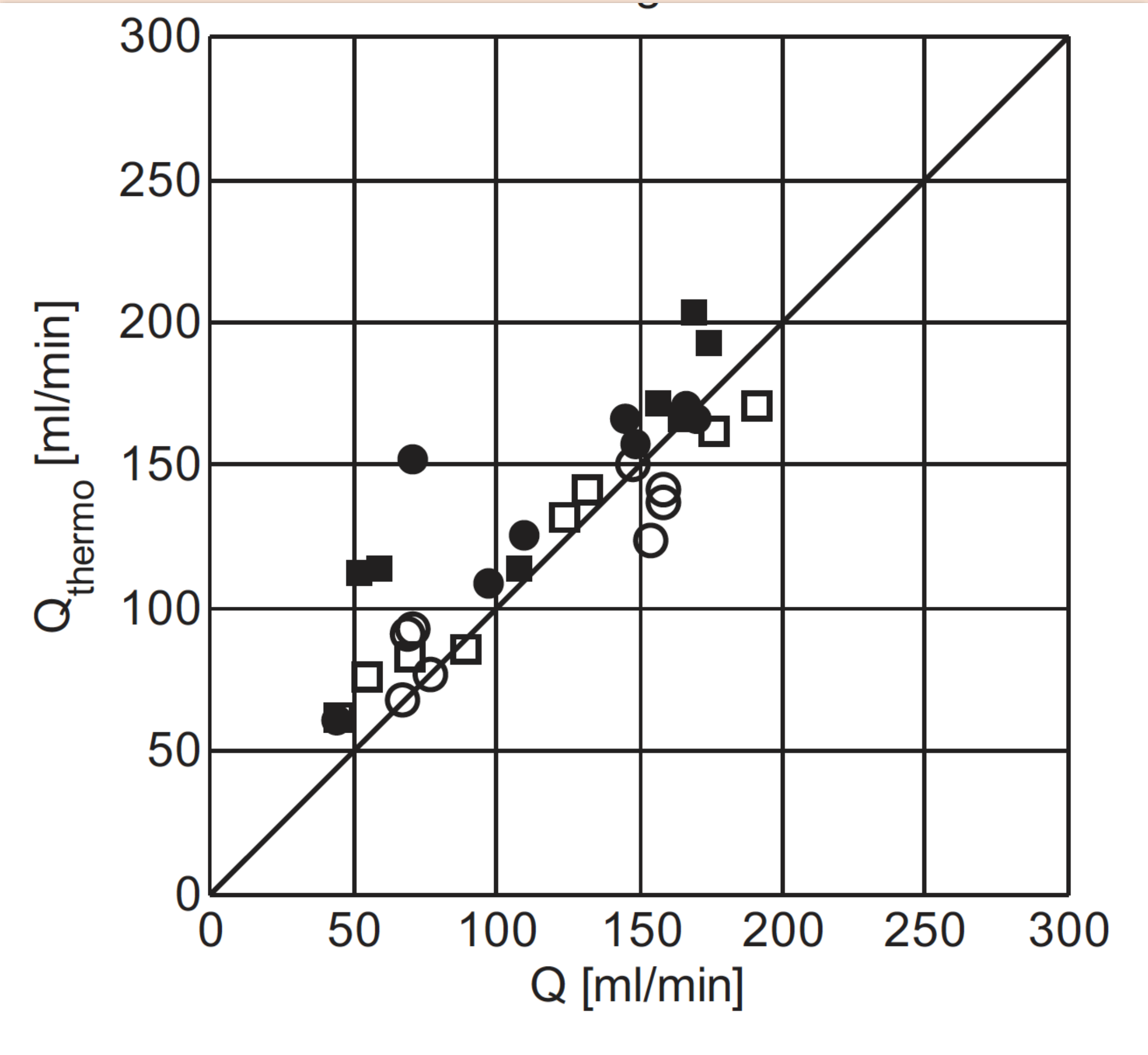
In vitro



van 'tVeer M, Toth G et al EuroInterv 2016;12:701-707

Accuracy

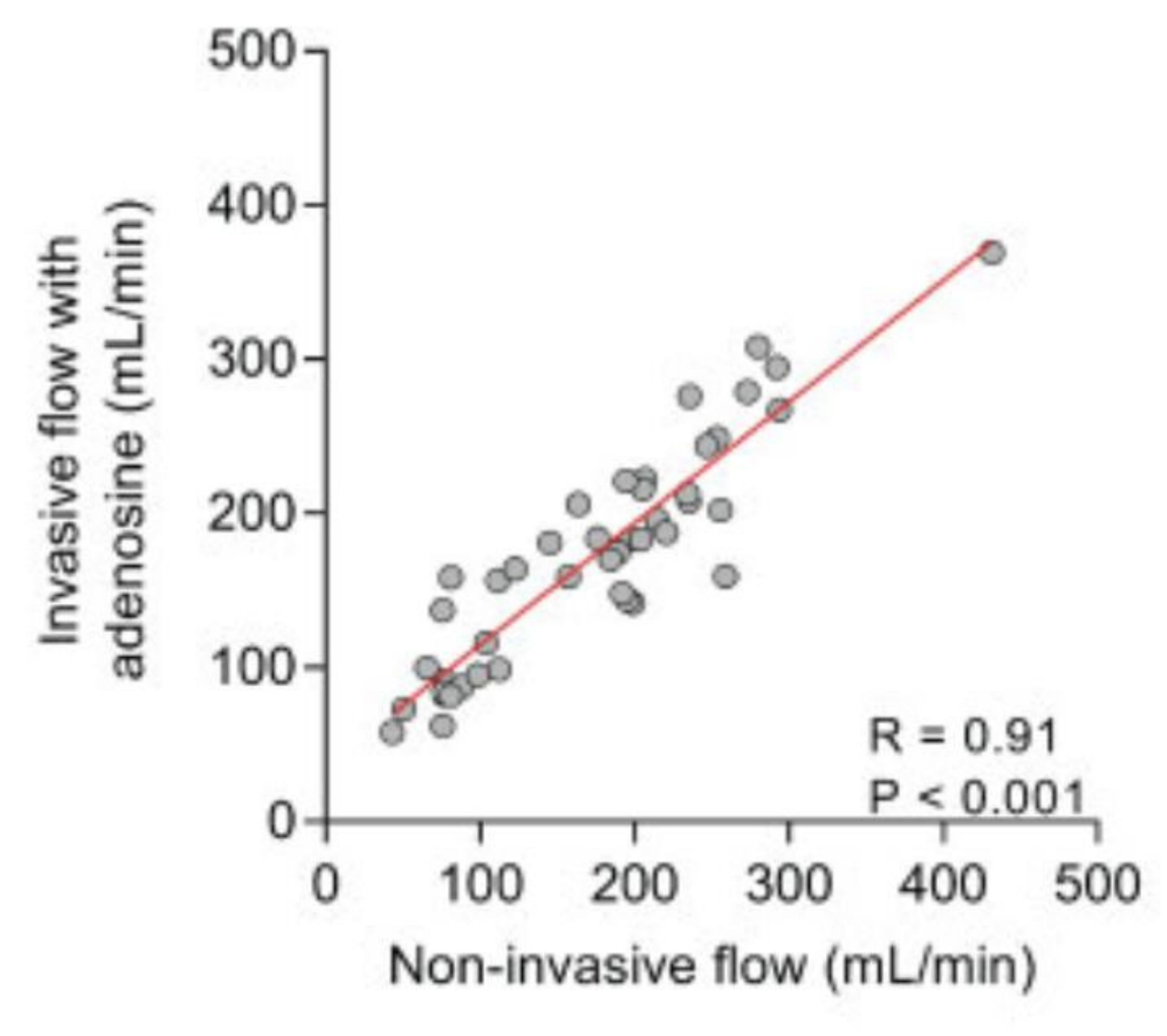
In dogs



van 'tVeer M, Toth G et al EuroInterv 2016;12:701-707

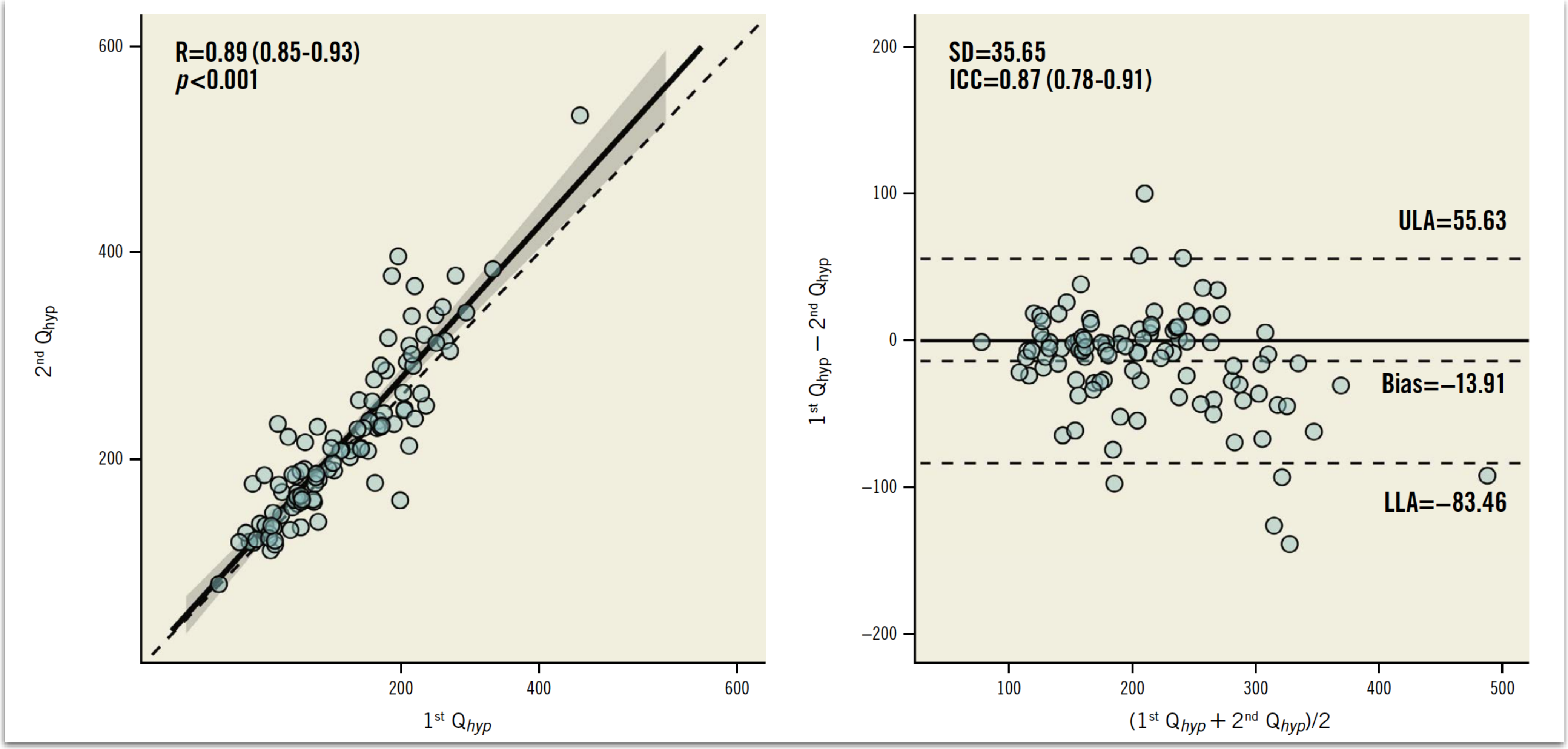
Accuracy

In humans using H_2O-PET



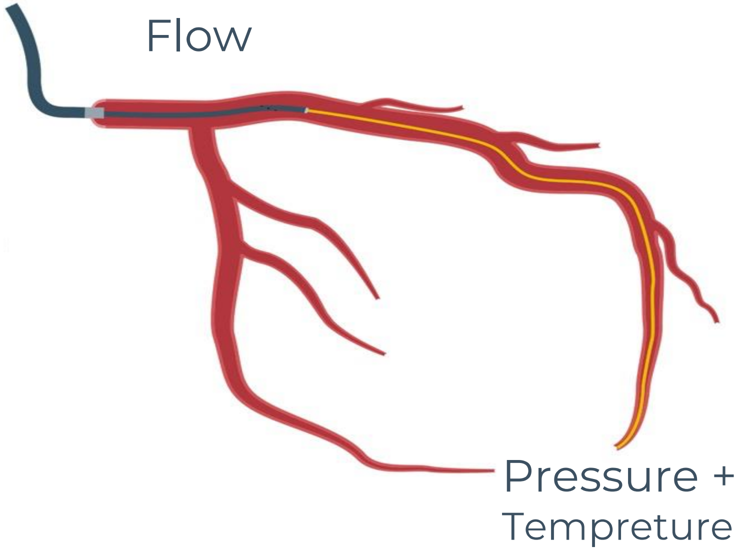
Everaars H. et al. European Heart Journal 2019;40: 2350–2359

