MICROVASCULAR RESISTANCE RESERVE

Basics of The Principle of MRR

Madrid Microcirculation Meeting 4th Edition
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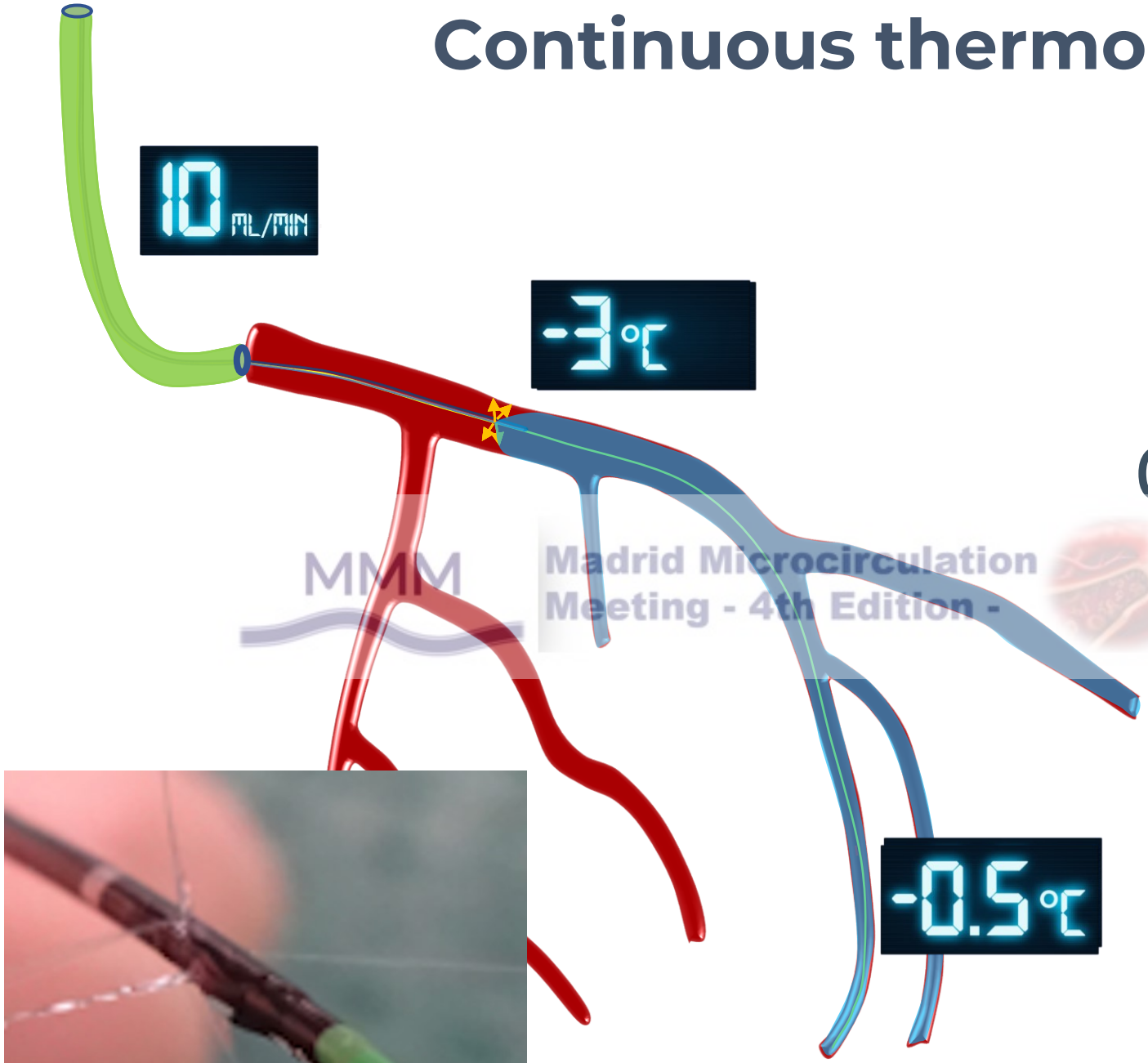
Absolute measurement of microvascular resistance

In conjunction with FFR, all flow and resistance measurements can be performed within a few minutes:

- position the pressure/temp wire in the coronary artery
- advance the RayFlow® monorail multi-side holes infusion catheter (ultrathin profile)
- connect infusion catheter to saline pump and perform measurements *(resting and hyperemia)*

(Either 2 separate runs, or 'one run': 10 ml/min → 20 ml/min → 10 ml/min)

Continuous thermodilution for absolute Q & R measurements

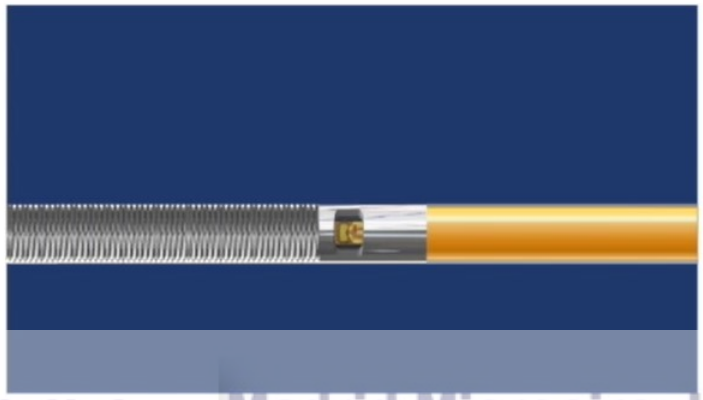


$$Q = Q_{saline} \times \frac{T_{saline}}{T_{mixture}} \times 1.08$$

Q = 65 mL/min

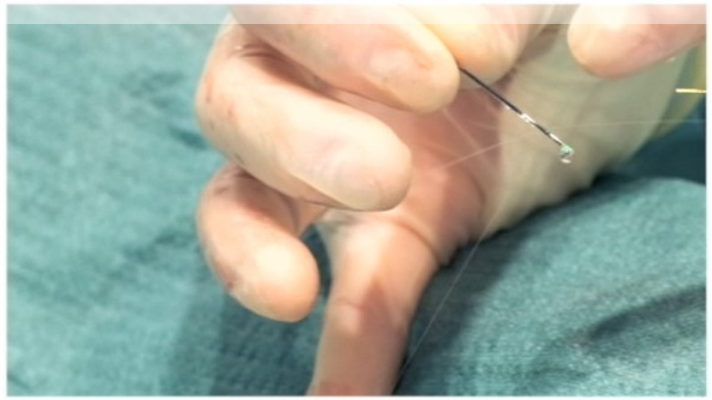
Q_{saline} is known infusion rate of saline (mL/min)
T_{saline} , T_{mix} are the **difference** vs body temperature (°C)
1.08 accounts for **specific heats** of saline and blood

Equipment to perform Continuous Thermodilution



PRESSURE/TEMPERATURE WIRE (Abbott)

