TCT Asia Pacific 2023

30 Years of History of FFR

From The Concept to Current Status

Seoul, May 7th, 2023

CATHARINA-ZIEKENHUIS

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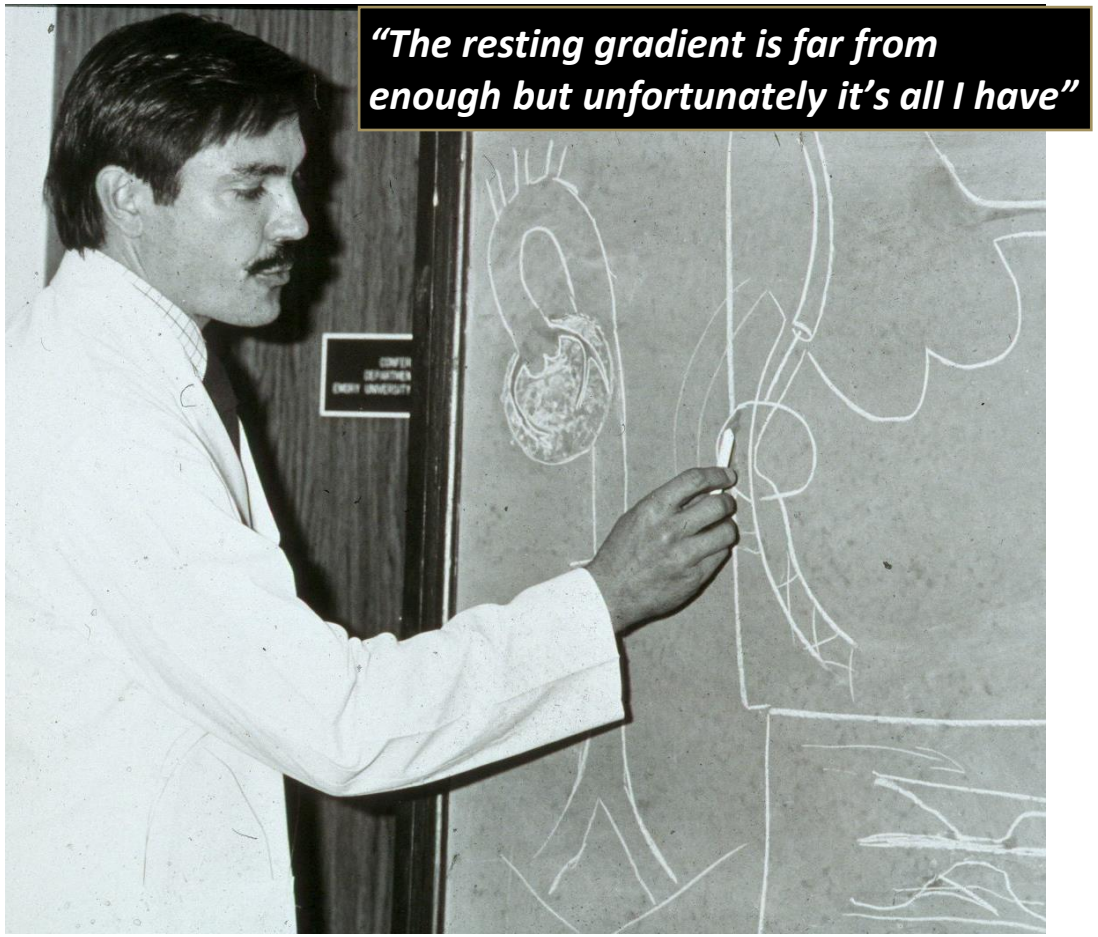
Potential conflicts of interest

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

History: Andreas Gruntzig already recognized the value of coronary pressure measurements but he was hampered by 3 limitations:



no reliable measuring device (pressure wire).

Balloon catheter greatly influenced coronary pressure in those days

no hyperemic stimulus available

Andreas had just to rely on the gradient,
no FFR available yet.

With the introduction of monorail balloons, coronary pressure measurement disappeared for more than a decade

History:

Mid- and late eighties: discovery of reliable and safe **maximum hyperemic stimuli** *(Melvin Marcus, Bob wilson)*

Early nineties: **Prototypes of "Pressure guidewires"** *(RADI)*

And : introduction of **Fractional Flow Reserve** *(Nico Pijls & Bernard De Bruyne)*

What means FFR?