Repeatability



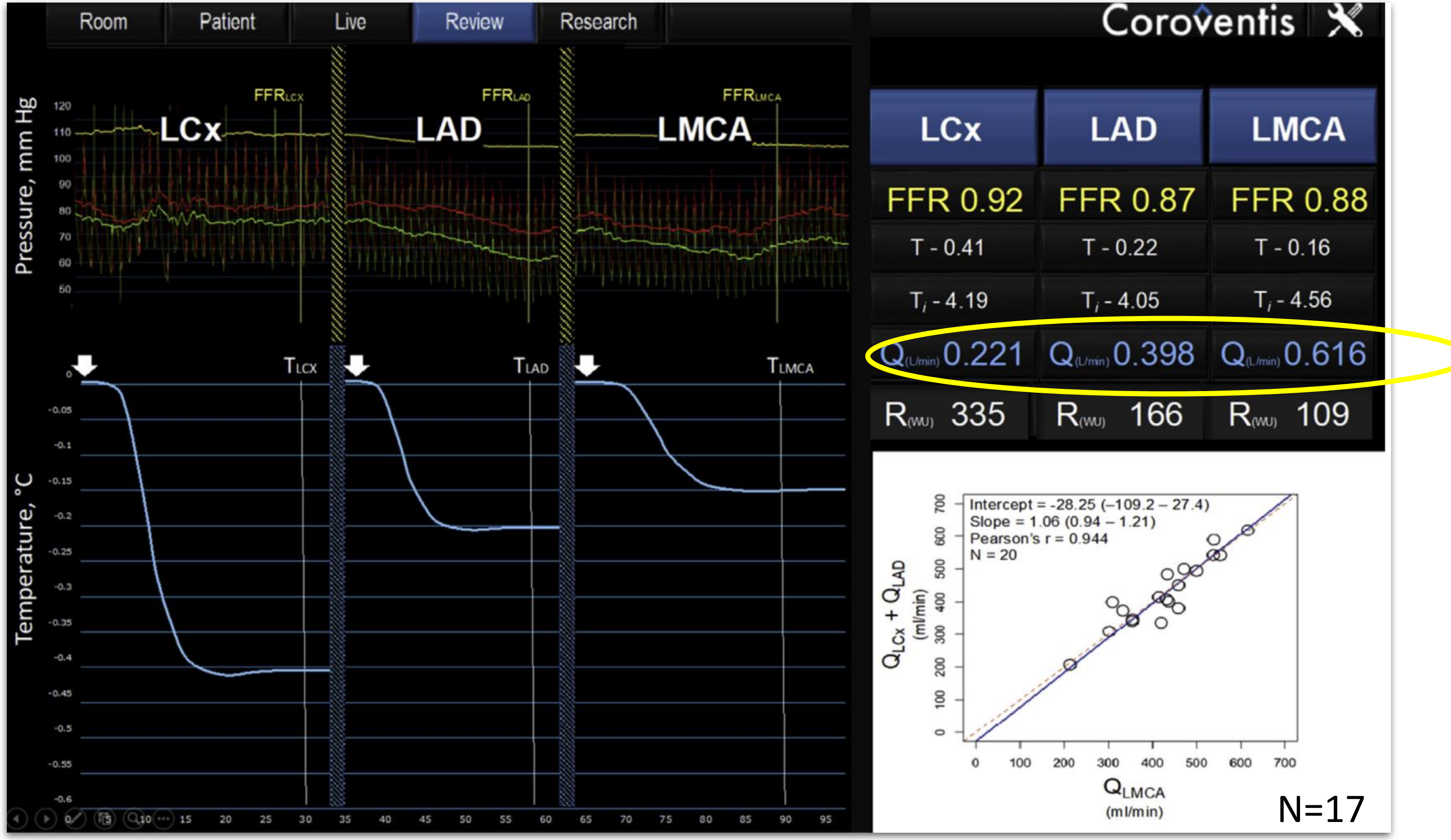
"1 + 1 = 2" study

→ indicates the extreme accuracy of these measurements

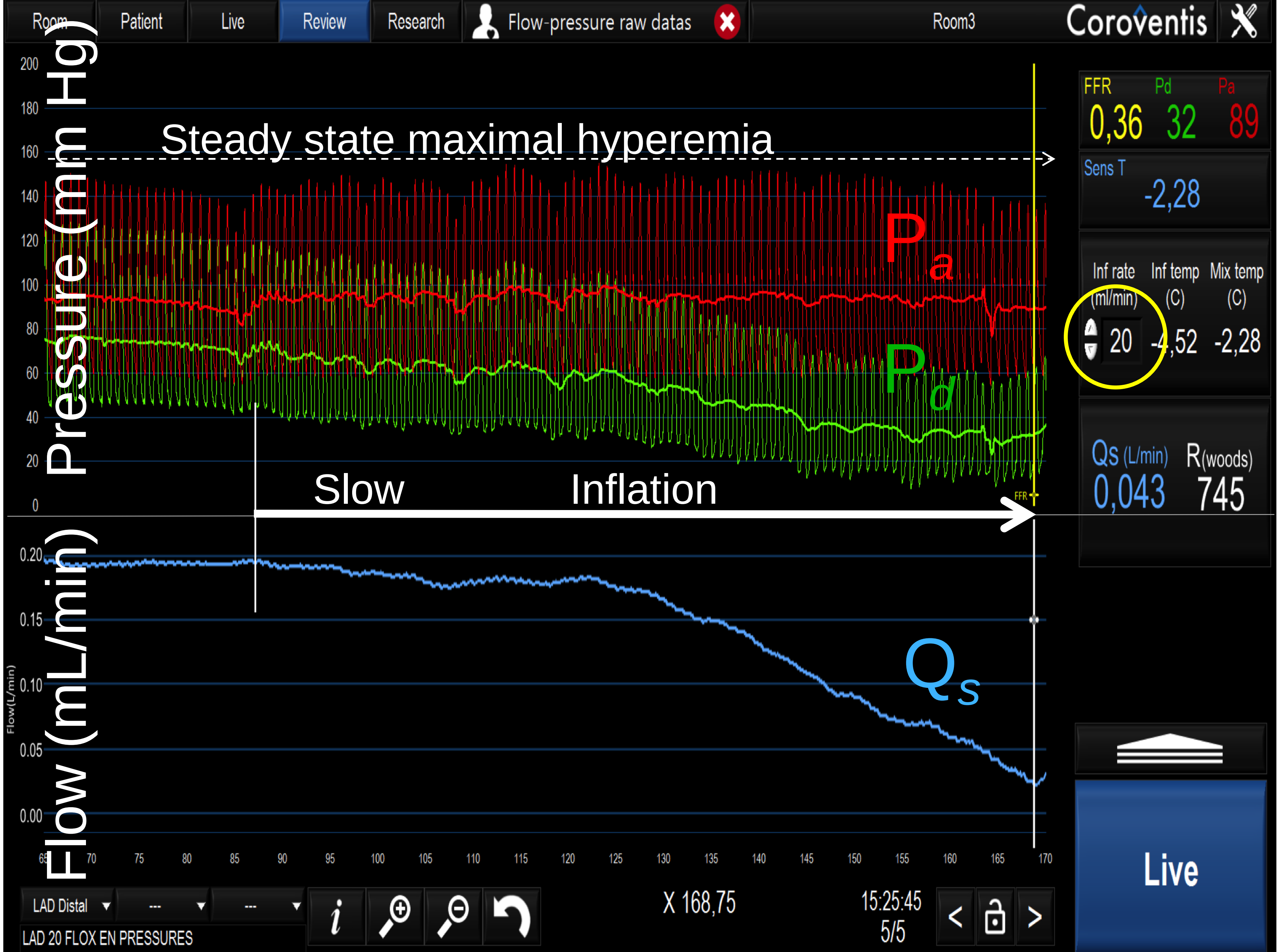


In humans

LAD + LCx = LM (!)



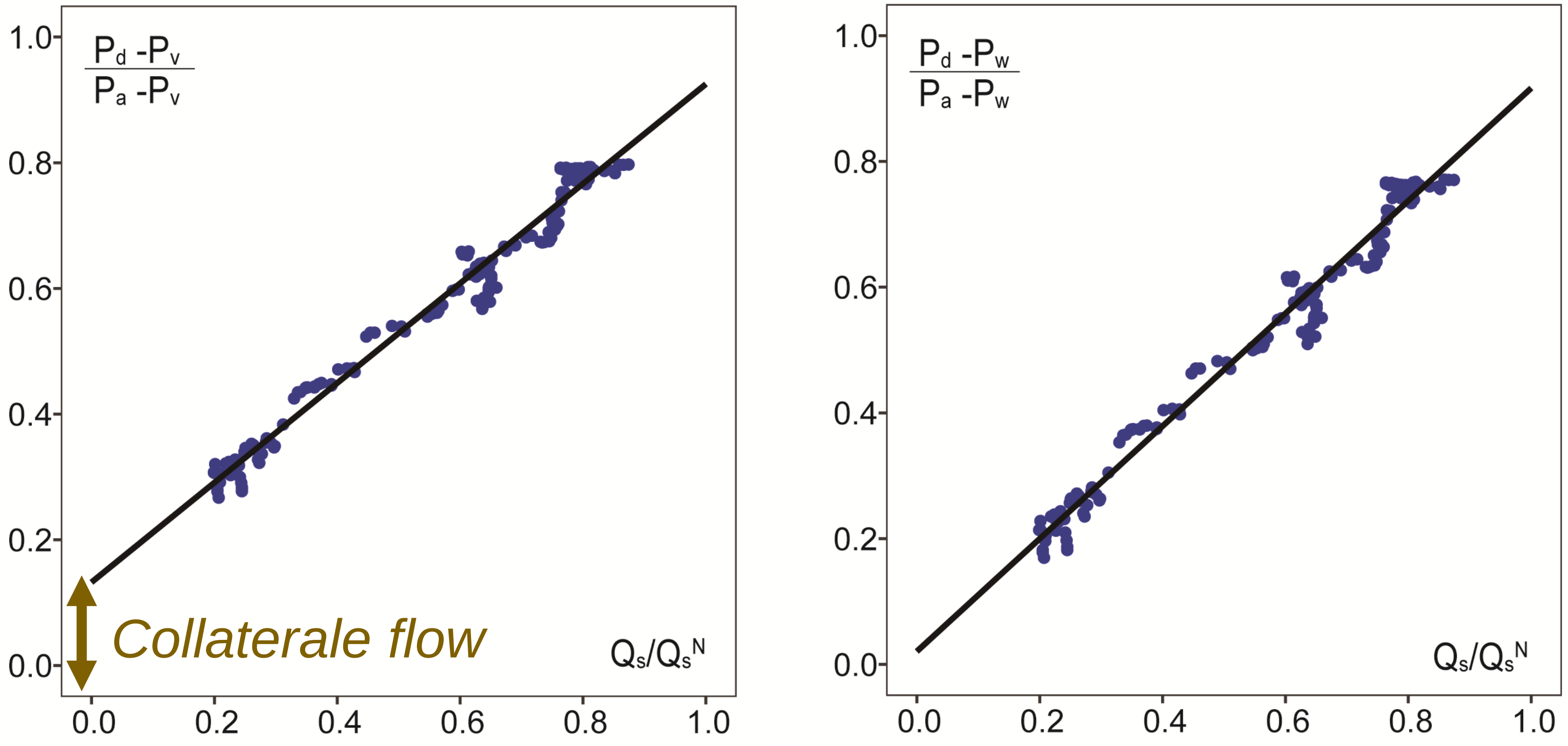
398 ml/min + 221 ml/min = 619 ml/min ~ 616 ml/min



Room
Patient
Live
Review
Research
Flow-pressure raw datas
Room3
Coroventis
Steady state maximal hyperemia
Pressure (mm Hg)
200
180
160
140
120
100
80
60
40
20
0
Pa
Pd
Slow Inflation
Flow (mL/min)
0.20
0.15
0.10
0.05
0.00
Flow(L/min)
Qs
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
150
155
160
165
170
FFR
FFR Pd Pa
0,36 32 89
Sens T
-2,28
Inf rate (ml/min)
Inf temp (C)
Mix temp (C)
20
-4,52
-2,28
Qs (L/min) R(woods)
0,043 745
Live
LAD Distal

LAD 20 FLOX EN PRESSURES
X 168,75
15:25:45
5/5

Pressure-Flow Relationship at hyperemia in Humans



S. Fournier and B. De Bruyne JACC JACC 2019

Safety:

- Keulards et al: EuroIntervention 2021; 17: 229-232

  213 coronary arteries in 100 consecutive patients:

  - 1 dissection related to Amplatz guiding
  - 6 times transient AV-block in RCA
    (stop infusion and repeat at lower infusion rate)

- In literature: one case of coronary dissection due to mistake in pump-setting: 20 ml/**sec** instead of 20 ml/**min** ("60 x overdose")

- NOTE: - generally, the *patient does not feel anything.*
  - complete resting and hyperemic measurement takes 5-10 minutes
  - but you can continue infusion much longer without problems.
  - 5 % of patients feel a little bit of "adenosine-like" chest pain during hyperemia

Summary

- Continuous thermodilution allows ***absolute coronary flow (Q)*** and ***microvascular resistance (R_{μ})*** measurements

- These measurements are accurate, reproducible, quantitative and ***operator-independent***

- This degree of precision opens the door to the ***investigation of the microcirculation***

- Finally: absolute flow & Resistance is "perfusion territory dependent" , but that problem is solved by:

  ⟶ ***Microvascular Resistance Reserve (MRR)***

but……………let's first go to a live case from OLV Heart Center Aalst (Dr De Bruyne and team)

! Don't forget one last slide !