COROVENTIS

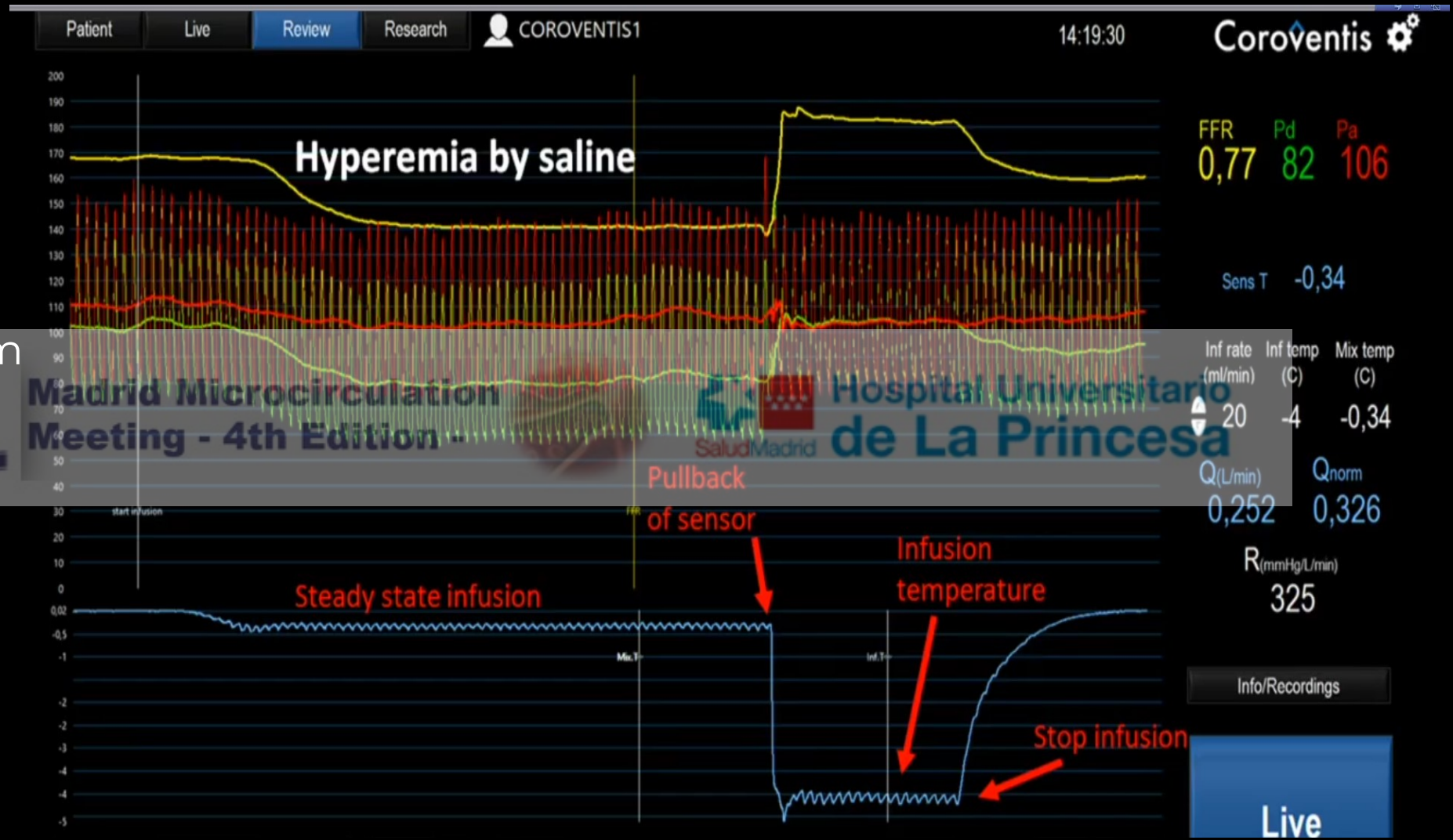


RAYFLOW Catheter (Hexacath)

INFUSION PUMP (POWER INJECTOR)

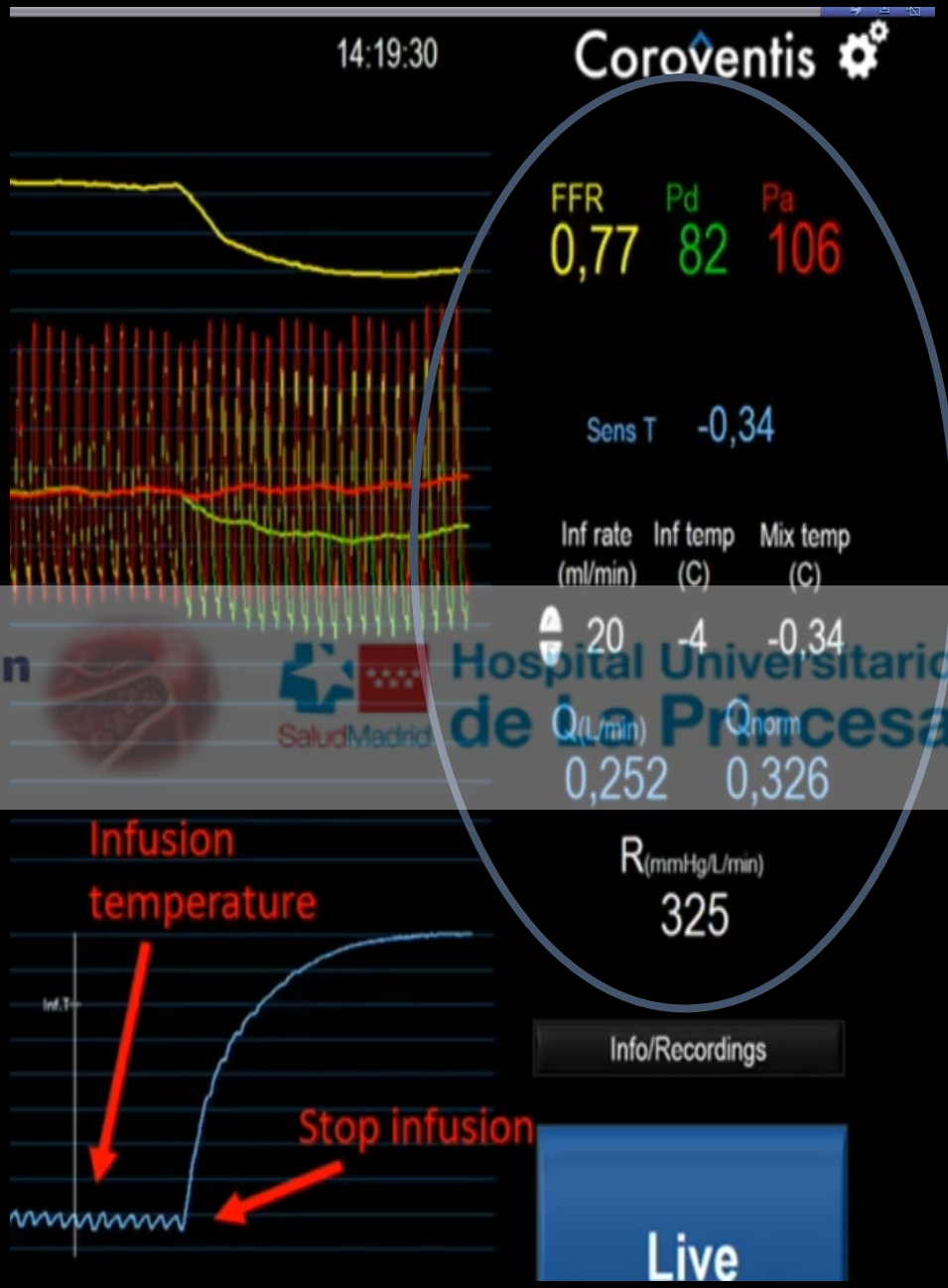
Example of one hyperemic run (20ml/min)

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



CATHARINA-ZIEKENHUIS

All relevant parameters for epicardial artery and microcirculation are obtained within 5 minutes and clearly displayed in one nice simple screen, together with the normal values.