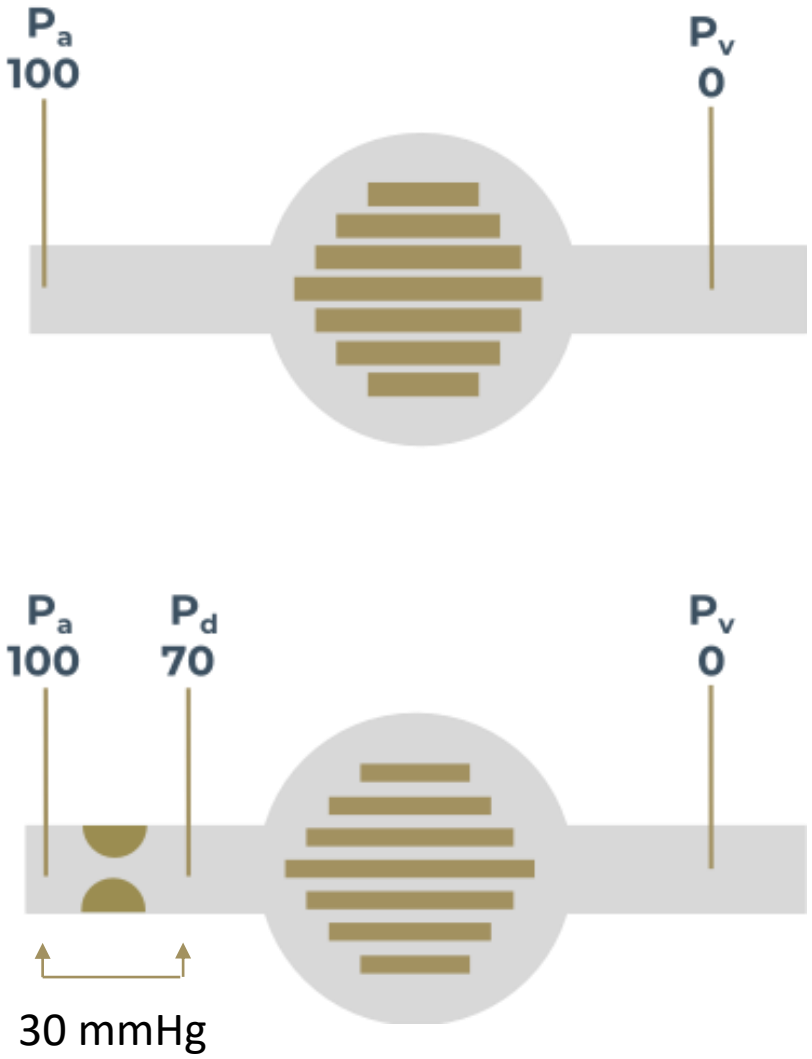
Fractional flow reserve

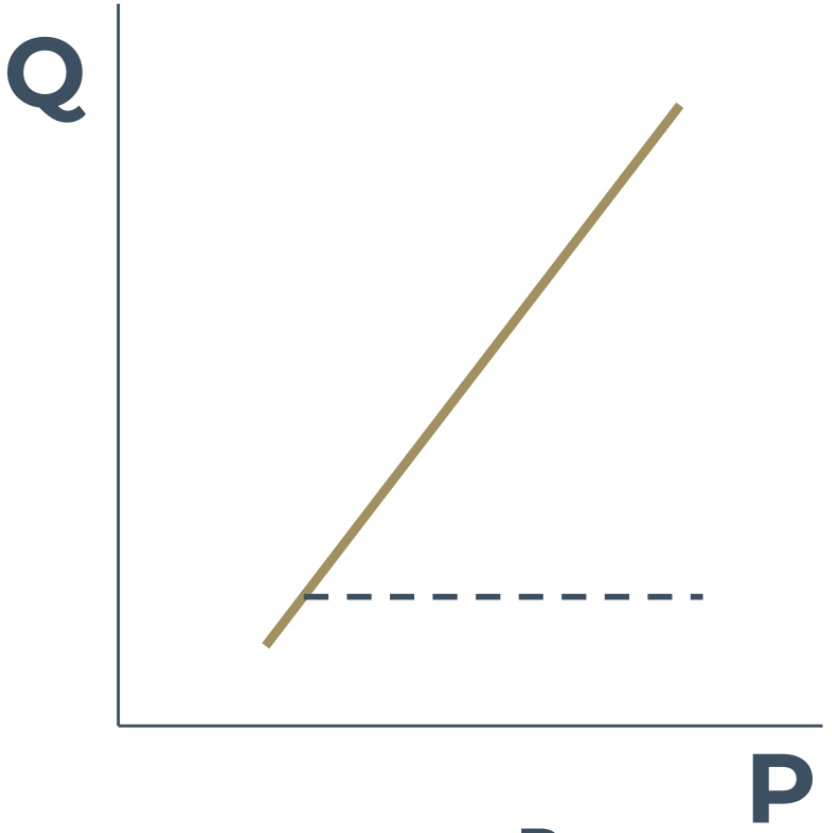
The FFR index (Fractional Flow Reserve) is based upon the two following principles:

- It is not resting flow, but ***maximum achievable flow*** which determines the functional capacity (exercise tolerance) of a patient
  ("hyperemia is the windtunnel for the coronary circulation")

- At maximum vasodilation (corresponding with maximum hyperemia or with maximum exercise), blood flow to the myocardium is proportional to ***myocardial perfusion pressure (~hyperemic distal coronary pressure)***

During maximal vasodilatation





$$FFR_{myo} = \frac{P_d}{P_a} = 0.70$$

During maximal vasodilatation

$$FFR = \frac{P_d}{P_a} \quad \textit{at max hyperemia}$$

P_a = mean aortic pressure at maximum hyperemia

P_d = mean distal coronary pressure at maximum hyperemia

FFR = 0.6 means:

Due to this particular stenosis, maximum achievable blood flow to the myocardium supplied by this artery, is only 60% of what it would be if this coronary artery were completely normal

If, after PCI, FFR increases to 0.9, this means:

Maximum achievable flow (and therefore maximum oxygen supply) has increased by 50% and is 90 % now of the value achievable if the artery were completely normal”

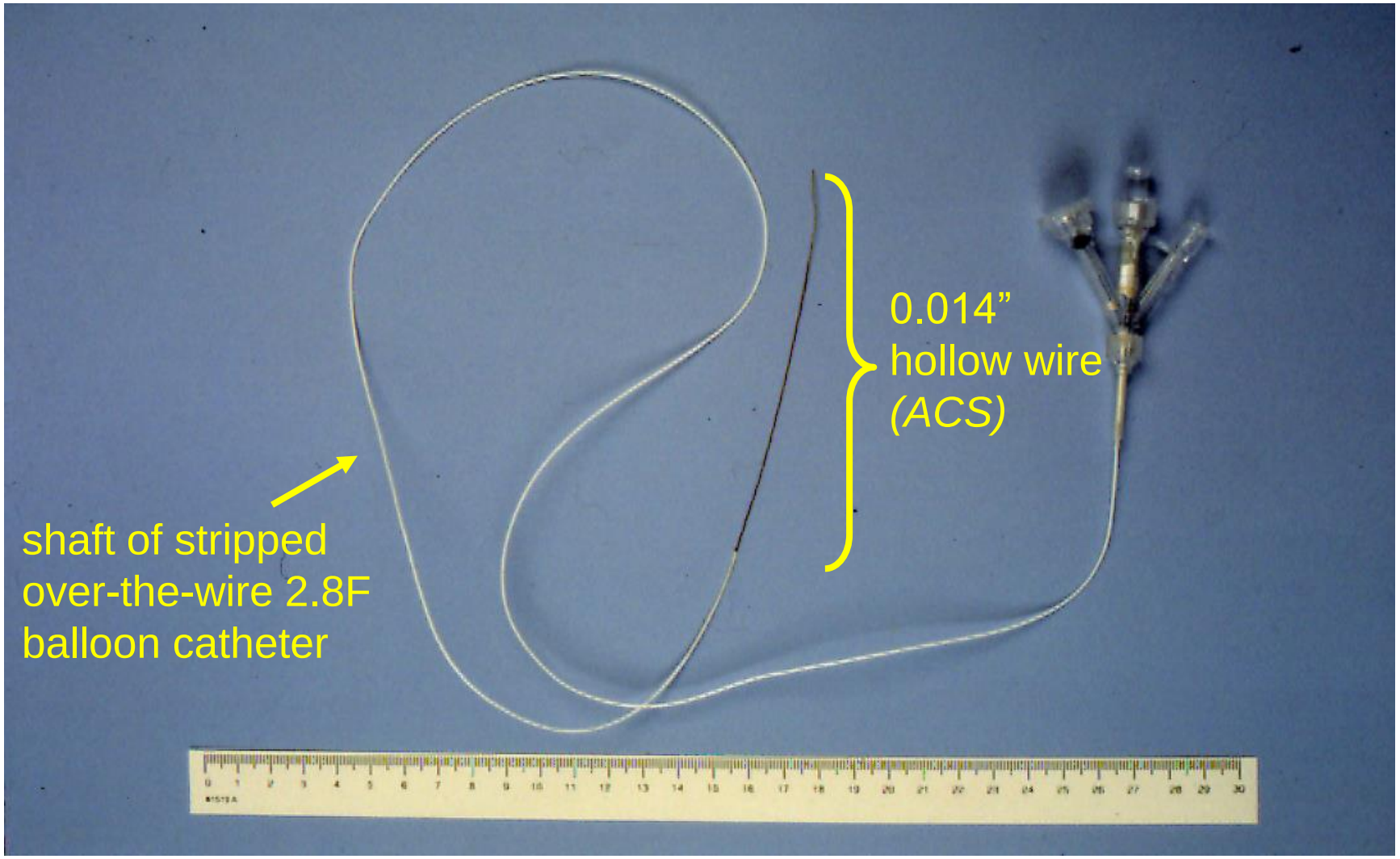
How to Validate This Concept 30 years ago ?