More Information and Practical Instructions for Absolute Coronary Blood Flow Microvascular Resesistance Measurements, and Microvascular Resistance Reserve (MRR) :

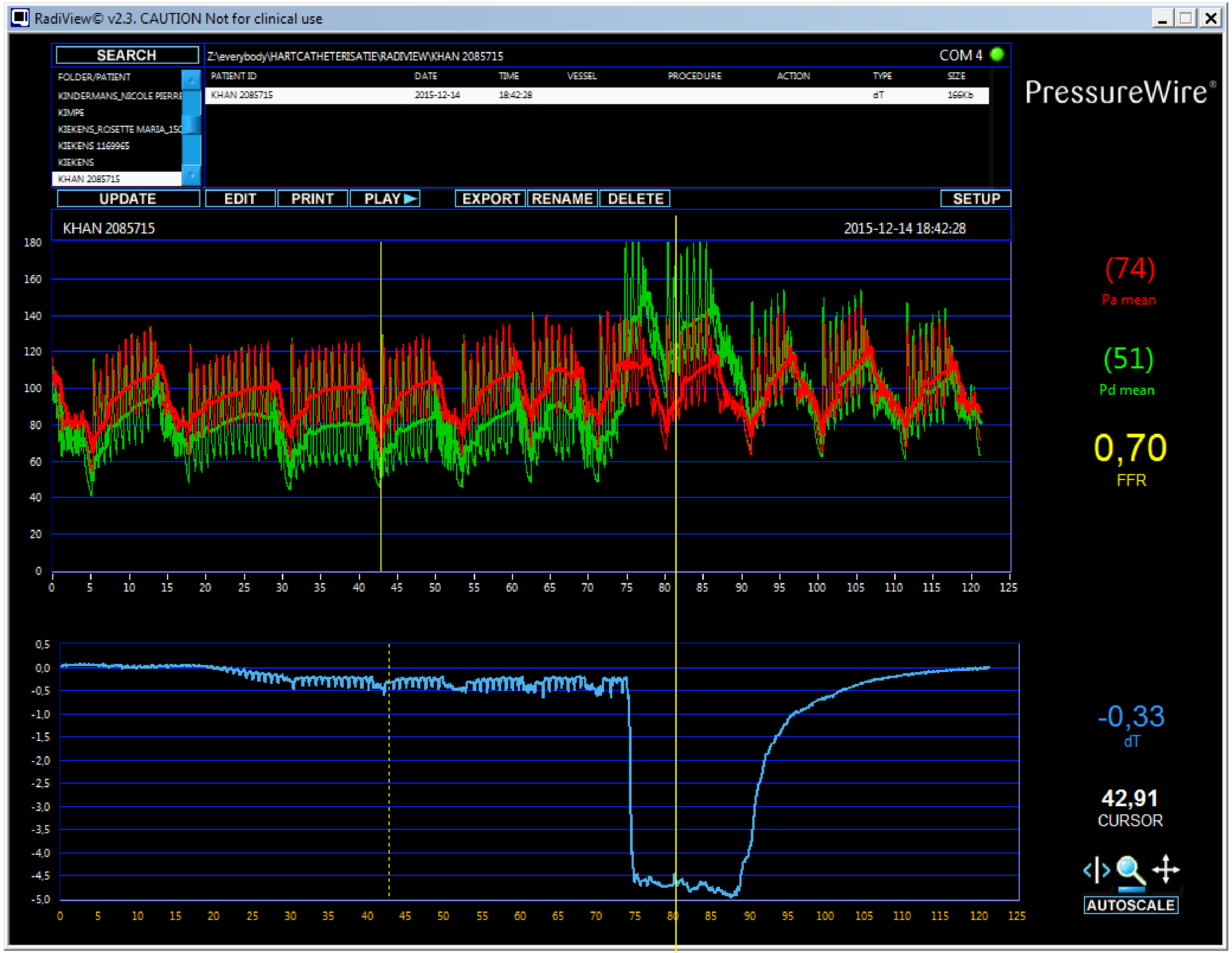
Send e-mail to:

ingrid.aarts@catharinaziekenhuis.nl

for receiving:

- **complete portfolio with all available literature**
- **practical manual to perform the measurements**
- **paper princeps about Microvascular Resistance Reserve (MRR)**
- **the video with live case from Aalst**