……but we can even go
one step beyond !

MICROVASCULAR RESISTANCE RESERVE (MRR)

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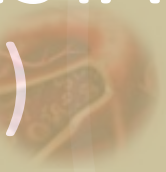

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CoreAalst | OPTIMA

If you have at your disposal:

- Resting and hyperemic (=**maximum**) blood flow:

  Q_{rest} and Q_{max}

- Resting and hyperemic (=**minimum**) resistance of the respective microvascular bed:

  $R_{\mu,rest}$ and $R_{\mu,hyp}$

- and simultaneously measured resting and hyperemic proximal and distal intracoronary pressures:

  $P_{a,rest}$ and $P_{d,hyp}$

→ **Microvascular Resistance Reserve (MRR)**

Important note!

It is evident that we are looking for something as “resting microvascular resistance / hyperemic microvasc resistance”

But what does ‘resting microvascular resistance’ mean??

If you wish to define a completely **specific** index of microvascular resistance reserve, you should realize that this does **NOT** equal **actually measured** resting microvascular resistance divided by hyperemic microvascular resistance…

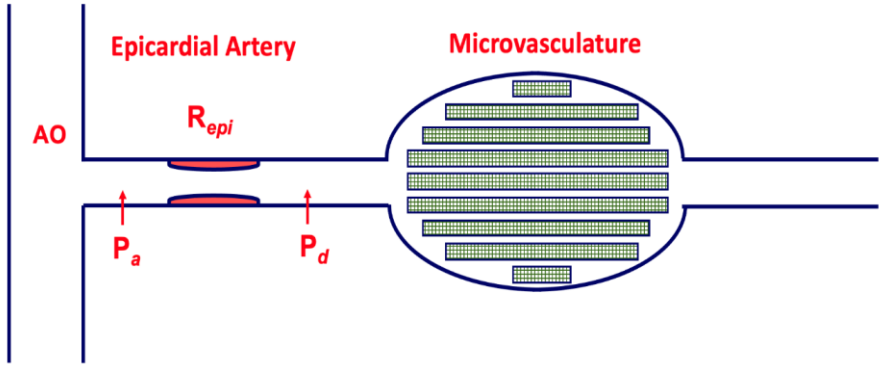
…because actually measured resting resistance is influenced by the presence of epicardial disease!

(It is a kind of compensated resting state, due to partially-consumed autoregulation).

So to calculate MRR, we need to know **true** $R_{\mu,rest}$ as not affected by epicardial disease) and $R_{\mu,hyper}$

De Bruyne, Pijls, Fearon, et al; JACC 2021; 78: 1541-1549

How to calculate (true) R_{μ}, rest? (not evident!)



In case of a completely normal epicardial conduit, $P_a = P_d$ **and:** $R_{\mu, rest, N} = P_a / Q_{rest, N}$

In the presence of epicardial disease (represented by R_{epi} in the figure above which might be focal or diffuse) $R_{\mu,rest}$ shows some compensatory decrease (autoregulation) and is given by:

(actual) $R_{\mu, rest, sten} = P_d / Q_{rest, sten} < R_{\mu, rest, N}$

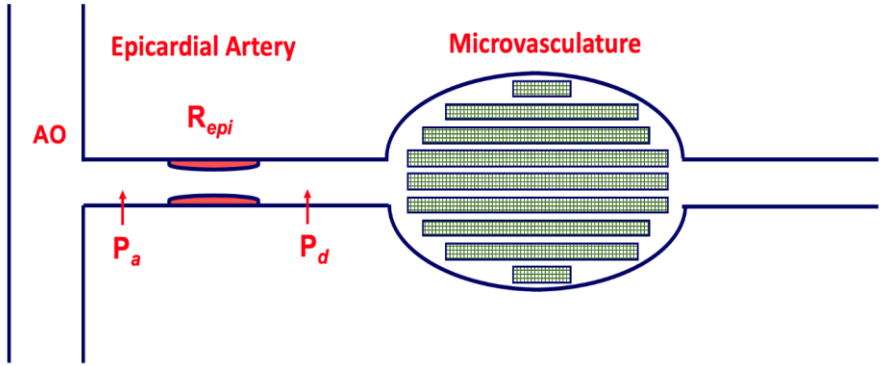
As such, $R_{\mu, rest, sten}$ can be re-written as: $R_{\mu, rest, sten} = R_{\mu, rest, N} - R_{epi}$

or: (true) $R_{\mu, rest, N} = R_{\mu, rest, sten} + R_{epi}$

$= P_d / Q_{rest, sten} + (P_a - P_d) / Q_{rest, sten} = P_a / Q_{rest, sten}$

Because $Q_{rest, sten} = Q_{rest, N}$, this can be re-written as **(true)** $R_{\mu, rest} = P_{a, rest} / Q_{rest}$ **Equation 1**

How to calculate $R_{\mu\ hyper}$ (evident!)



The presence of epicardial disease does not influence hyperemic (minimal) microvascular resistance.

Therefore (whether this is epicardial disease or not):

$$R_{\mu,\ hyper} = P_{d,\ hyper} / Q_{max}$$

Equation 2

We define: **MRR = (true)** $R_{\mu,\ rest} / R_{\mu,hyper}$

or (by substation of equations 1 and 2:

$$MRR = Q_{max} / Q_{rest} \times P_{a,rest} / P_{d,hyper}$$

Equation 3

Microvascular Resistance Reserve (MMR)

NOT simply ratio of actually measured resting resistance and hyperemic resistance

('actually measured' would introduces confounding, like in CFR, RRR, etc)

BUT MRR is defined as:

"Ratio of **true resting** microvascular resistance ($R_{\mu,rest}$) *as it would be in the hypothetical case that the epicardial artery would be completely normal,* and hyperemic microvascular resistance ($R_{\mu,hyp}$)"

$$MRR = Q_{max} / Q_{rest} \times P_{a,rest} / P_{d,hyp}$$

De Bruyne, Pijls, Fearon, et al; JACC 2021; 78: 1541-1549

For the coronary microcirculation,
MRR is in fact the **corollary** of what **FFR** means for the epicardial artery

How to understand *intuitively* the core of MRR ?

$MRR = Q_{max} / Q_{rest} \times P_{a,rest} / P_{d,hyp}$ **(Equation 3)***

Written slightly differently, the beauty of this index is revealed:

$MRR = Q_{max} / Q_{rest} \times P_{a,rest} / P_{a,hyp} \times P_{a,hyp} / P_{d,hyp}$