The first problem was to have an 0.014” guidewire for reliable intracoronary pressure measurements without influence on coronary hemodynamics

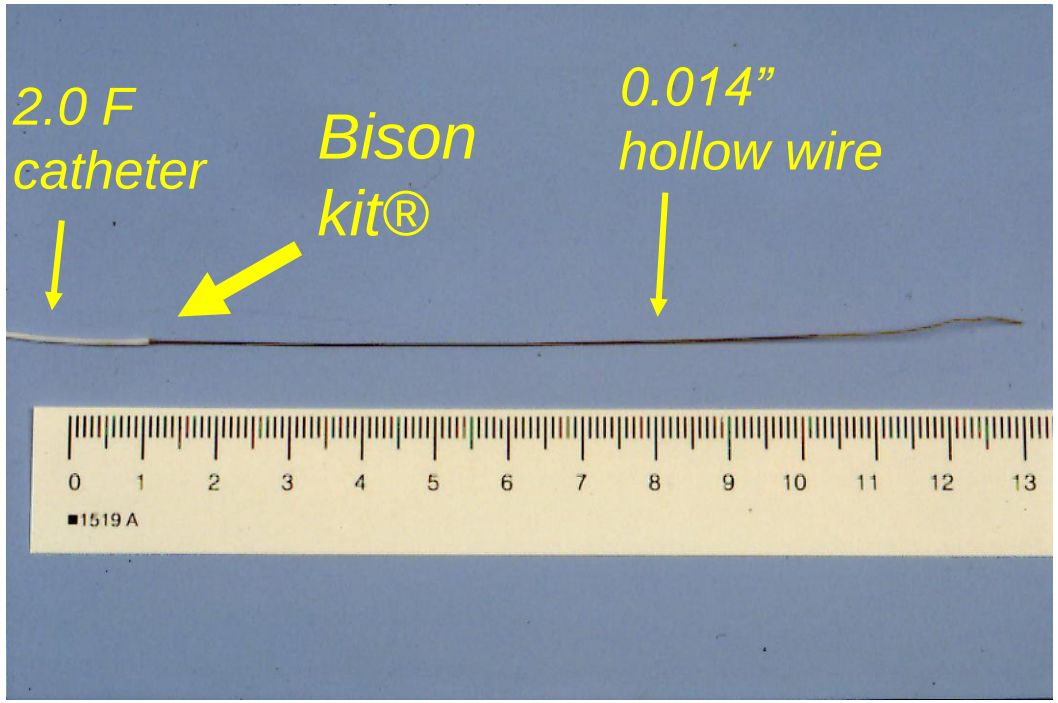
Such wire didn’t exist……

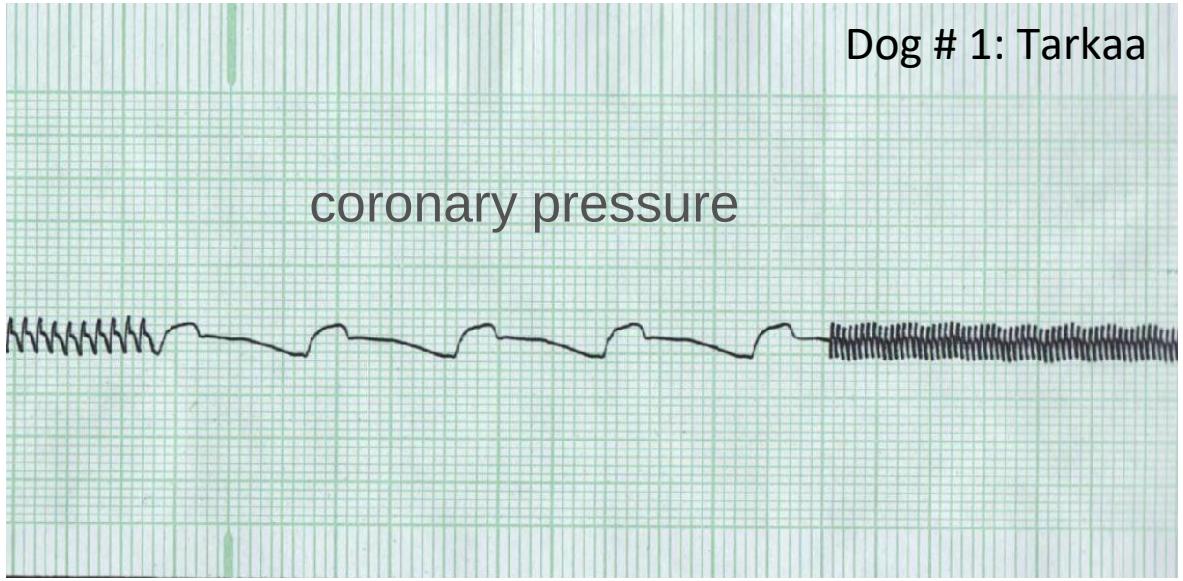
……therefore we had to make it ourselves

First “pressure-monitoring guidewire”