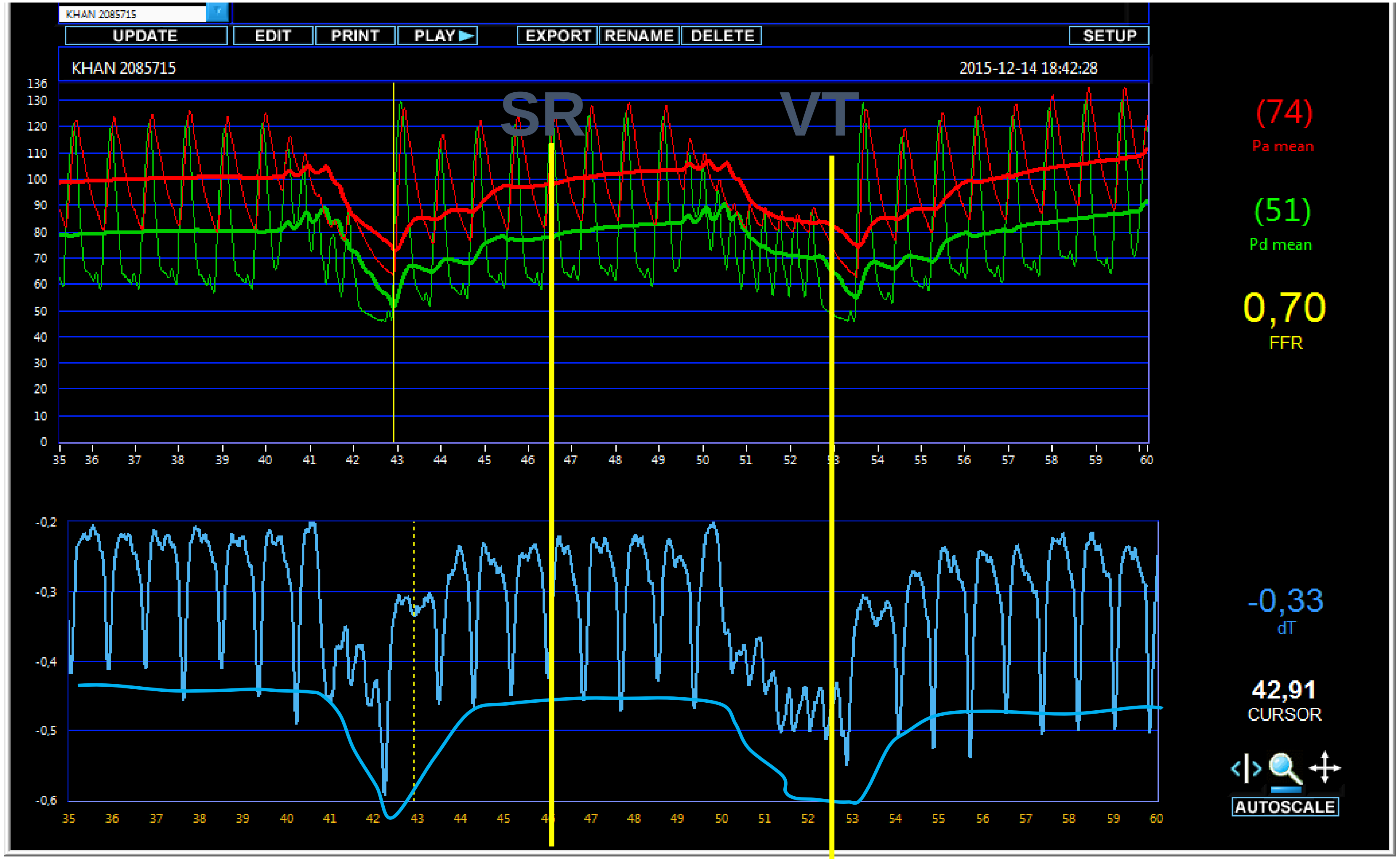
Thank you

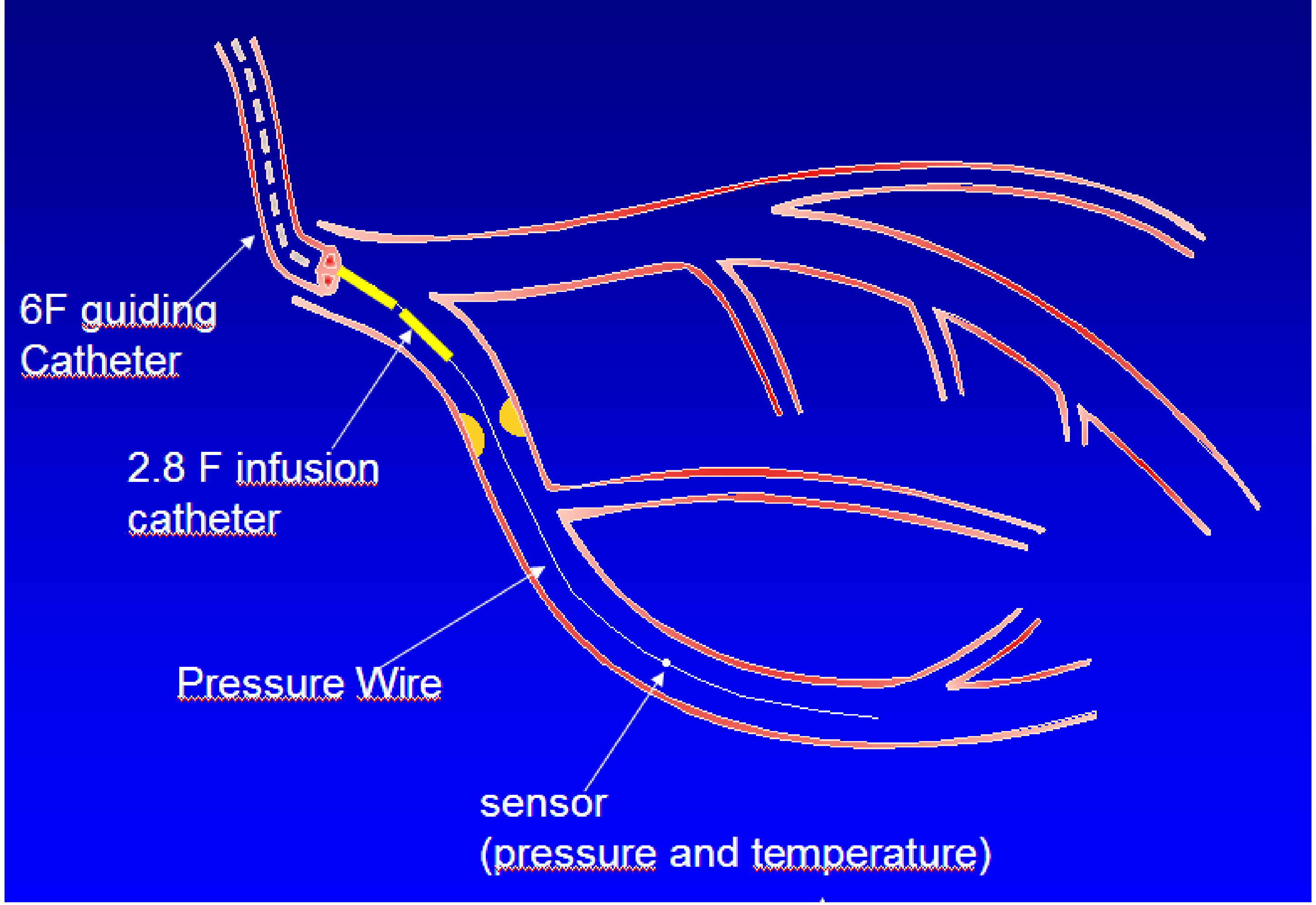


Patient with repetitive short runs of VT

During SR: Q = 280 ml/min R= 292 Wood Units

During VT: Q = 200 ml/min R= 301 Wood Units



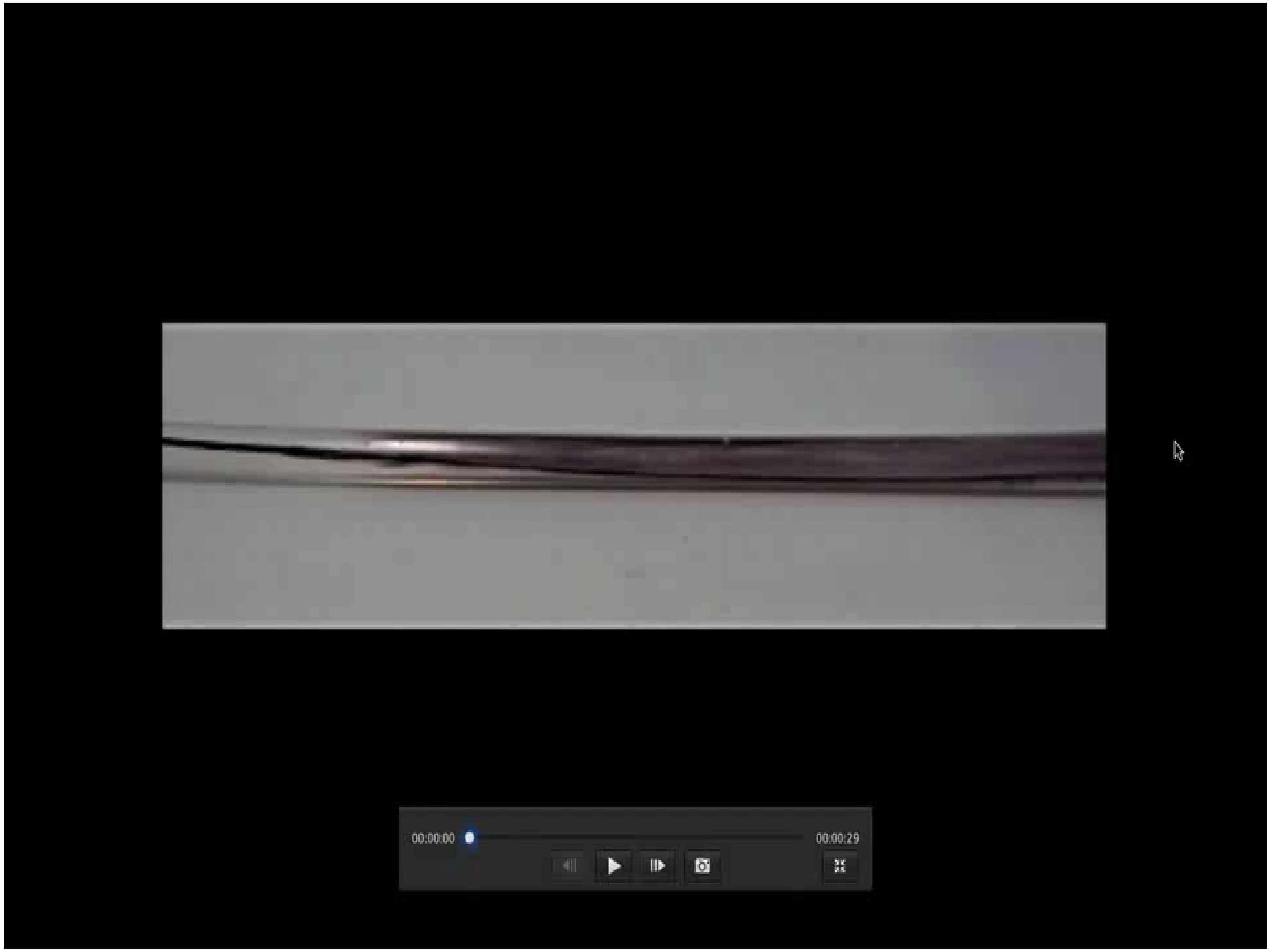


saline infused at 20 ml/min

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

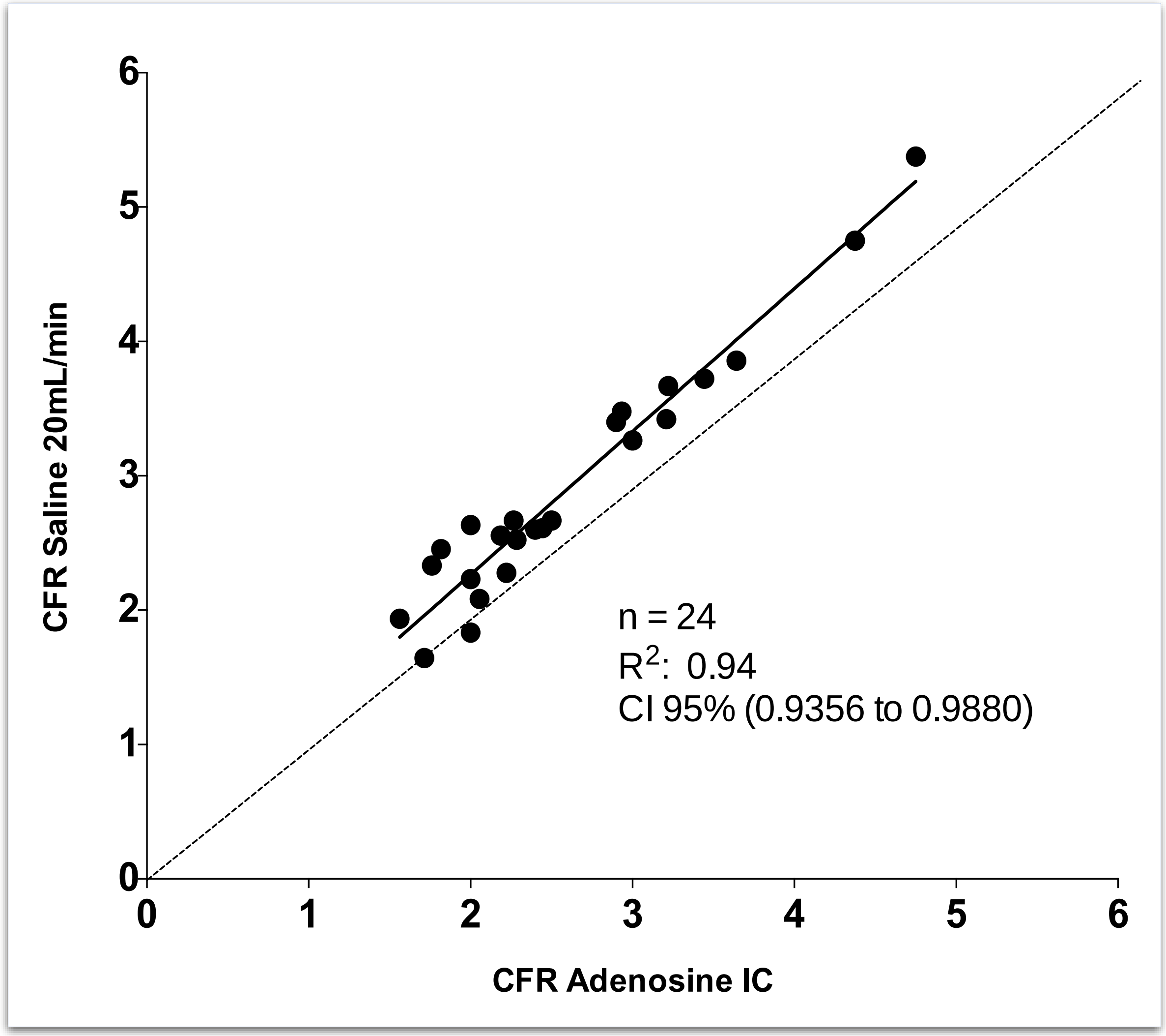


Sideholes are needed to obtain complete mixing of the indicator
Without the 4 sideholes, mixing is incomplete and unpredictable

RayFlow ® multifunctional infusion catheter

- **<u>Monorail</u> infusion catheter with double lumen** *(Hexacath, Paris)*
- **<u>Inner lumen</u> to measure the infusion temperature**
- **<u>Outer lumen</u> to infuse saline via side holes**

Hyperemic response after Saline Infusion vs Adenosine



Adjedj J et al, JACC 2016

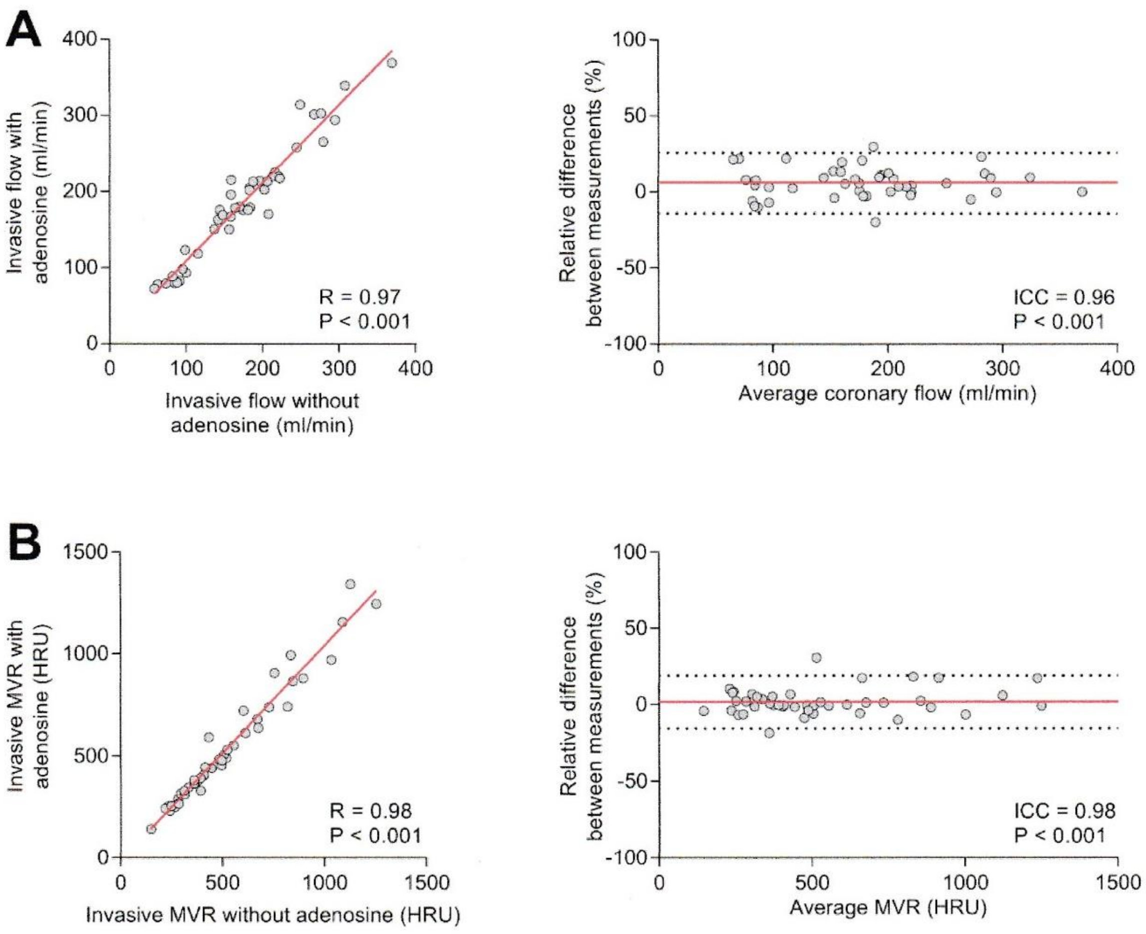
Saline infusion induces true maximum hyperemia:

Flow

(saline + adeno
Vs
Saline alone)

Resistance

(saline + adeno
Vs
Saline alone)



Scatterplots and corresponding Bland-Altman plots comparing invasive measurements of absolute hyperemic flow (**A**) and microvascular resistance (**B**) with and without adenosine. Abbreviations as in figure 3.