“traditional” CFR as you know it, but calculated with high accuracy

compensation for changes in blood pressure

compensation for presence of epicardial disease

or: **$MRR = CFR / FFR \times P_{a,rest} / P_{a,hyp}$** **(Equation 4)***

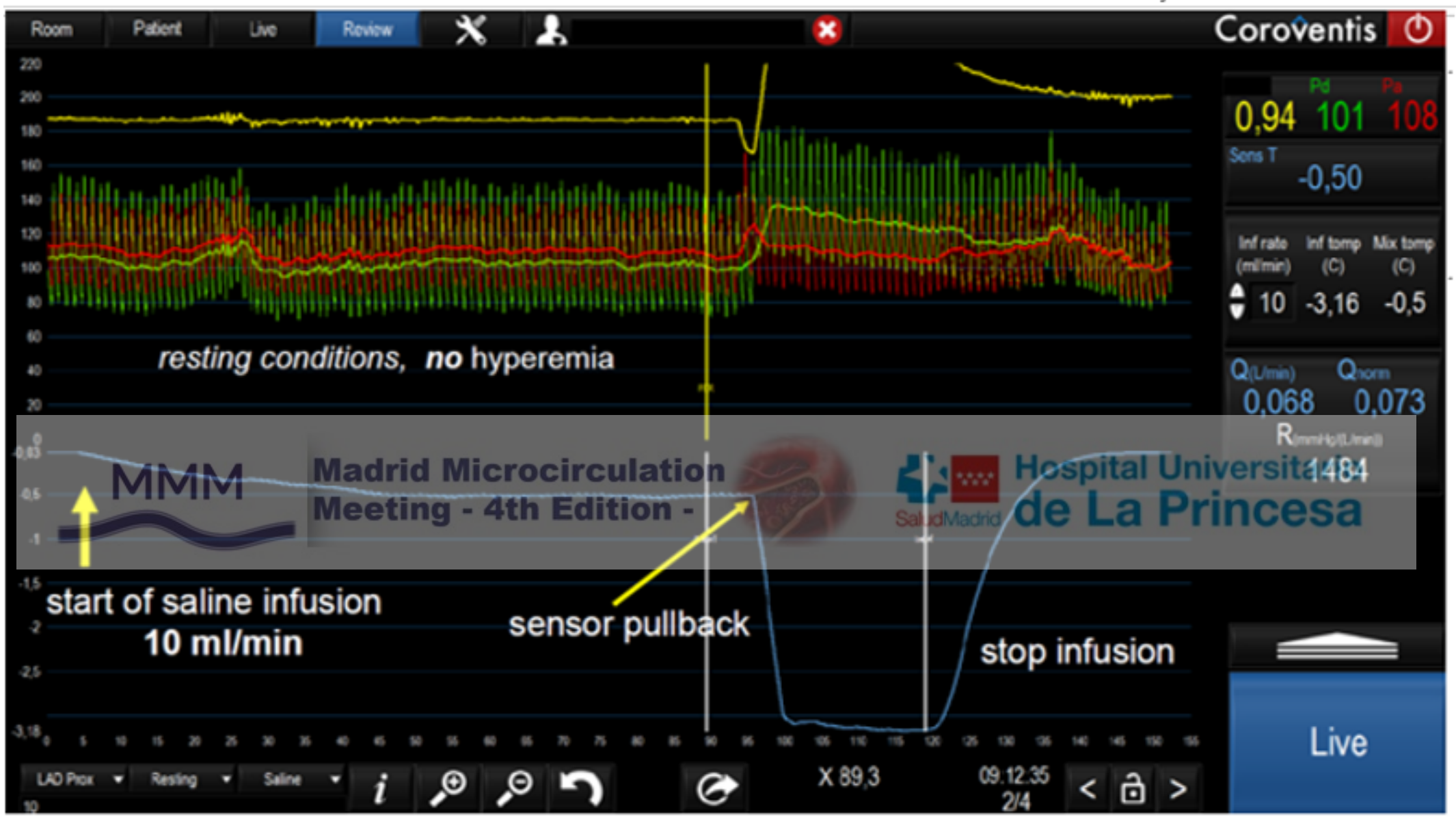
* De Bruyne, Pijls, Fearon, et al; JACC 2021; 78: 1541-1549

$$MRR = Q_{max} / Q_{rest} \times P_{a,rest} / P_{d,hyp}$$

MRR is the **universally valid index** to characterize the coronary microcirculation . **MRR is**:

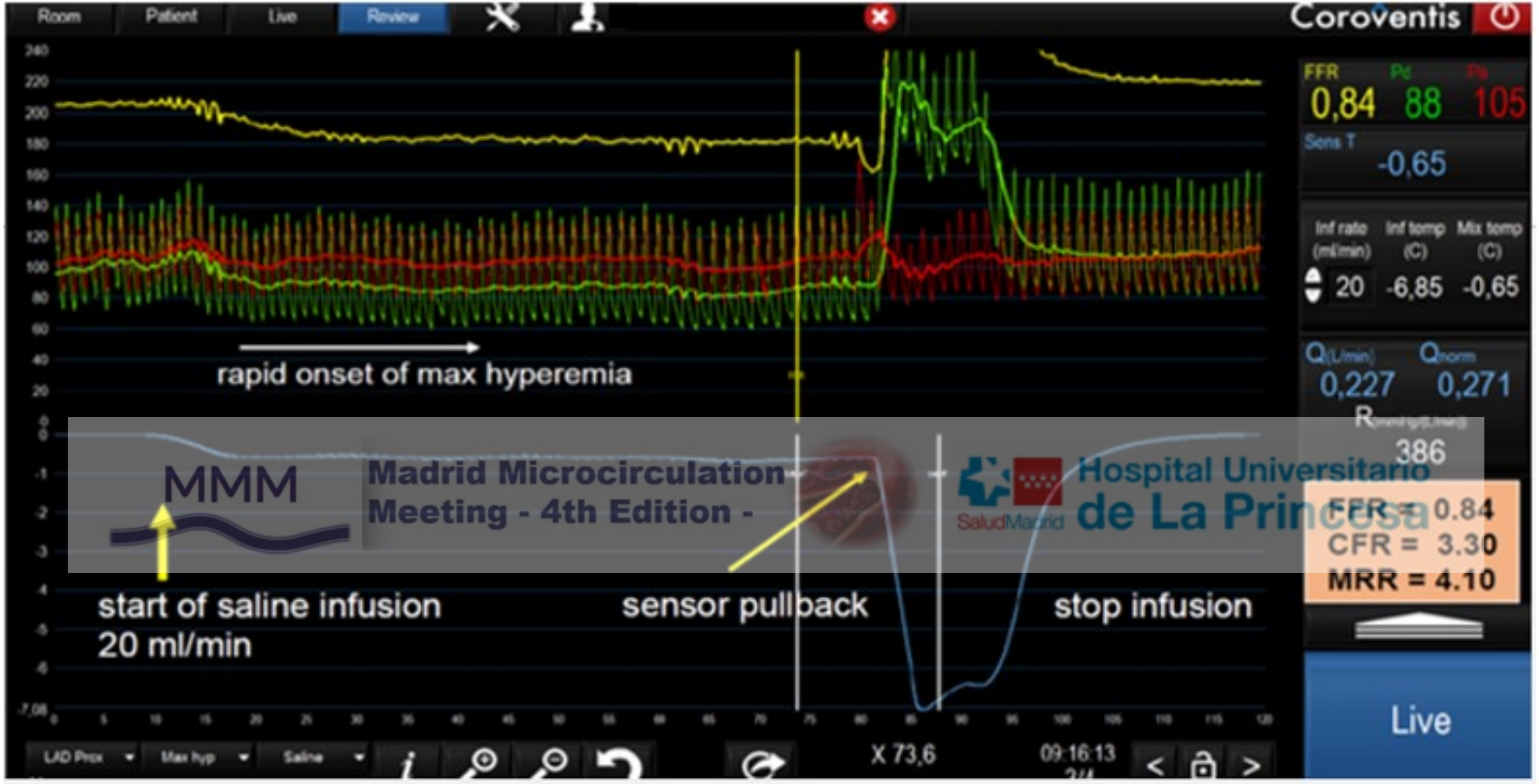
- 100% specific for the microcirculation
- independent of changes in blood pressure
- independent of myocardial mass
- Accurate,quantitative and reproducible *(if measured at least by a reliable method for flow measurement, like continuous thermodilution or PET),*
- time-effective: it can be obtained within few minutes following regular FFR measurement (with the Abbott PW)
- no need for additional adenosine
- completely ***operator-independent***