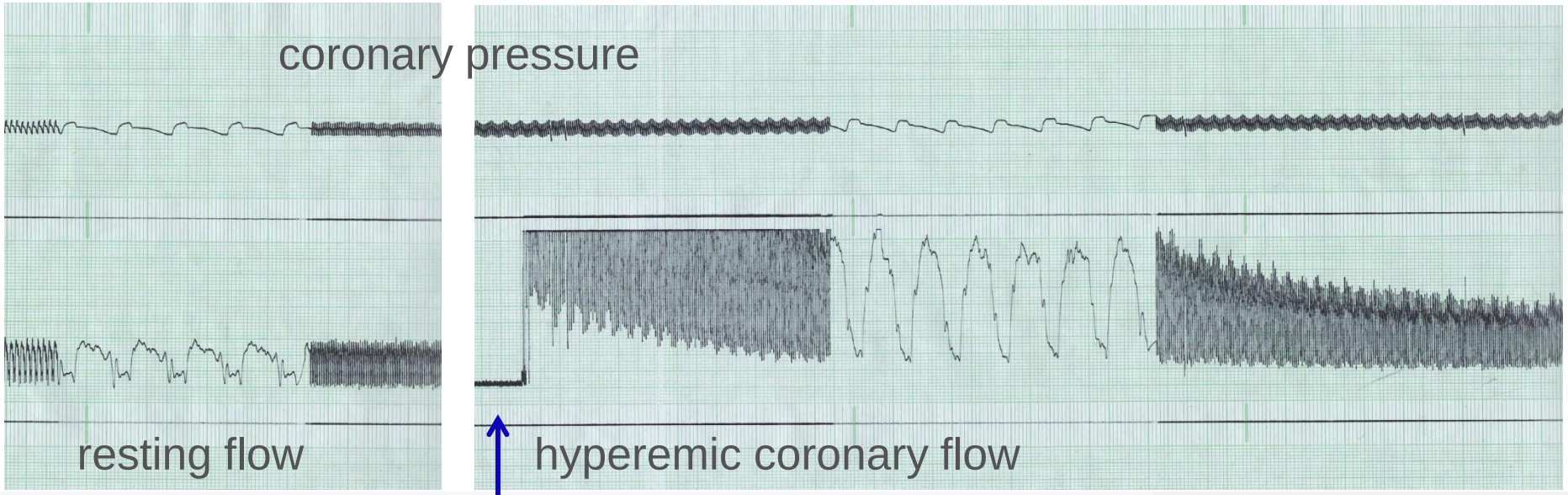


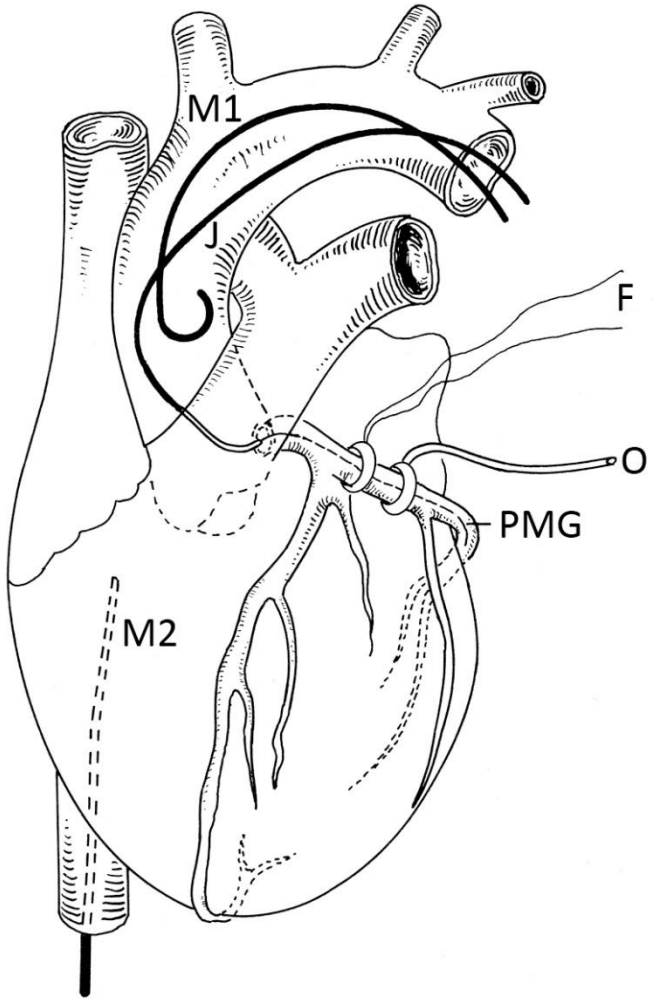
(Produced on the kitchen table of the Pijls family in Malden, NL)





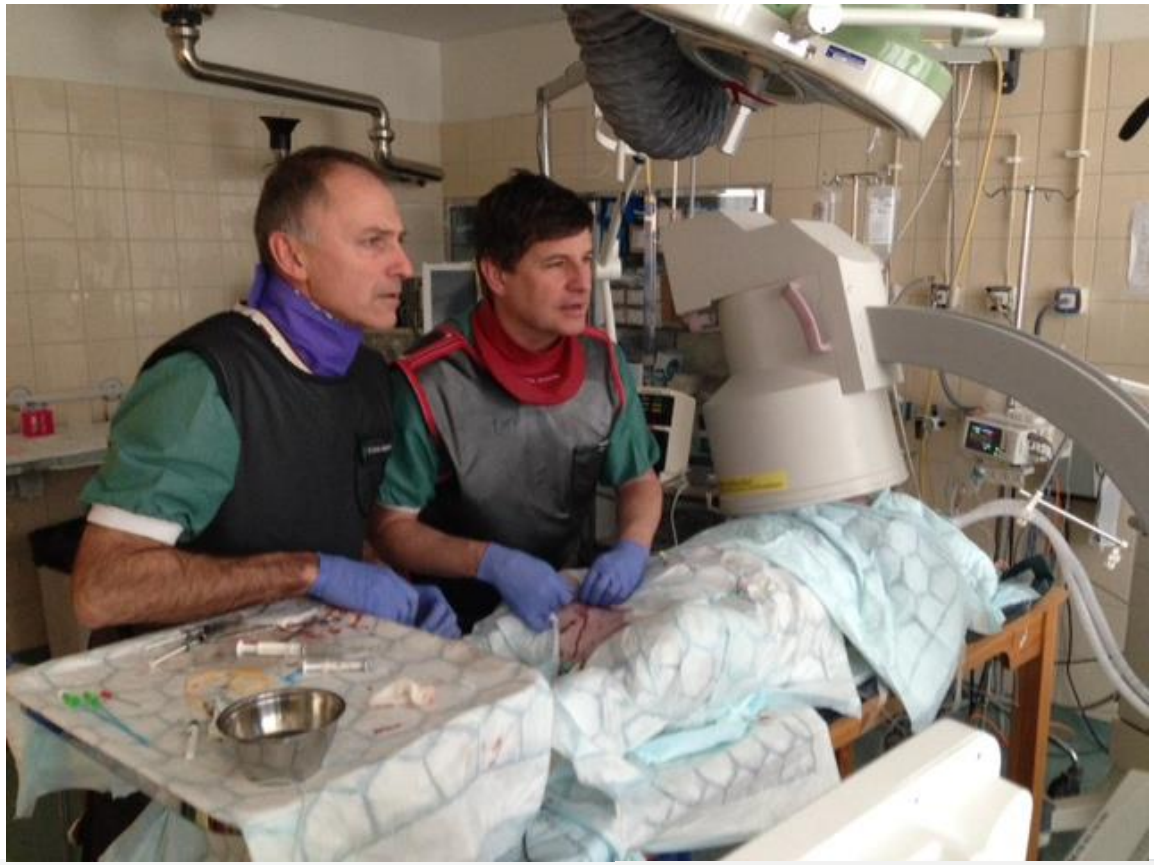
very first wire-based coronary pressure measurement ever