Everaars et al, Europ Heart J, submitted

Side Effects ?? → Safety study (N=100)

- Actually, the *only* side effects can be transient and innocent AV block with infusion of too high dose of saline in RCA

- Disappears within seconds after stopping infusion

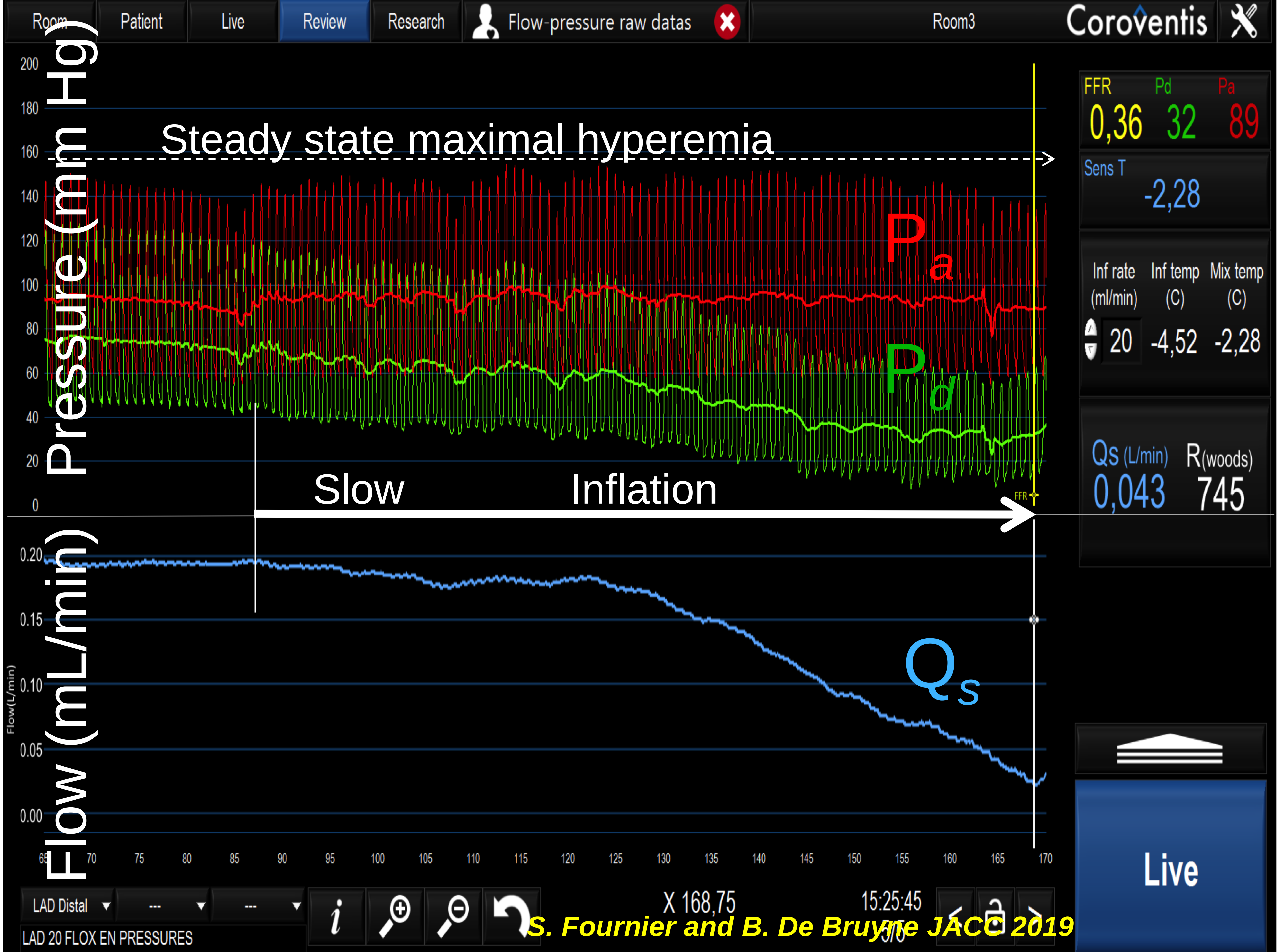
- Repeat measurement at lower infusion rate

- You can continue measurement for many minutes and repeat it within 1 minute

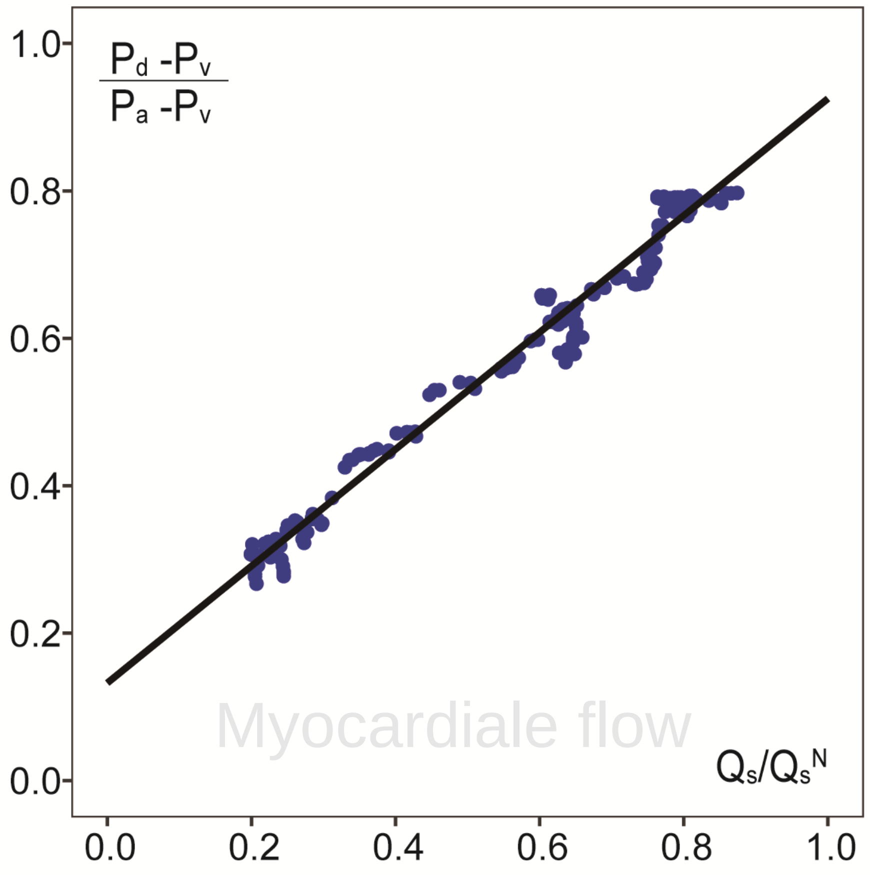
- No drugs, no touch, operator-independent, and higly reproducible

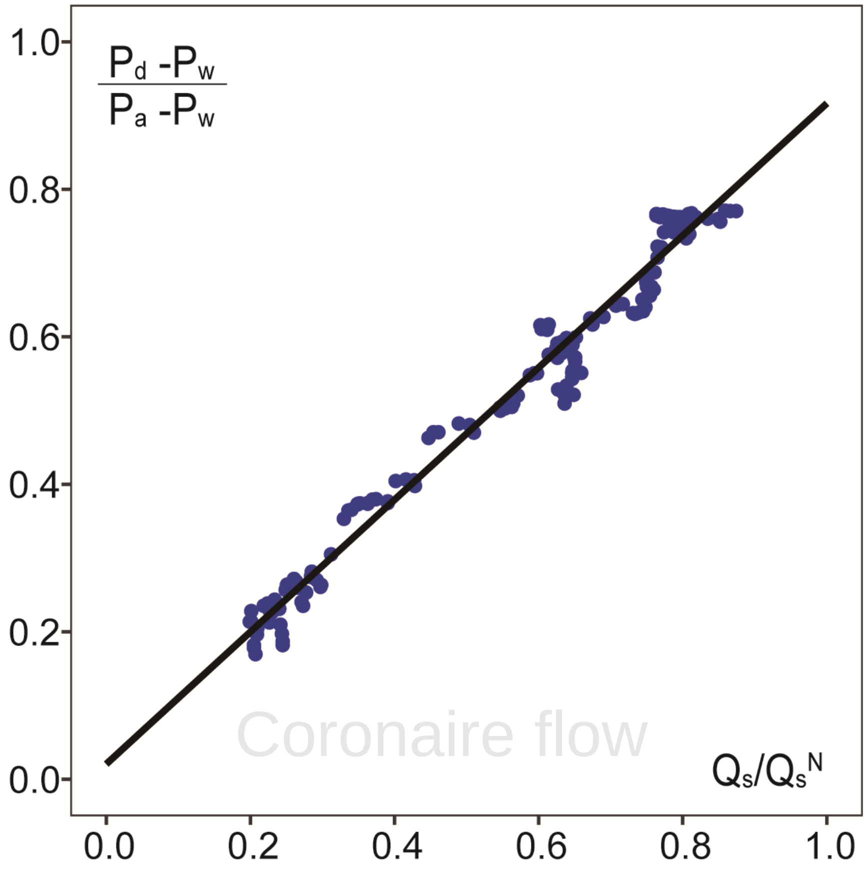

ARCHIVE
CUSTOM
D:\Mijn documenten\radi_download\RADI 211215 RayFlow1
OFF
FOLDER
RULO
Rokven FAME3P220168 RADI
REGADENOSON_081_Peters
REGADENOSON_034_Vogels
RADI 211215 RayFlow1
PILOT-CONTRASTDanielsDhr.
PATIENT ID
DATE
TIME
VESSEL
PROCEDURE
ACTION
TYPE
SIZE
211215_absoluteflow 2015-12-21 17:09:06 RCA MID dT 152Kb
211215_absoluteflow 2015-12-21 17:02:00 RCA MID dT 109Kb
211215_absoluteflow 2015-12-21 17:00:06 RCA MID dT 49Kb
211215_absoluteflow 2015-12-21 16:58:39 RCA MID dT 71Kb
211215_absoluteflow 2015-12-21 16:52:45 RCA MID CFR 42Kb
211215_absoluteflow 2015-12-21 16:49:38 RCA MID ADO IV FFR 63Kb
PRINT
EDIT
RENAME
EXPORT
ERASE
SETUP
211215_absoluteflow
RCA MID
2015-12-21 17:00:06
RADI VIEW
(43)
Pa mean
(40)
Pd mean
0,92
FFR
-0,64
dT
29,99
CURSOR
RESET

21122015


Room
Patient
Live
Review
Research
Flow-pressure raw datas
Room3
Coroventis
Steady state maximal hyperemia
Pressure (mm Hg)
Pa
Pd
Slow
Inflation
Flow (mL/min)
Qs
FFR Pd Pa
0,36 32 89
Sens T
-2,28
Inf rate (ml/min)
Inf temp (C)
Mix temp (C)
20 -4,52 -2,28
Qs (L/min) R(woods)
0,043 745
Live
LAD Distal
LAD 20 FLOX EN PRESSURES
X 168,75
15:25:45
S. Fournier and B. De Bruyne JACC 2019