De Bruyne, Pijls, Fearon, et al; JACC 2021; 78: 1541-1549



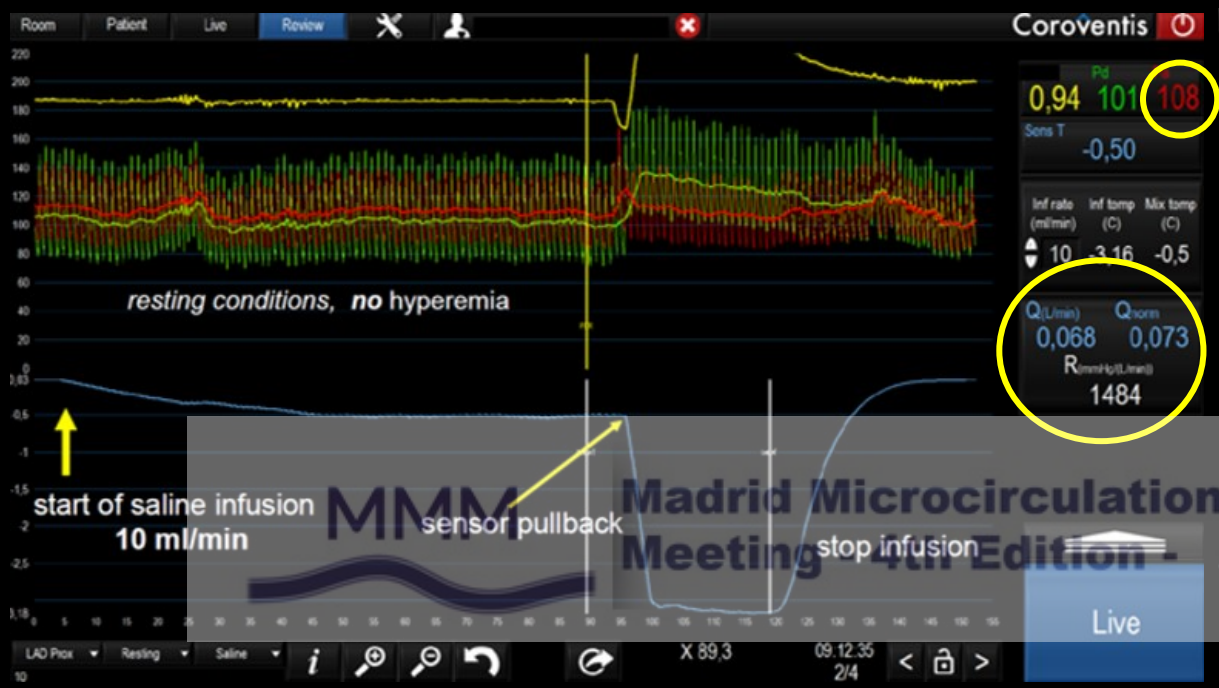
Resting flow (Q_{rest}) in LAD artery / anterior wall: 68 ml/min

Resting microvascular resistance ($R_{\mu,rest}$) in anterior wall myocardium: 1484 WU

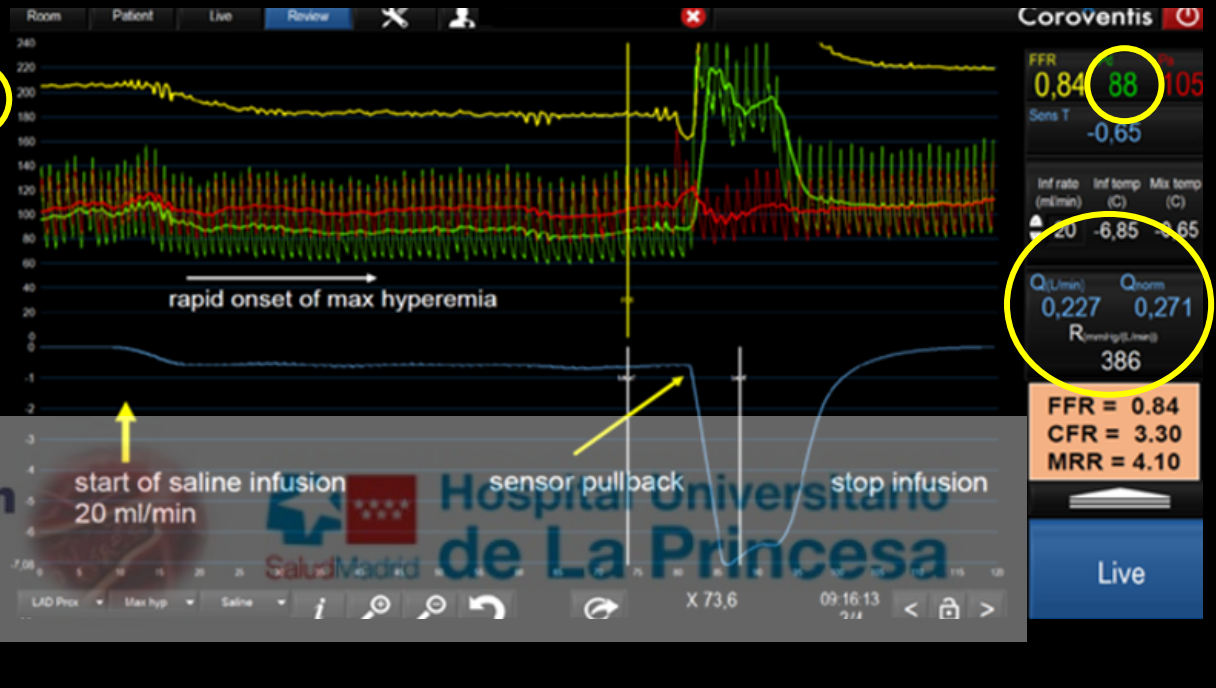


maximum flow (Q_{max}) in LAD artery / anterior wall: 227 ml/min

Minimum microvascular resistance ($R_{\mu,hyper}$) in anterior wall myocardium: 386 WU



Resting flow measurement
(10 ml/min saline infusion)



hyperemic flow measurement
(20 ml/min saline infusion)