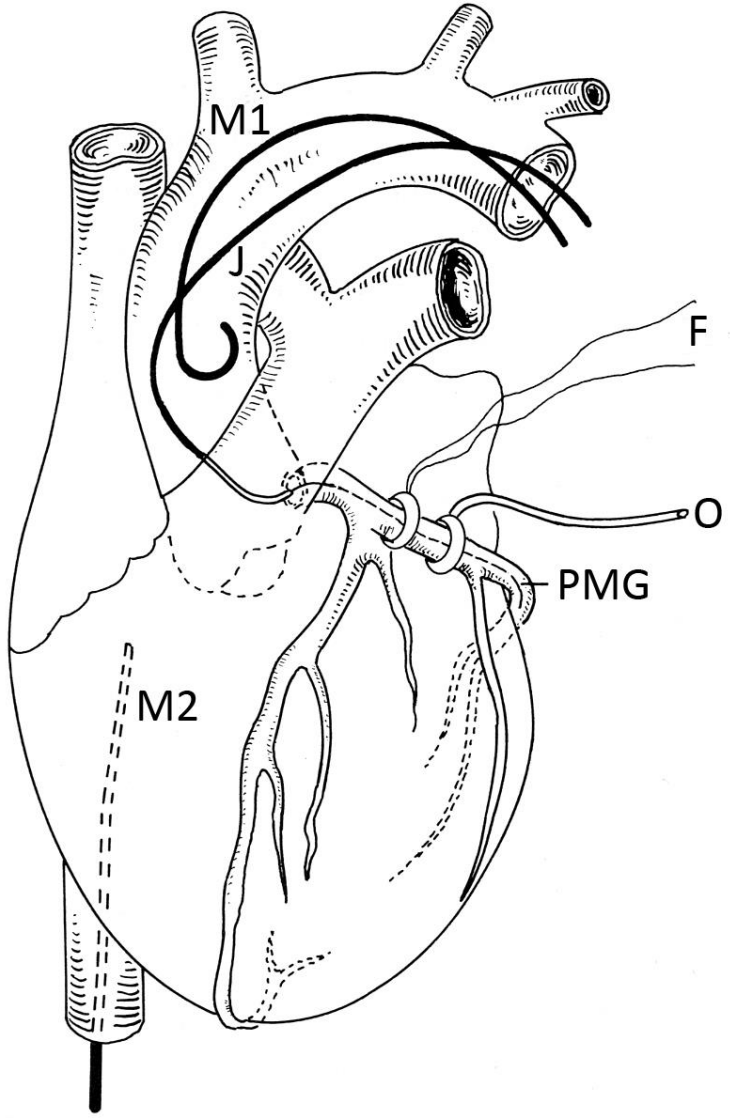


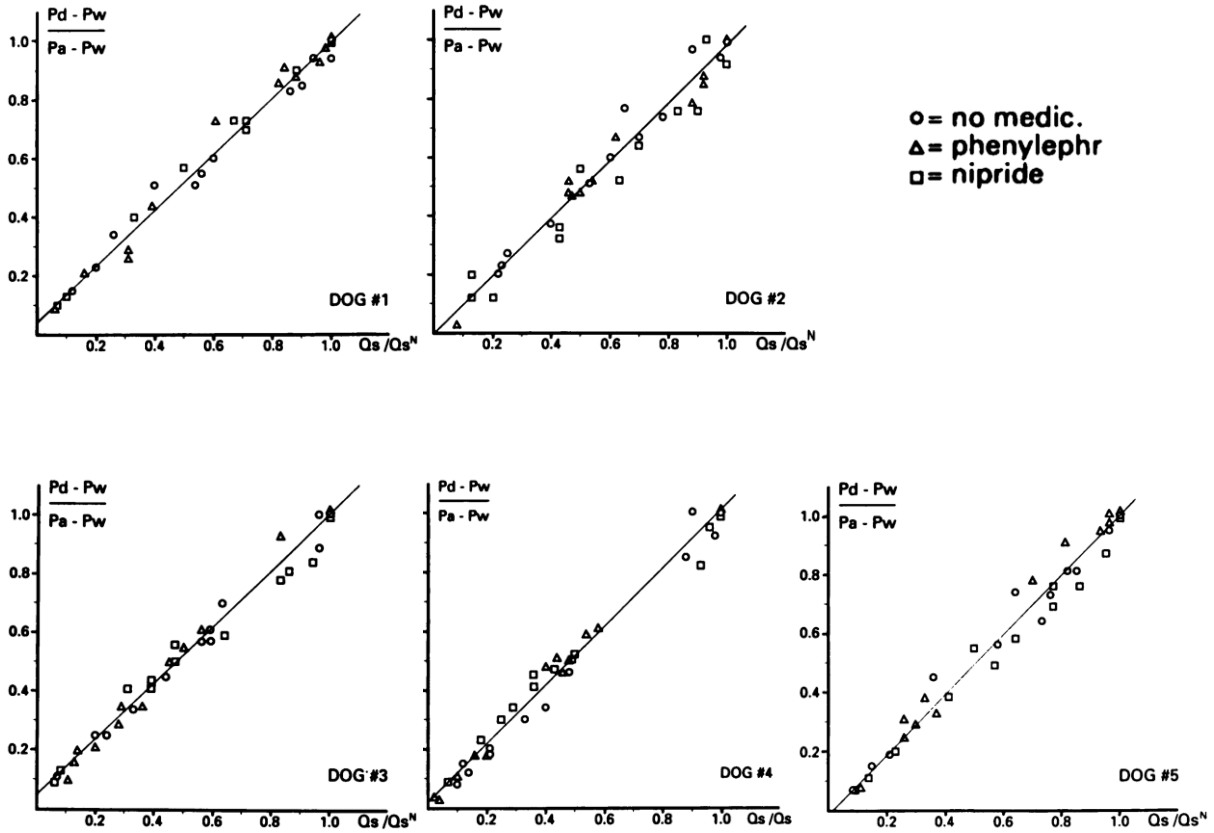
FFR:
experimental validation
in chronic dog studies