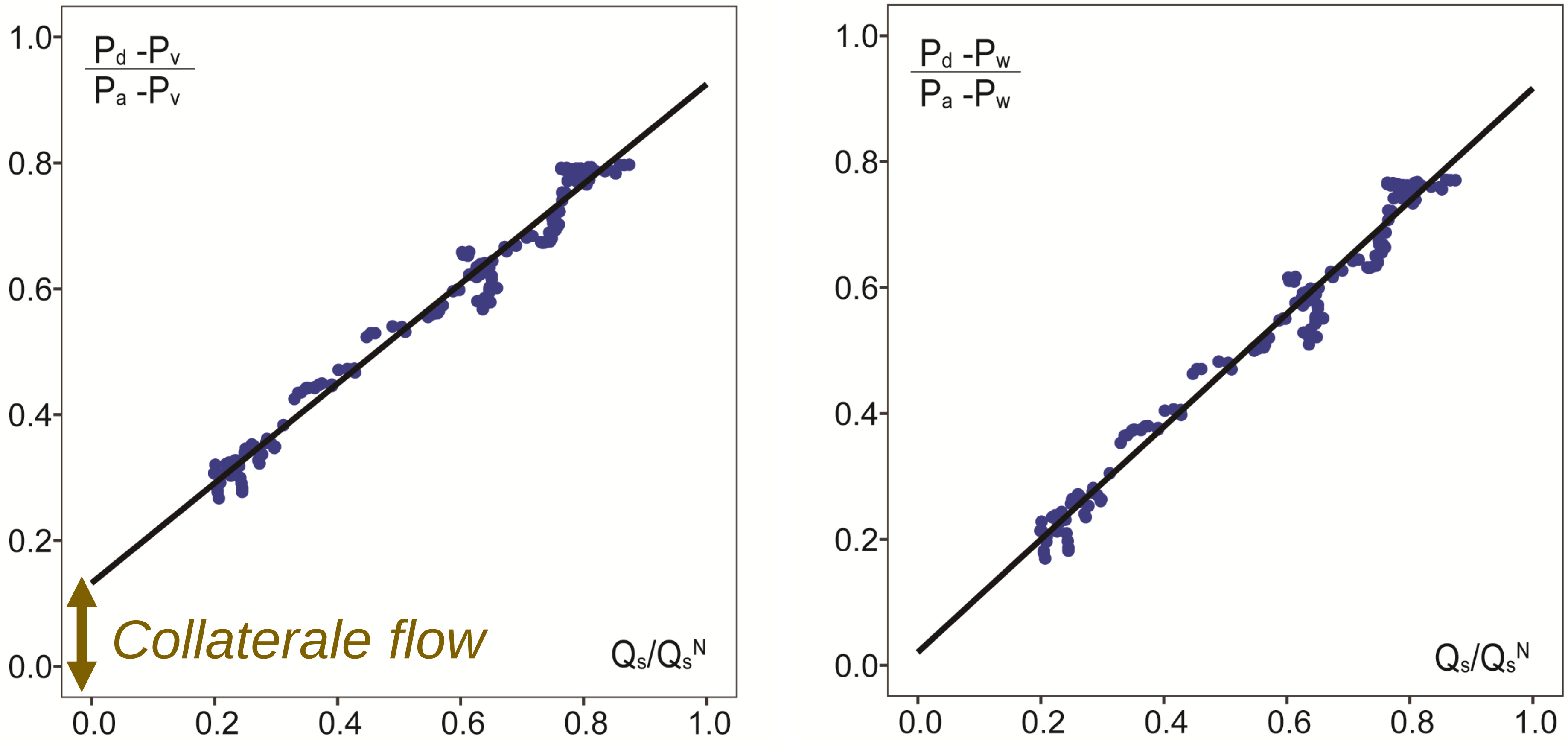
Pressure-Flow Relationship in Humans





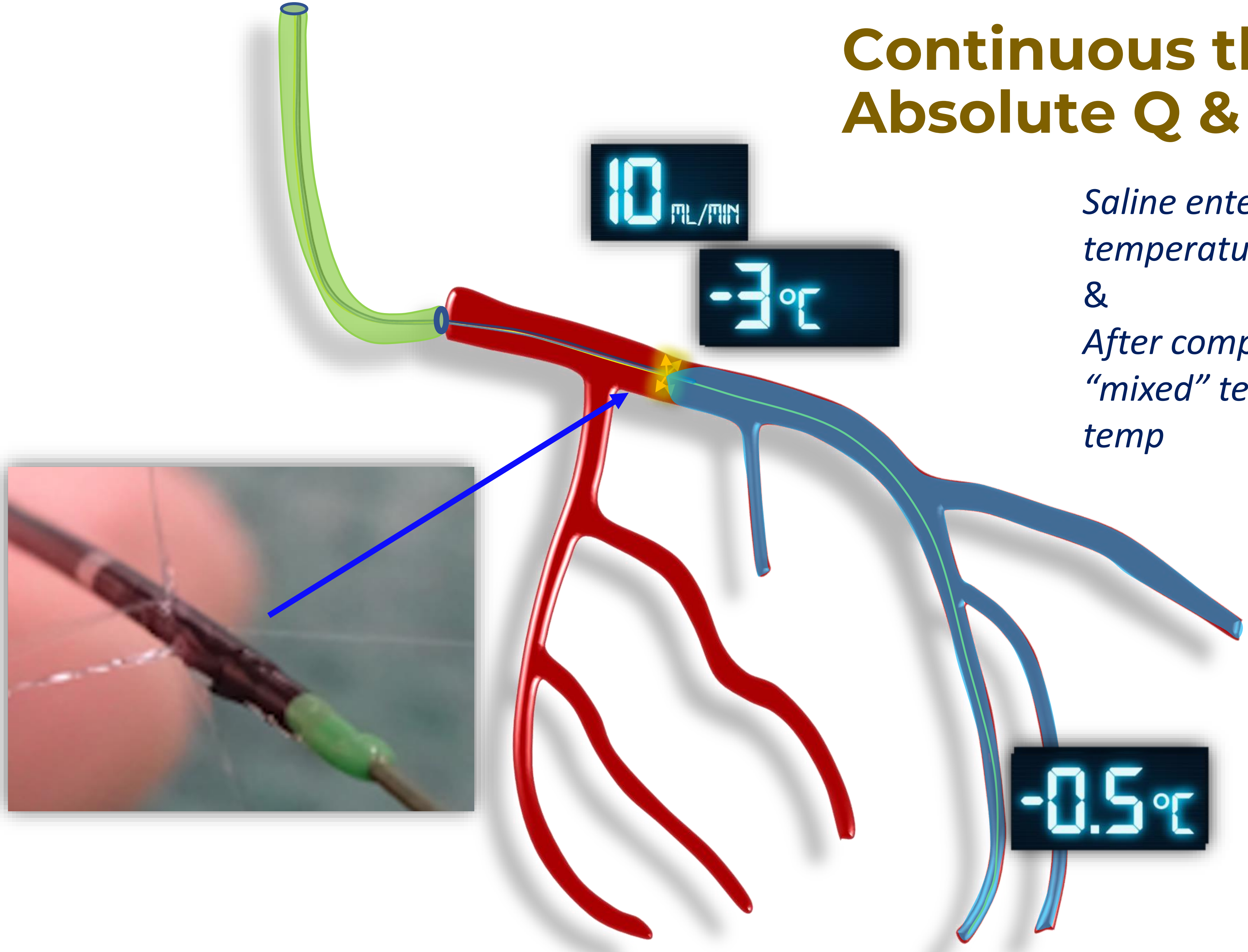
S. Fournier and B. De Bruyne JACC JACC 2019

Pressure-Flow Relationship at hyperemia in Humans



S. Fournier and B. De Bruyne JACC JACC 2019

Continuous thermodilution for Absolute Q & R measurements



Saline enters the proximal coronary artery at a temperature of 3°C below blood temperature

&

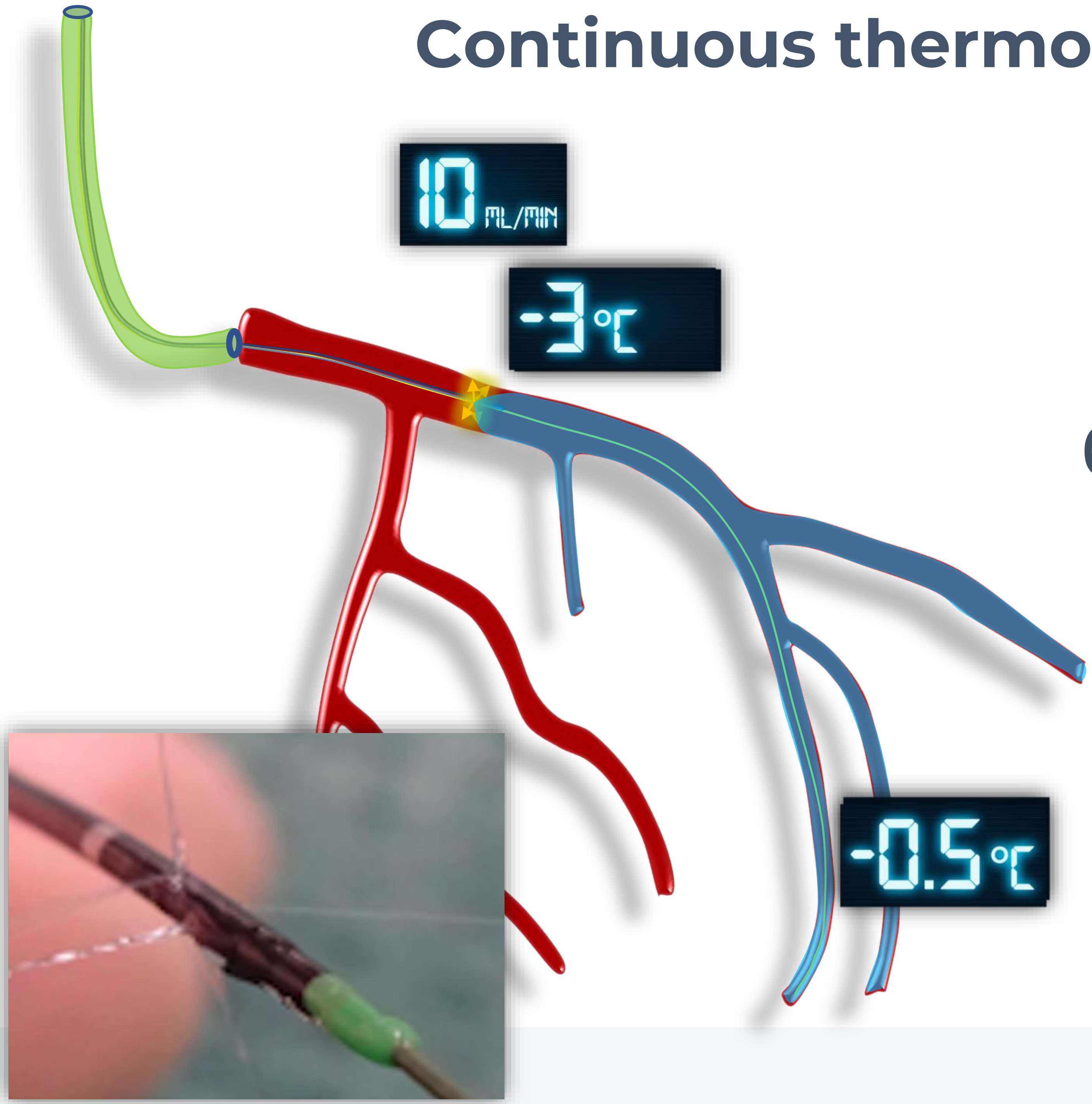
After complete mixing of blood and saline, the "mixed" temperature equals 0.5 °C below blood temp

↓

Blood flow must be 6 x infusion flow of saline

60 ml/min

Continuous thermodilution for absolute Q & R measurements



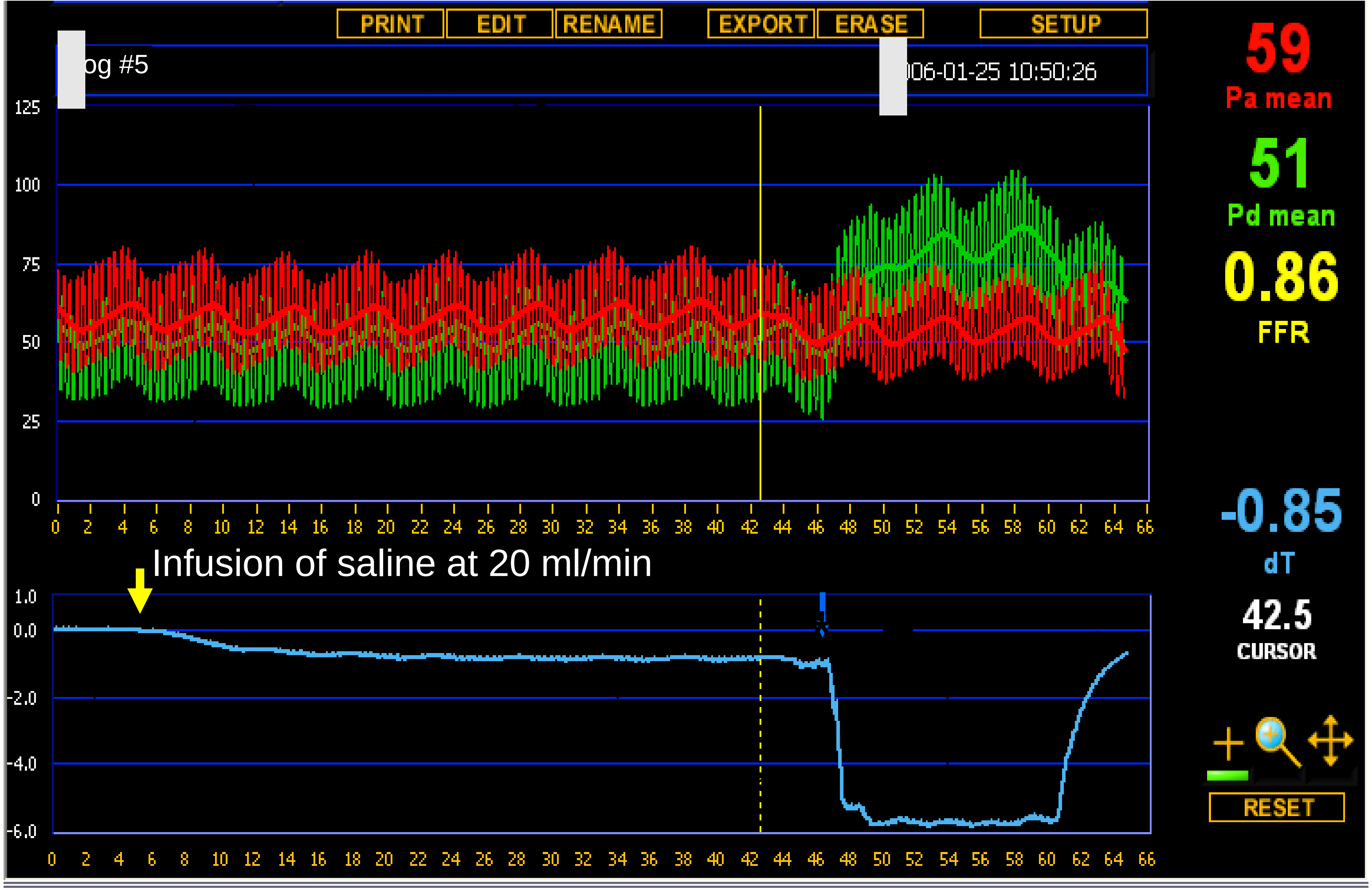
$$Q = Q_{saline} \times \frac{T_{saline}}{T_{mixture}} \times 1.08$$