FFR = 0.84

Absolute CFR = 227/68 = 3.30

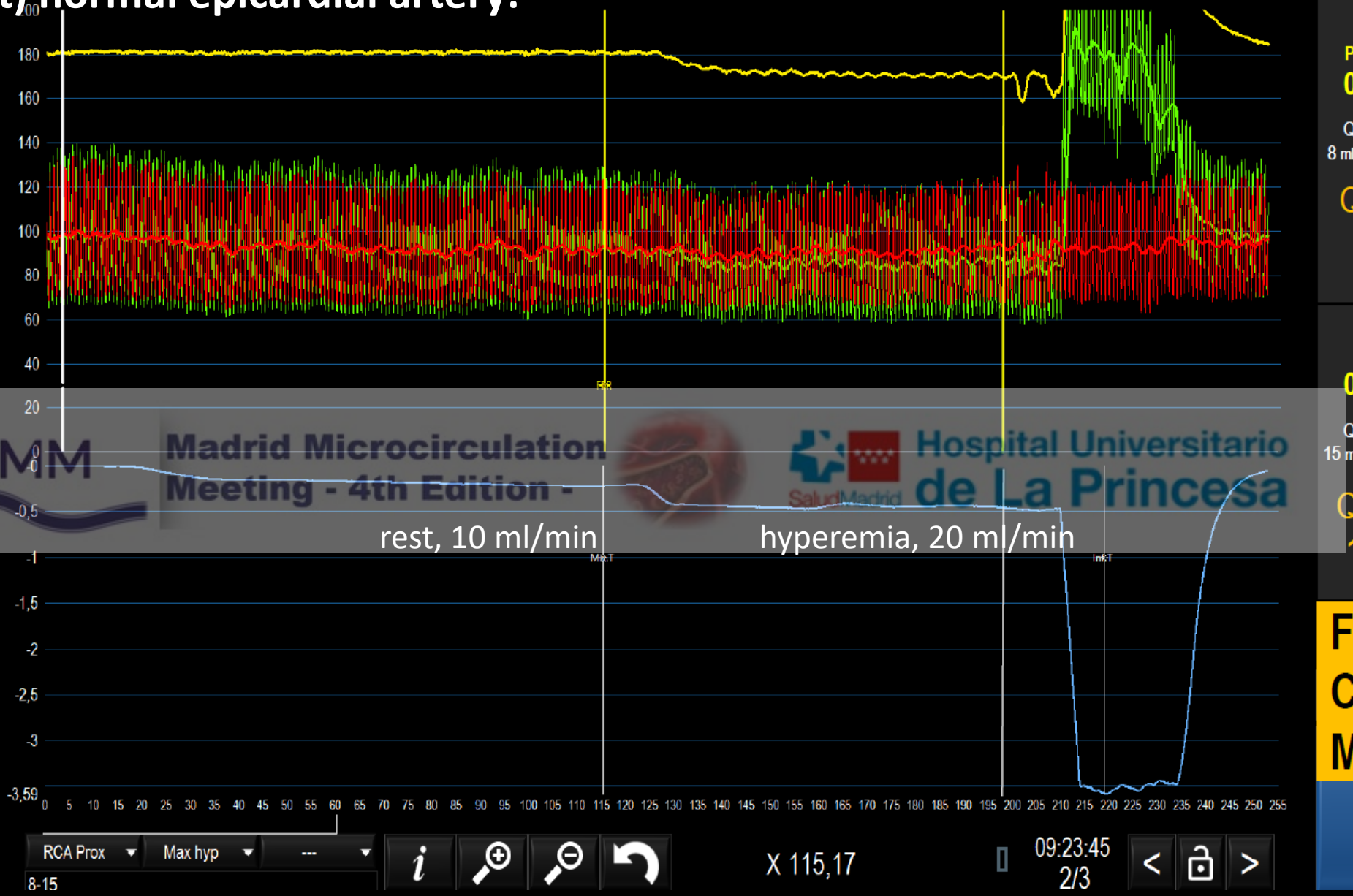
MRR = 227/68 x 108/88 = 4.1 ***(= 3.30/0.84 x 108/105)***

Example: (Almost) normal epicardial artery:

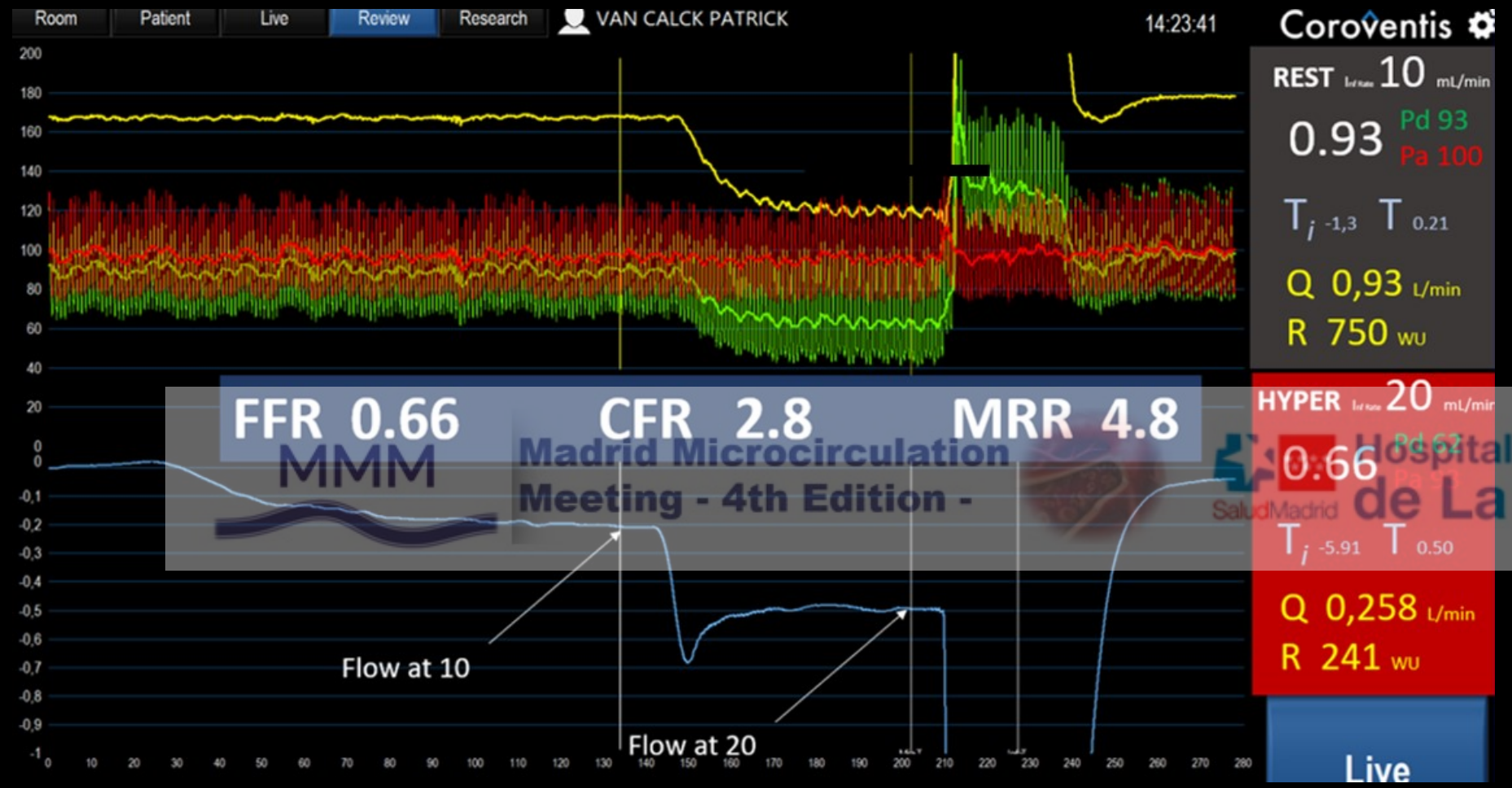
Note: almost no epicardial disease:

(FFR = 0.94)

→ CFR ~ MRR



Example: severe epicardial disease (focal LAD stenosis + diffuse disease):



Note:
epicardial severe disease (FFR = 0.66)
→ CFR << MRR

$$MRR = Q_{max} / Q_{rest} \times P_{a,rest} / P_{d,hyp} = 258/93 \times 100/62 = 4.6$$ Equation 3