(early nineties)



FFR: Experimental validation in chronic dog studies





Pijls N, de Bruyne B, Gould KL, et al, Circulation 1993

The birth of FFR

Experimental Basis of Determining Maximum Coronary, Myocardial, and Collateral Blood Flow by Pressure Measurements for Assessing Functional Stenosis Severity Before and After Percutaneous Transluminal Coronary Angioplasty

Nico H.J. Pijls, MD; Jacques A.M. van Son, MD; Richard L. Kirkeeide, PhD; Bernard De Bruyne, MD; and K. Lance Gould, MD

Circulation *Vol 87, No 4 April 1993*

Description of the Model

The purpose of this model was to derive equations relating pressures to the regional distribution of maximum perfusion. Maximum flow through a stenotic ar-

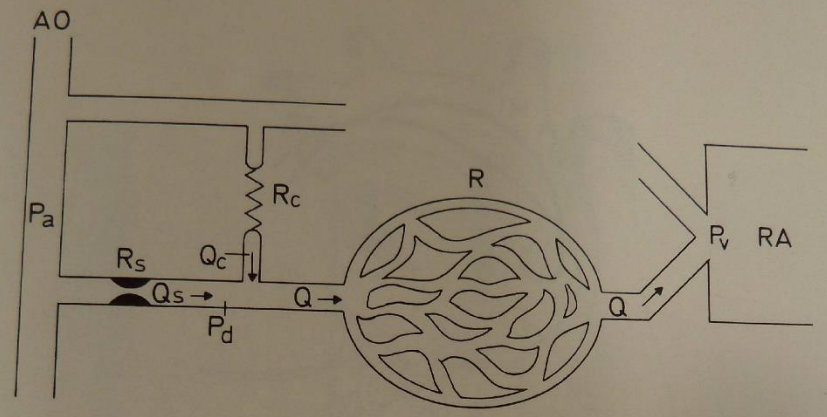


FIGURE 1. *Schematic model representing the coronary circulation. AO, aorta; P_a, arterial pressure; P_d, distal coronary pressure; P_v, venous pressure; Q, blood flow through the myocardial vascular bed; Q_c, collateral blood flow; Q_s, blood flow through the supplying epicardial coronary artery; R, resistance of the myocardial vascular bed; R_c, resistance of the collateral circulation; R_s, resistance of the stenosis in the supplying epicardial coronary artery; RA, right atrium.*

tery is compared with what maximum flow would be in that same artery in the absence of that stenosis. Consequently, we express coronary flow reserve for a stenotic artery as a fraction of its normal expected value in that same artery in the absence of a stenosis. We therefore use the term "fractional flow reserve" (FFR). In the literature, the term "relative flow" reserve is used in the sense of a flow reserve relative to an adjacent normal coronary artery.[1,2] However, a unique strength of the model described here is the theoretical capacity

From 1997 on, reliable pressure guidewires became available for routine use in humans:

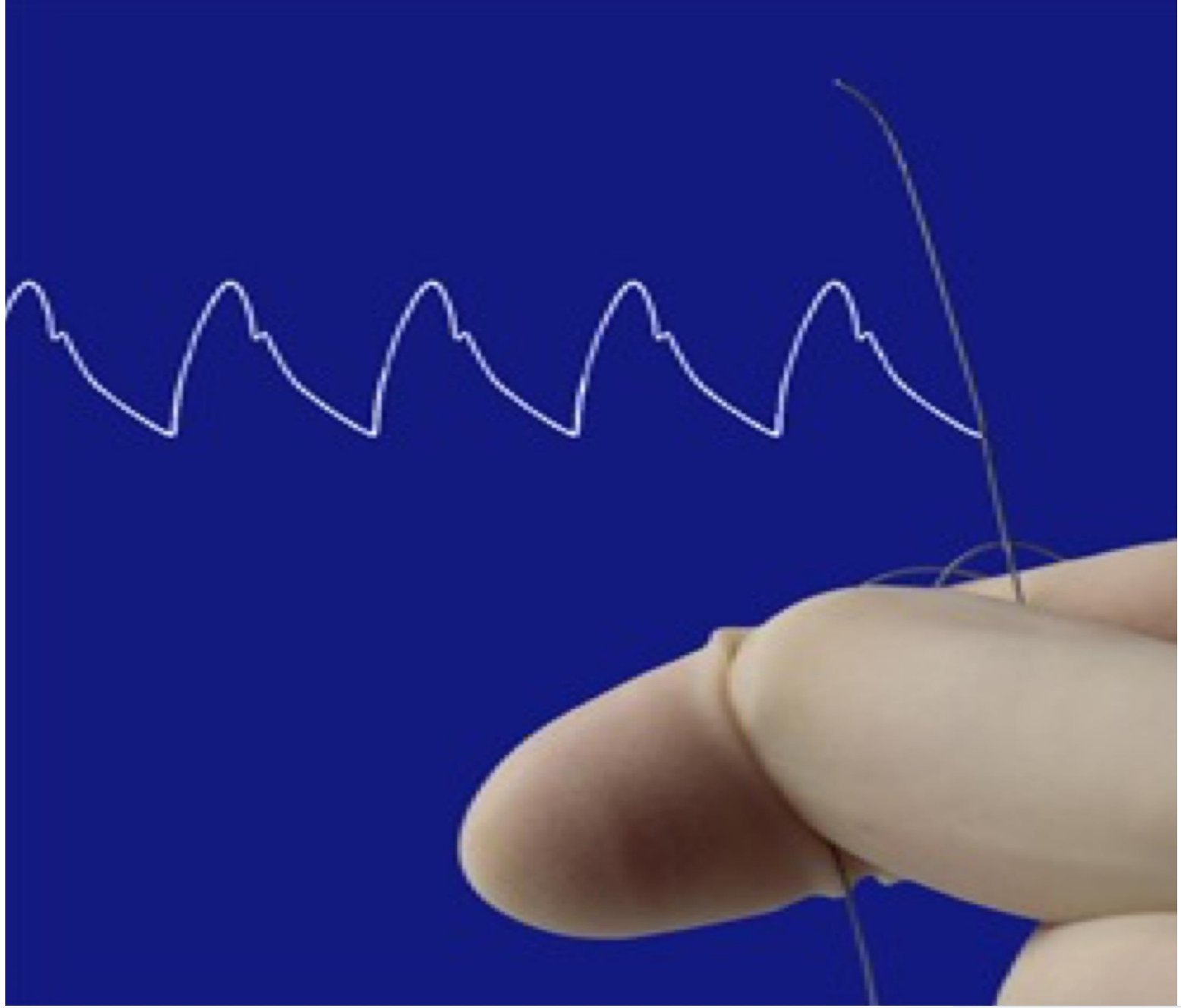
(Lars Tenerz and Leif Smith, RADI Medical Systems)