Q = 65 mL/min

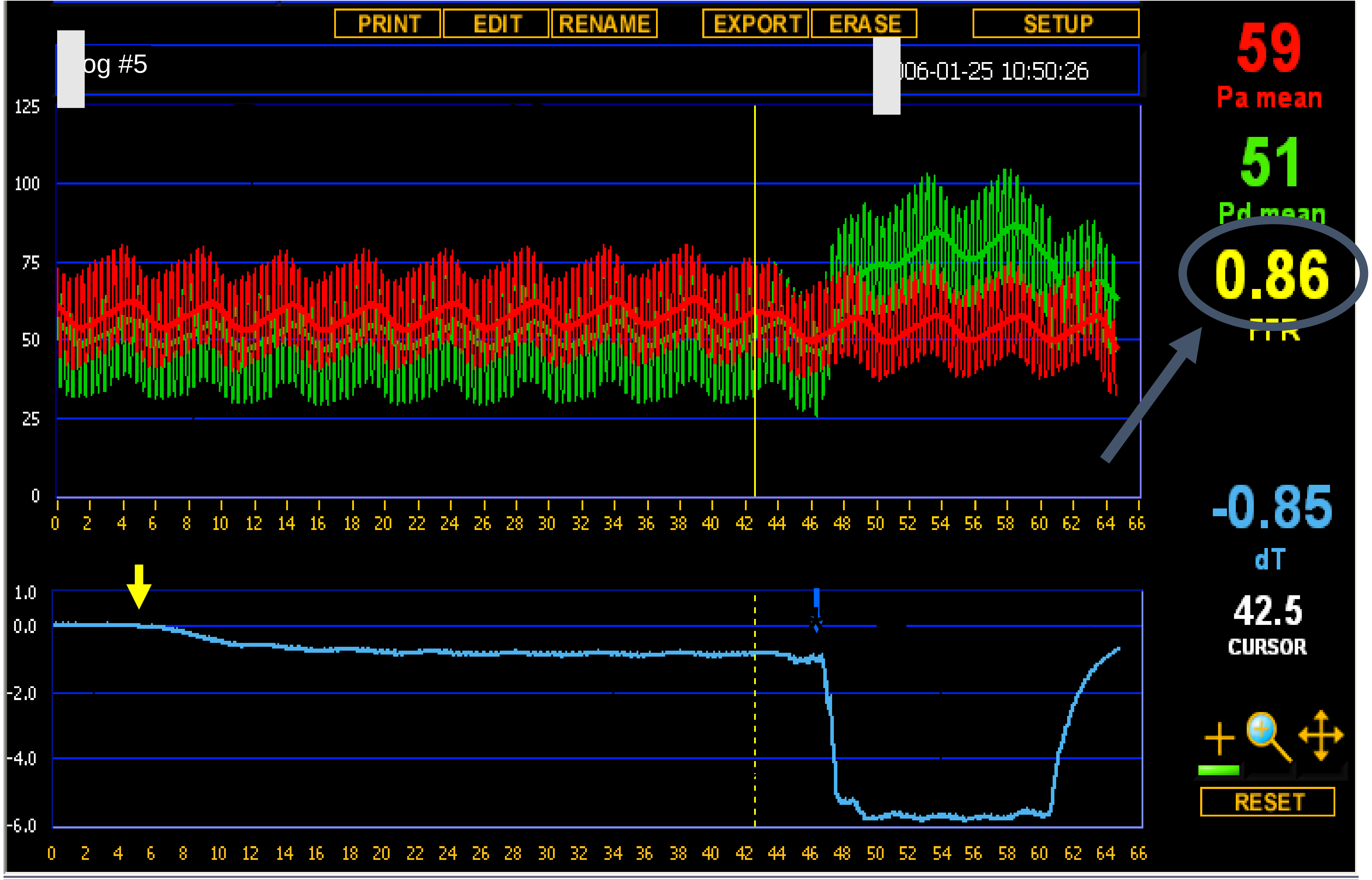
Q_{saline} is known infusion rate of saline (mL/min)

T_{saline} , T_{mix} are the **difference** vs body temperature (°C)

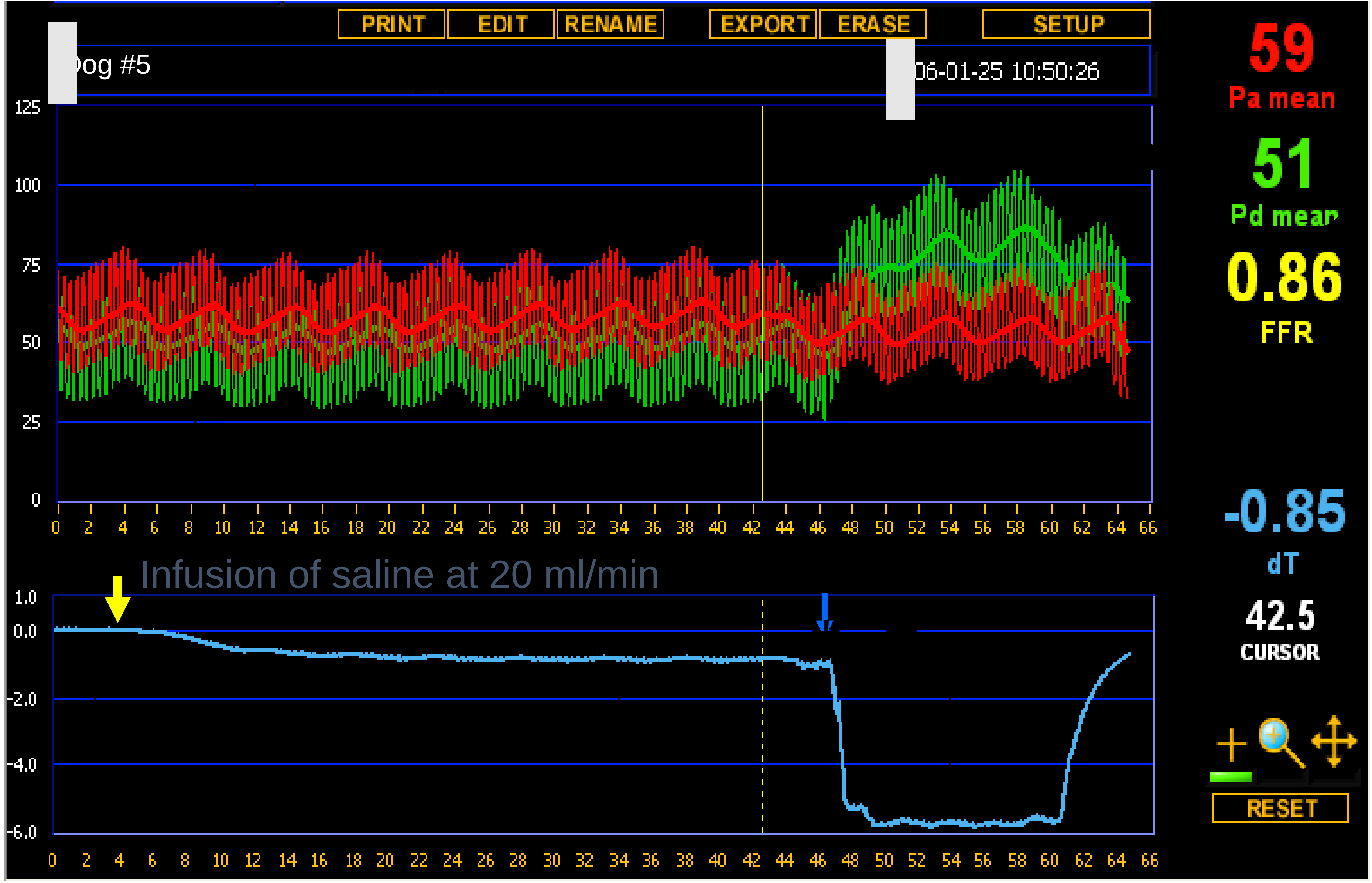
1.08 accounts for **specific heats** of saline and blood