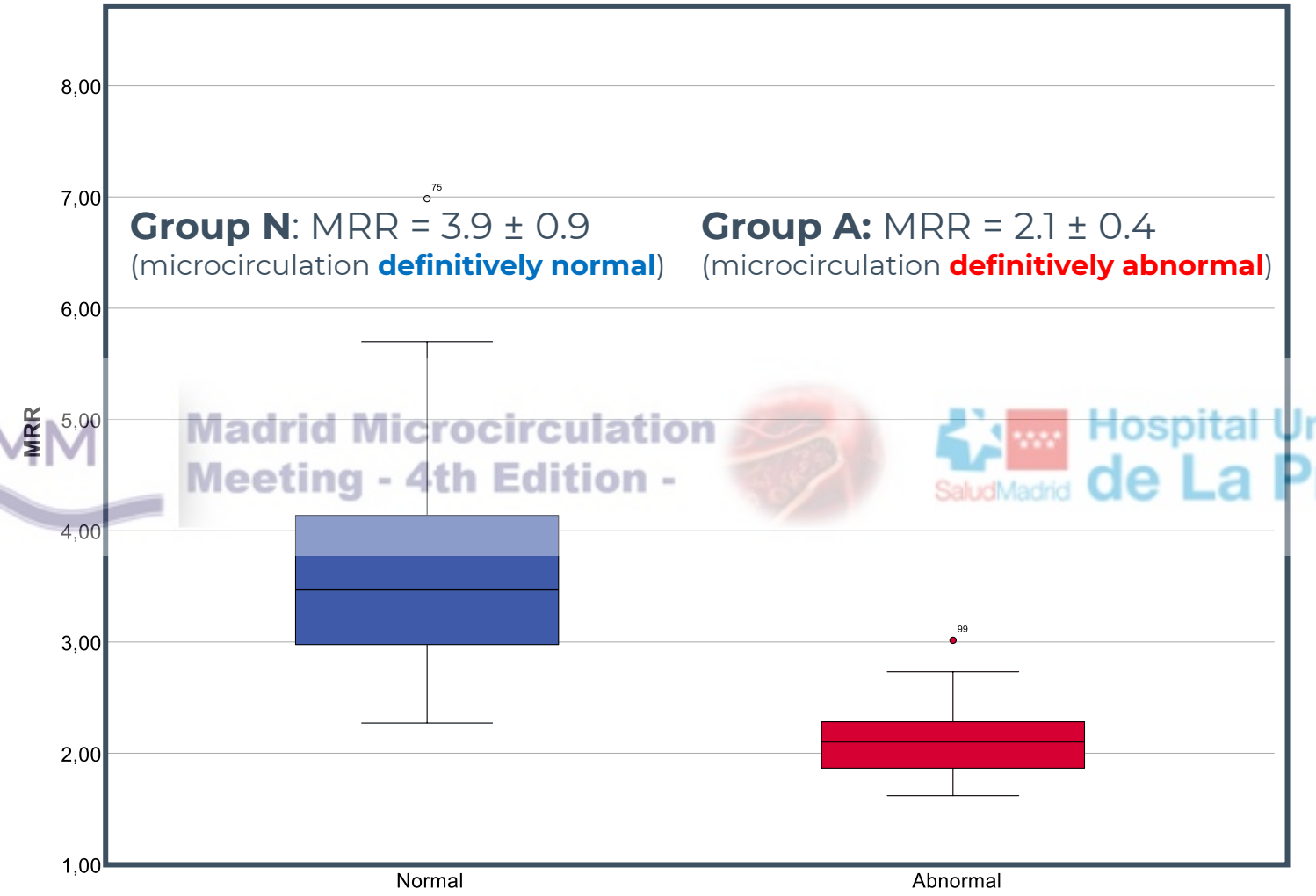
$$MRR = CFR / FFR \times P_{a,rest} / P_{a,hyp} = 2.8/0.66 \times 100/93 = 4.6$$ Equation 4

$$MRR = Q_{max} / Q_{rest} \times P_{a,rest} / P_{d,hyp}$$

Some notes and limitations:

- In completely healthy persons, MRR = CFR
- In patients with coronary artery disease, MRR is a kind of "super-CFR", normalized for hemodynamic changes and for epicardial disease.
- We should realize, however, that the variations of CFR related to genetic heterogeneity and age, are also present for MRR
- Therefore, a 100% dichotomy of patients is not expected, but a definitive diagnosis of microvascular disease is possible with high certainty now in many more patients!
- Extensive further validation studies are being performed,

NL-CFT trial: preliminary data



A. de Vos, P. Damman et al J Am Coll Cardiol Intv 2023;16:470–4

MRR to distinguish microvascular disease

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CAVEATS:

1. By just “applying” the mathematical equation : **MRR = CFR / FFR x $P_{a,rest}/P_{a,hyp}$**

   MRR can also be calculated by bolus thermodilution (substituting a ratio of transit times for CFR) or Doppler (substituting a ratio of flow velocities for CFR).

   Beware that such calculation of CFR is much less accurate than direct absolute CFR measurement with continuous thermodilution). ***This will be reflected in MRR !***

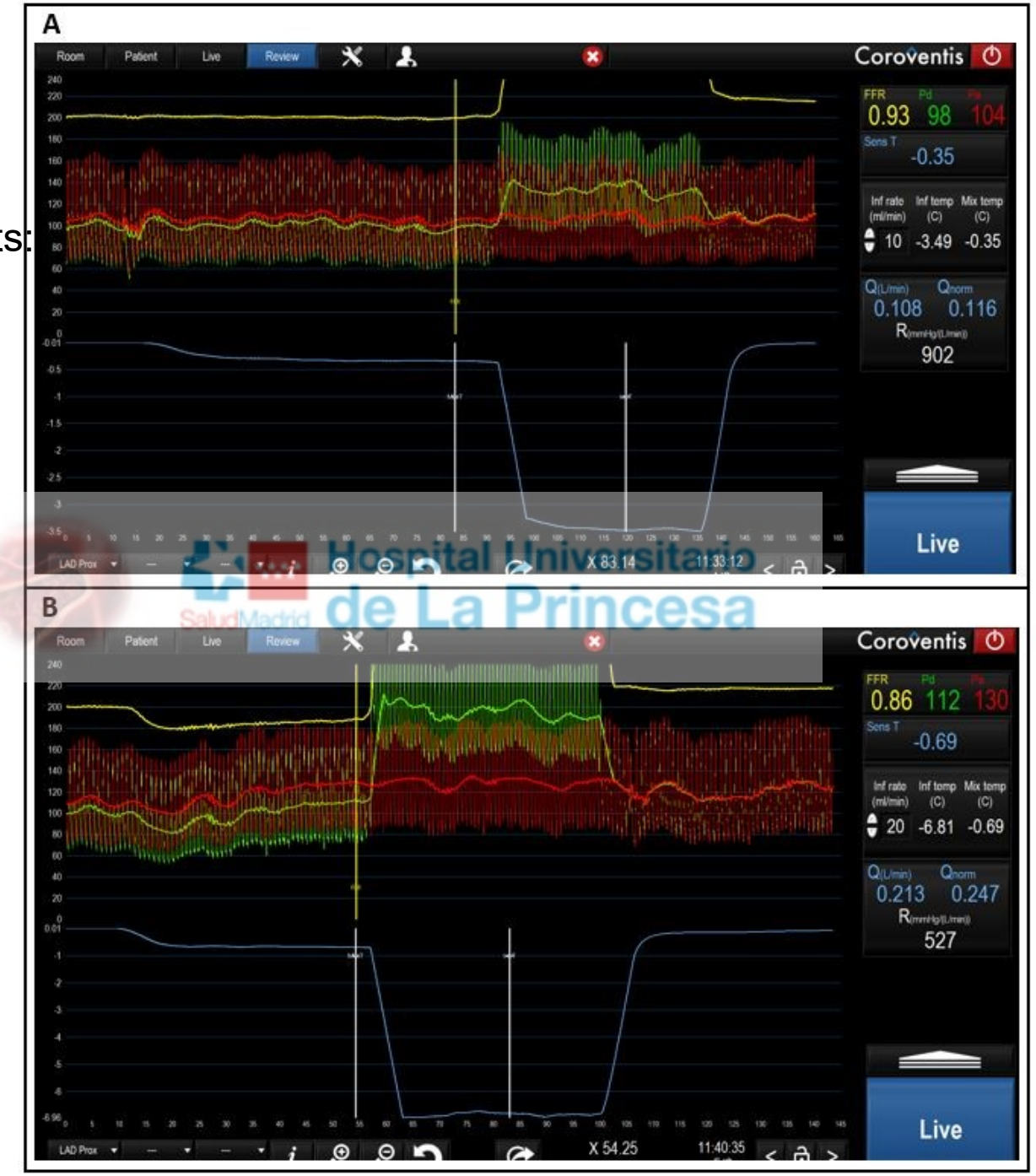
2. In addition to the ***decrease of accuracy with Doppler and bolus thermodilution ,*** these do ***not*** allow separate calculation of Q and R_{μ} , thereby ***precluding differentation between functional and structural MVD***