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

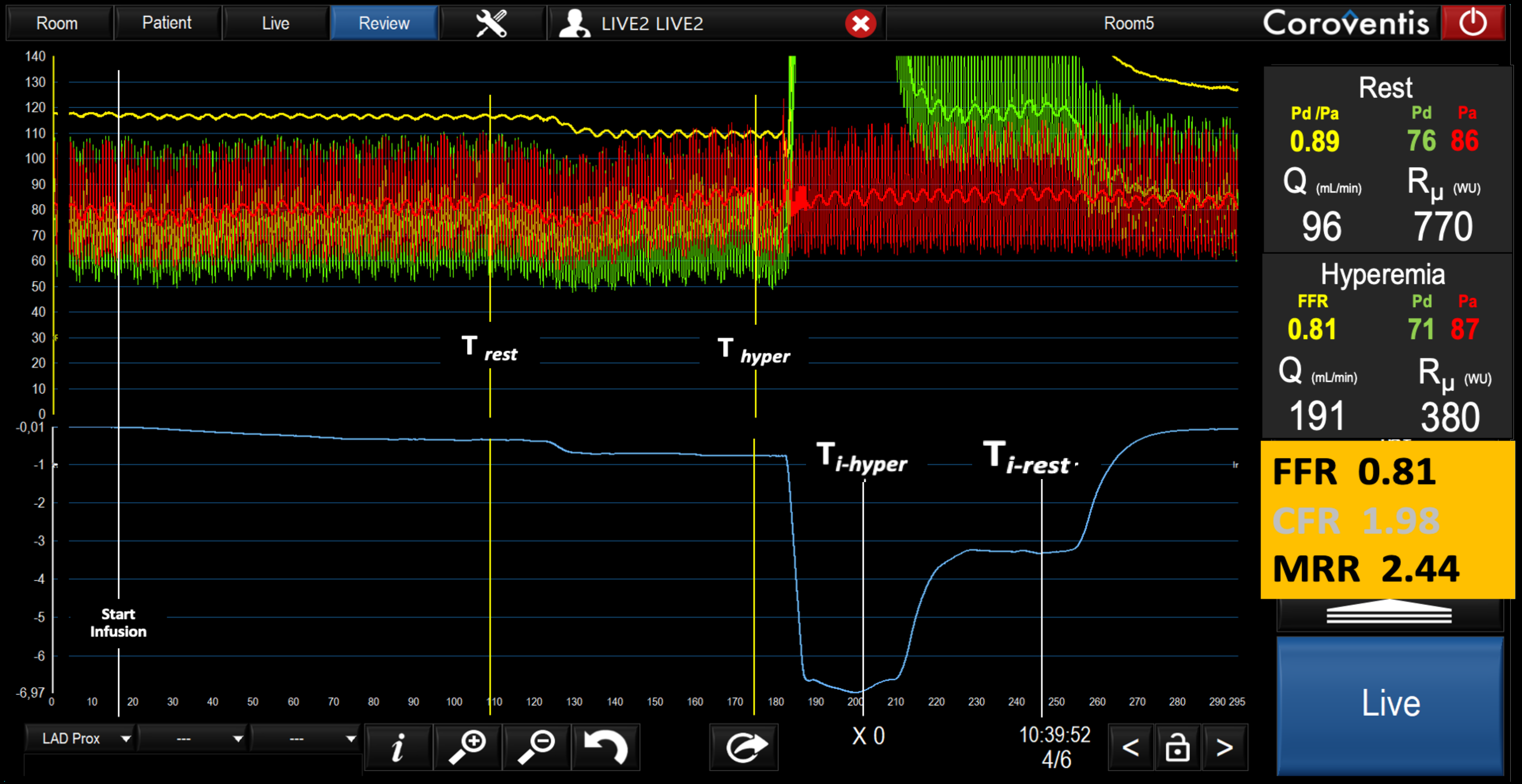


Q***b*** = 134 ml/min ⟶ normal max flow = 100/86 x 134 = 156 ml/min



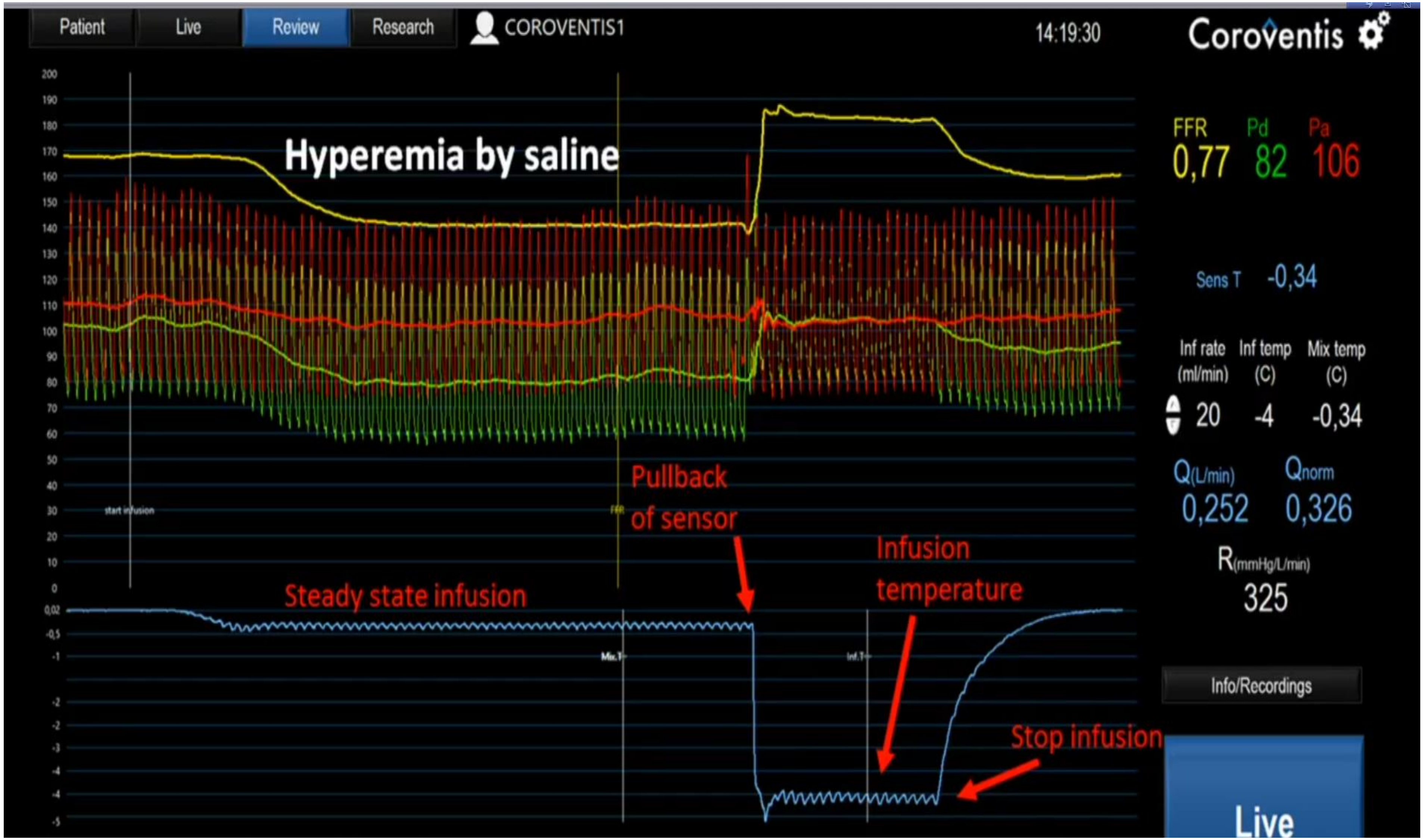
Q = 20 x (-5.27 **/** -0.85) x 1.08 = 134 ml/min

Absolute microvascular resistance = P_d / Q** (x80.000) **= 380 Wood Units



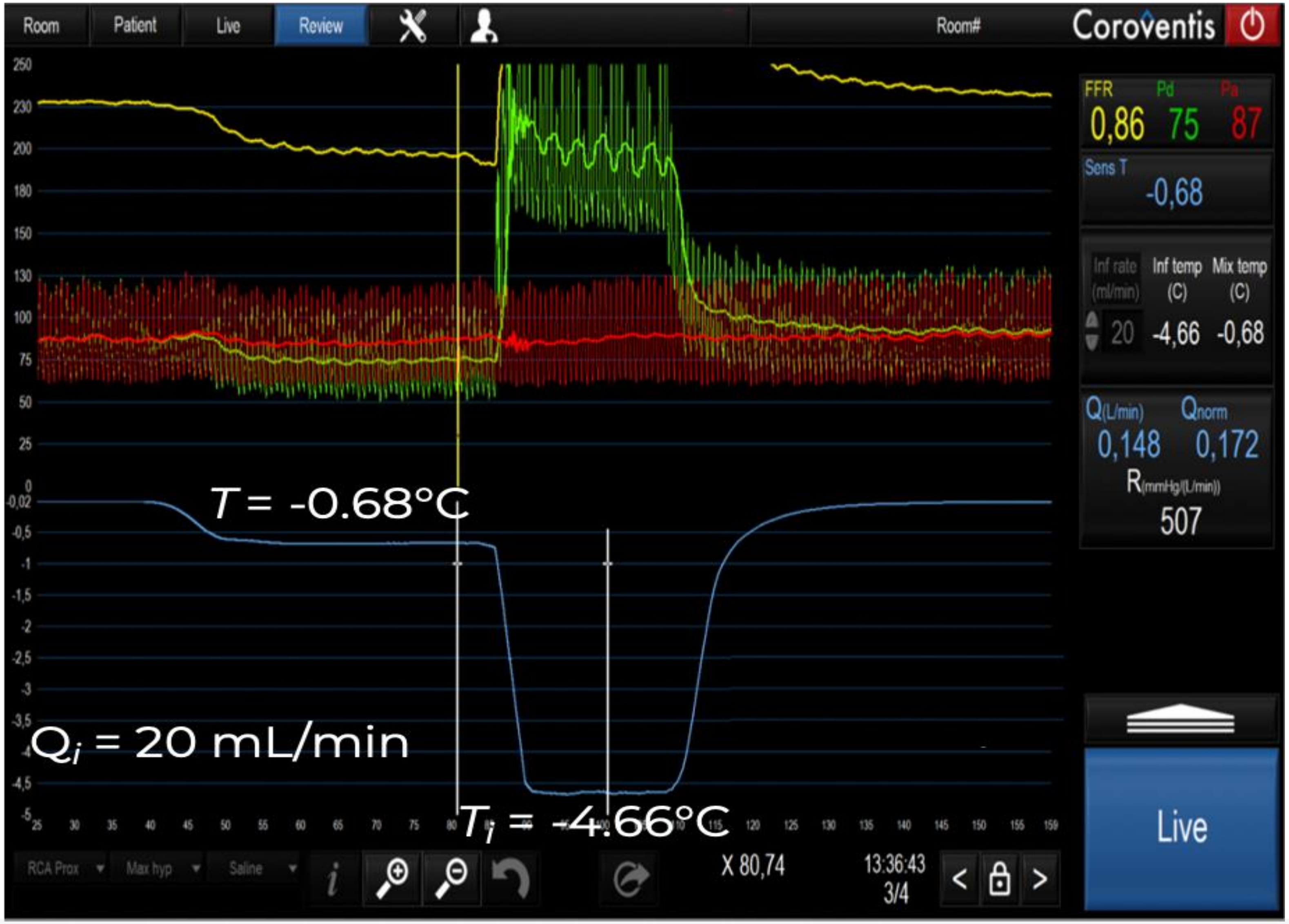
De Bruyne, Pijls, Collet, Fearon et al J Am Coll Cardiol 2021;78:1541–1549

CoreAalst | OPTIMA



Coroventis radio-receiver system (fully integrated in cath lab)

Continuous thermodilution for absolute Q & R measurements



$$Q = Q_{saline} \times \frac{T_{saline}}{T_{mixture}} \times 1.08$$

(mL/min)

$$Q = 20 \times \frac{-4{,}66}{-0{,}68} \times 1.08 = 148 \text{ mL/min}$$

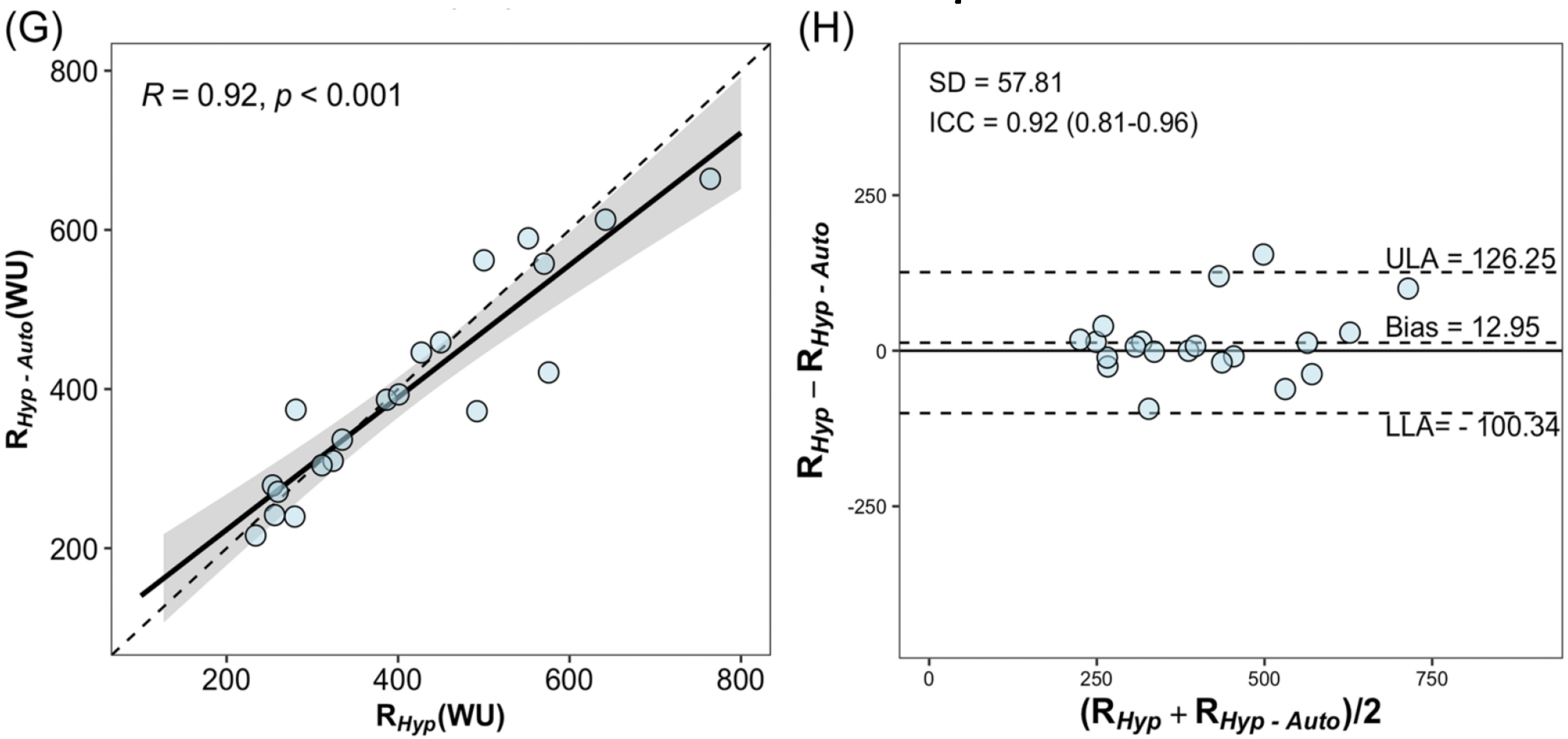
$$R = \frac{P_d}{Q}$$

(Wood Units)

R = 75 / 0.148 = 510 WU

Aarnoudse W, Pijls NHJ, De Bruyne B, van 't Veer M et al JACC 2007 50;2294-2304

Reproducibility: manual vs automatic R_{μ}



Candreva A, De Bruyne B et al. Catheter Cardiovasc Interv. 2022;100:199–2