   → *Example from live course at ORSI, april 10th 2023 (Thomas Keeble)*

64-y-old lady with ANOCA: normal left ventricular function and no significant epicardial disease with FFR of 0.86.

Panel A: resting continuous flow and resistance measurements: Q_{rest} is elevated to 108 ml/min (normal value < 75 ml/min) and $R_{\mu,rest}$ is decreased to 902 WU (normal value > 1125) characteristic of functional CMD.

Panel B: At the same time, hyperemic measurements show that Q_{max} is low-normal at 213 ml/min (normal value > 200) and that $R_{\mu,hyper}$ is increased to 527 WU (normal value < 400), characteristic of structural CMD.



MRR = 1.8 ,suggestive for the combination of structural and functional microvascular disease

(Case performed by Dr Th Keeble, Basidon, UK)

Hyperemic Pressure-Flow Relationship in conscious Man

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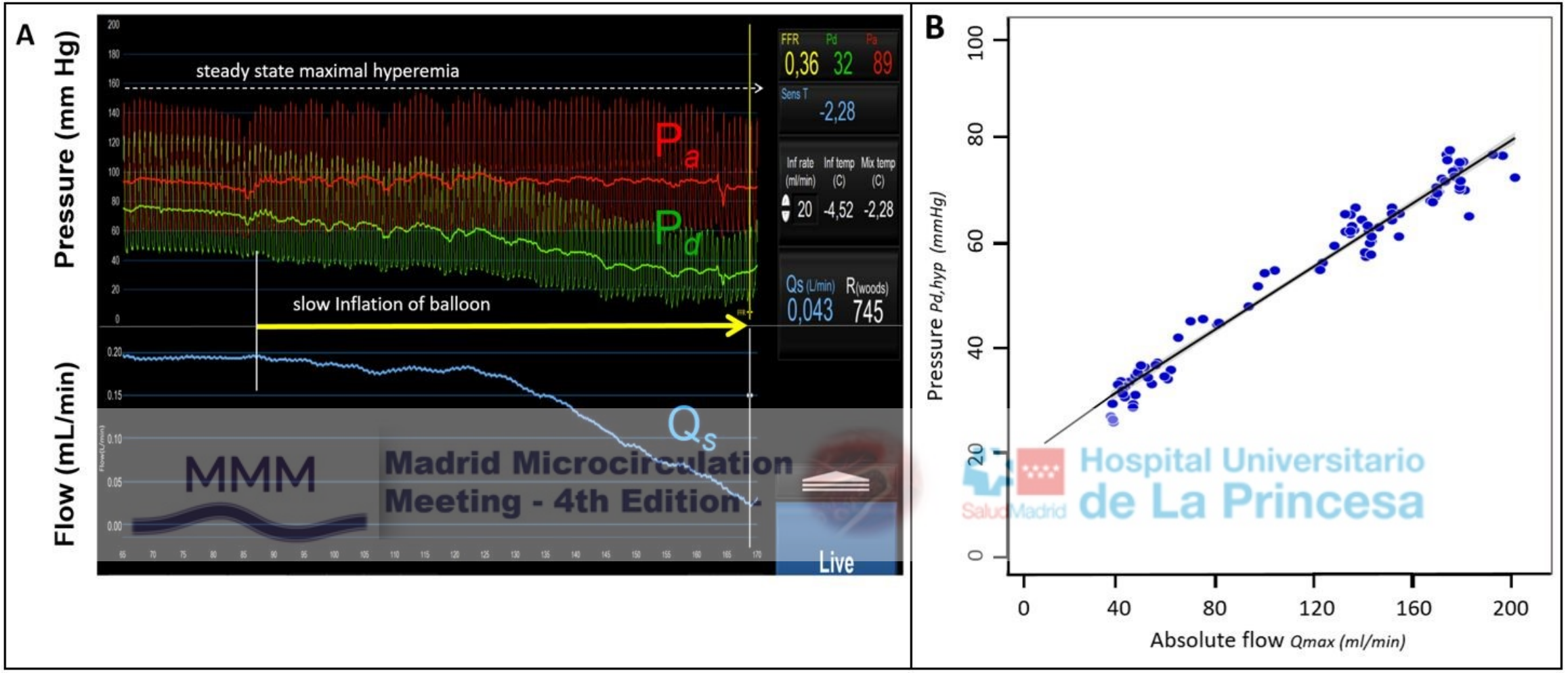

60-year old male, just after implantation of a 3.0 Φ stent in the LAD
A 3.5 compliant balloon is positioned exactly in the stent, using the so-called *triple-C infusion catheter ® which is a RayFlow catheter supplied with a compliant balloon.*
Next, hyperemic absolute flow measurement is performed, and during that measurement, the balloon is slowly inflated with flow sampled at a rate of 10/min.

The beautiful hyperemic pressure-flow relationship is revealed in conscious man

Key take-home messages

- Our knowledge and diagnosis of coronary microvascular disease is hampered by lack of accurate diagnostic indices.

  Present indices like IMR and bolus CFR or Doppler CFR are only qualitatively, have a rather large variability and are operator-dependent.

- **Microvascular Resistance Reserve (MRR)** is the first truly quantitative measure of microvascular disease, independent of epicardial disease, hemodynamic variations, or extent of perfusion territory.

  Using continuous thermodilution, MRR (but also absolute flow and resistance at rest and hyperemia, as well as absolute CFR), can be measured accurately, reproducibly, and rather quickly with minimal operator-dependency

- MRR and related issues are also valid for any other **reliable** invasive or non-invasive way (PET, CT, MRI) of determining FFR and flow or flow-substitutes. Further validation is mandatory: *MASTER-PACT study using FFR_{CT} and PET)*

Thank you

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Further practical information

Portfolio of all published papers on absolute flow/resistance measurement, send mail to: **ingrid.aarts@catharinaziekenhuis.nl**

- Instruction videos at:

Look at:
https://youtu.be/n-L5D50zB3I

And/or:
https://www.dropbox.com/s/b6xdrpex1kdp4rm/MRR%20final.m4v?dl=0

Don’t miss these 10-minute videos showing the easiness and elegance of this method