and clinical research in coronary physiology gained a large impetus

0.014

Sensor-tipped PTCA guidewire (electronic or fiberoptic)

- Abbott
- OpSens
- Philips
- Boston
- Acist
- LifeTech

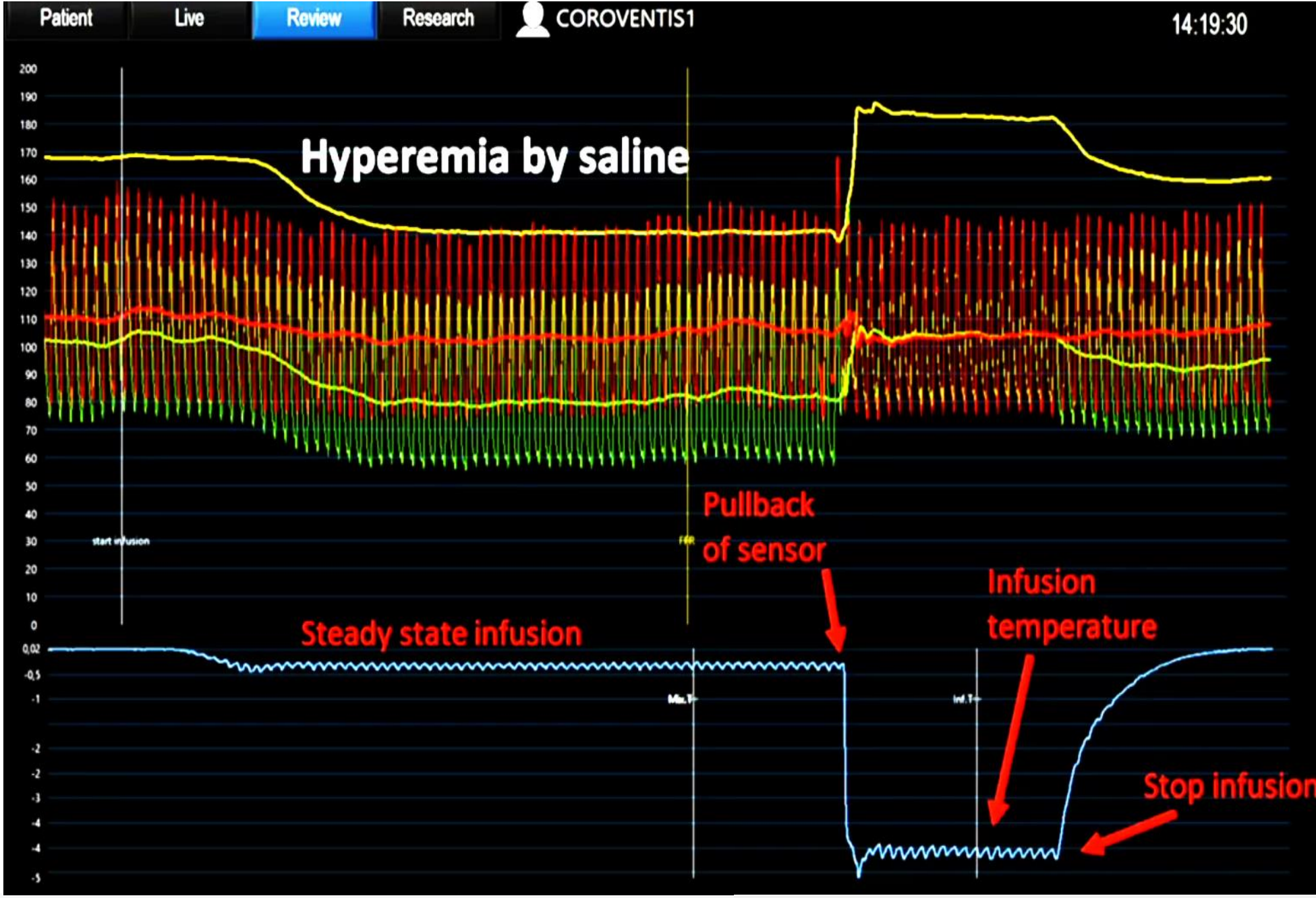


Interfaces

(*brand-specific or generic*), mostly integrated in cath lab

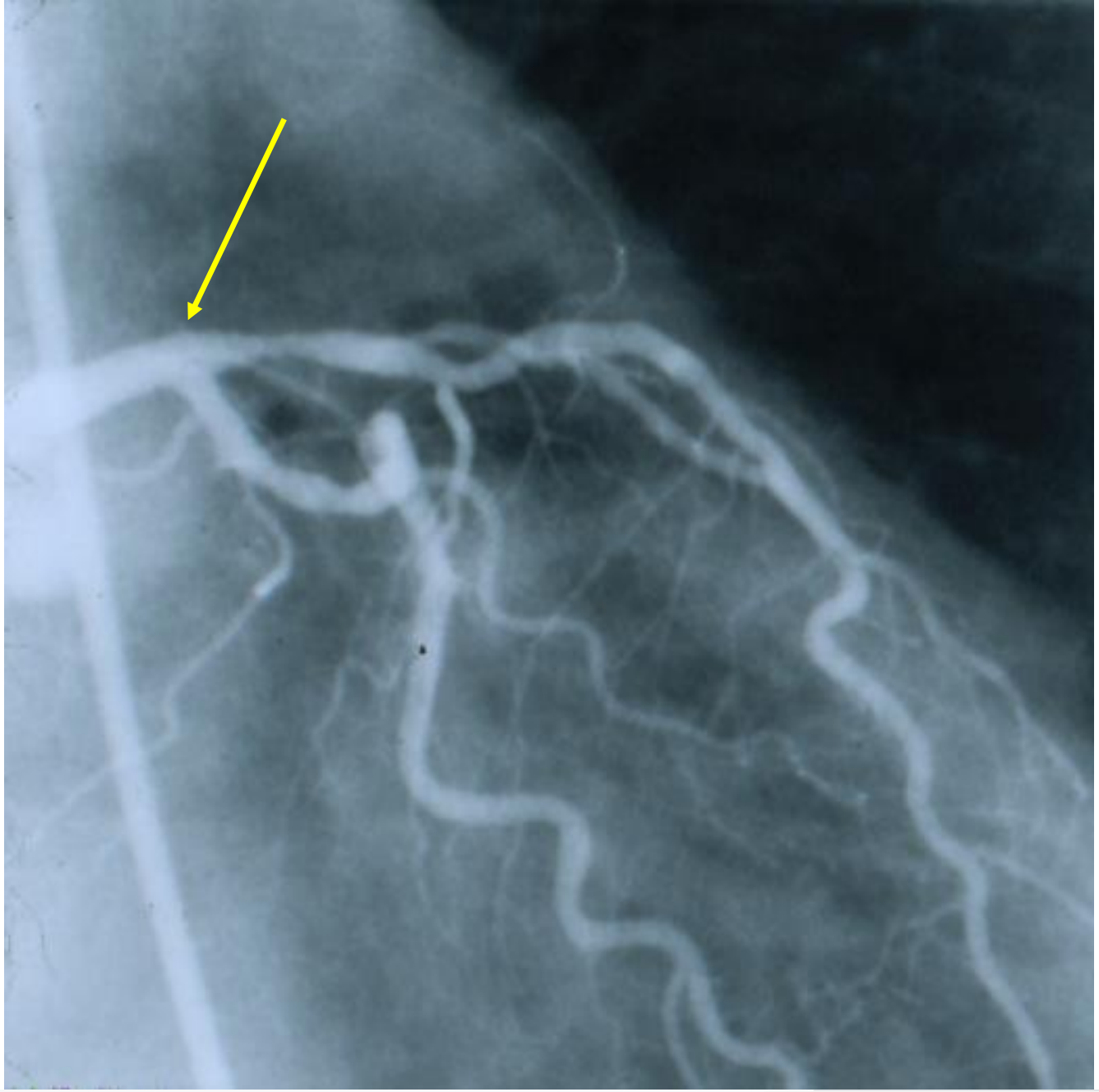
(*FFR, NHPR, IMR, CFR, absolute flow & resistance, MRR*)

Coroventis®

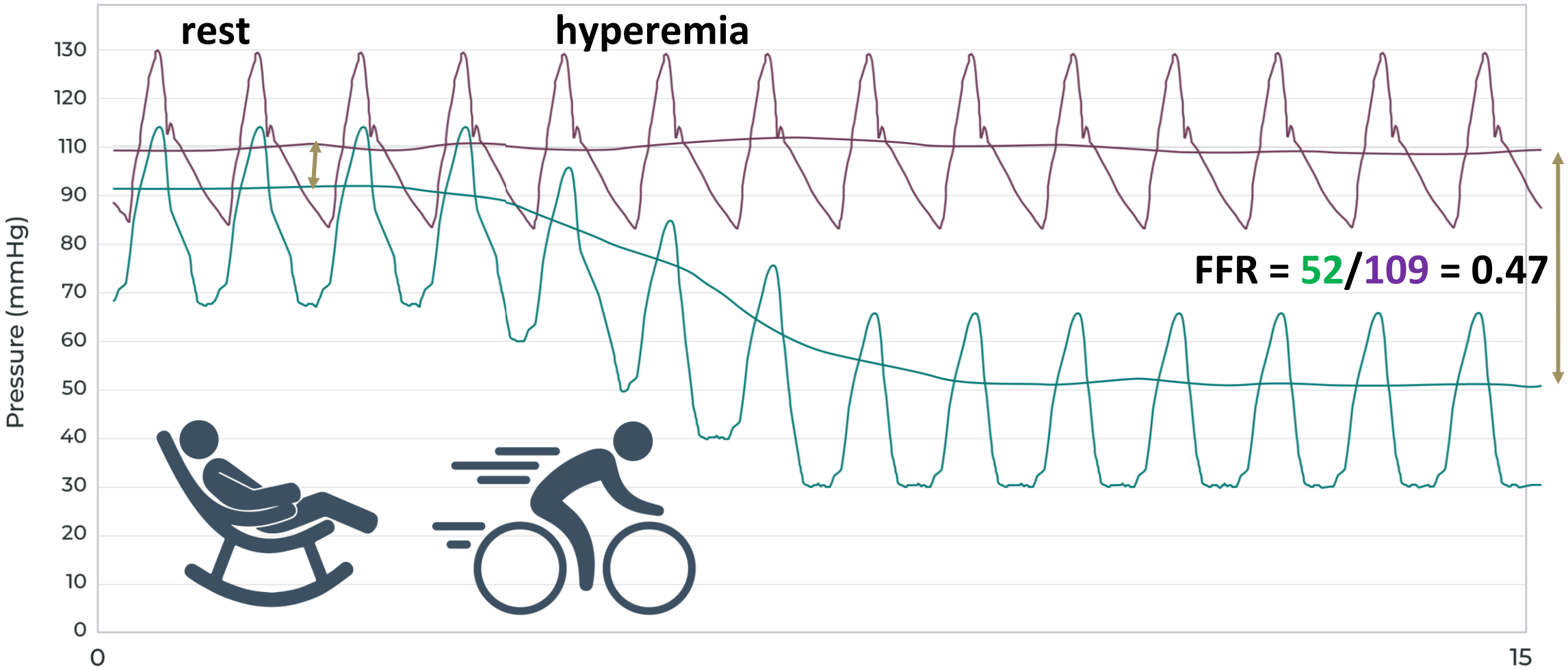


Clinical practice:

Mr van Z.
77 years,
stable ang 2-3
posit ET



Fractional flow reserve in clinical practice



Fractional flow reserve in normal coronary arteries

33 truly **normal** coronary arteries in normal persons without coronary artery disease:

FFR = 0.98 +/- 0.02 (range 0.93 – 1.00)

Pijls, Circulation 1995;92: 183-193

86 **apparently normal** contralateral arteries in patients with coronary disease:

FFR = 0.87 +/- 0.09 (range 0.64 – 0.97)

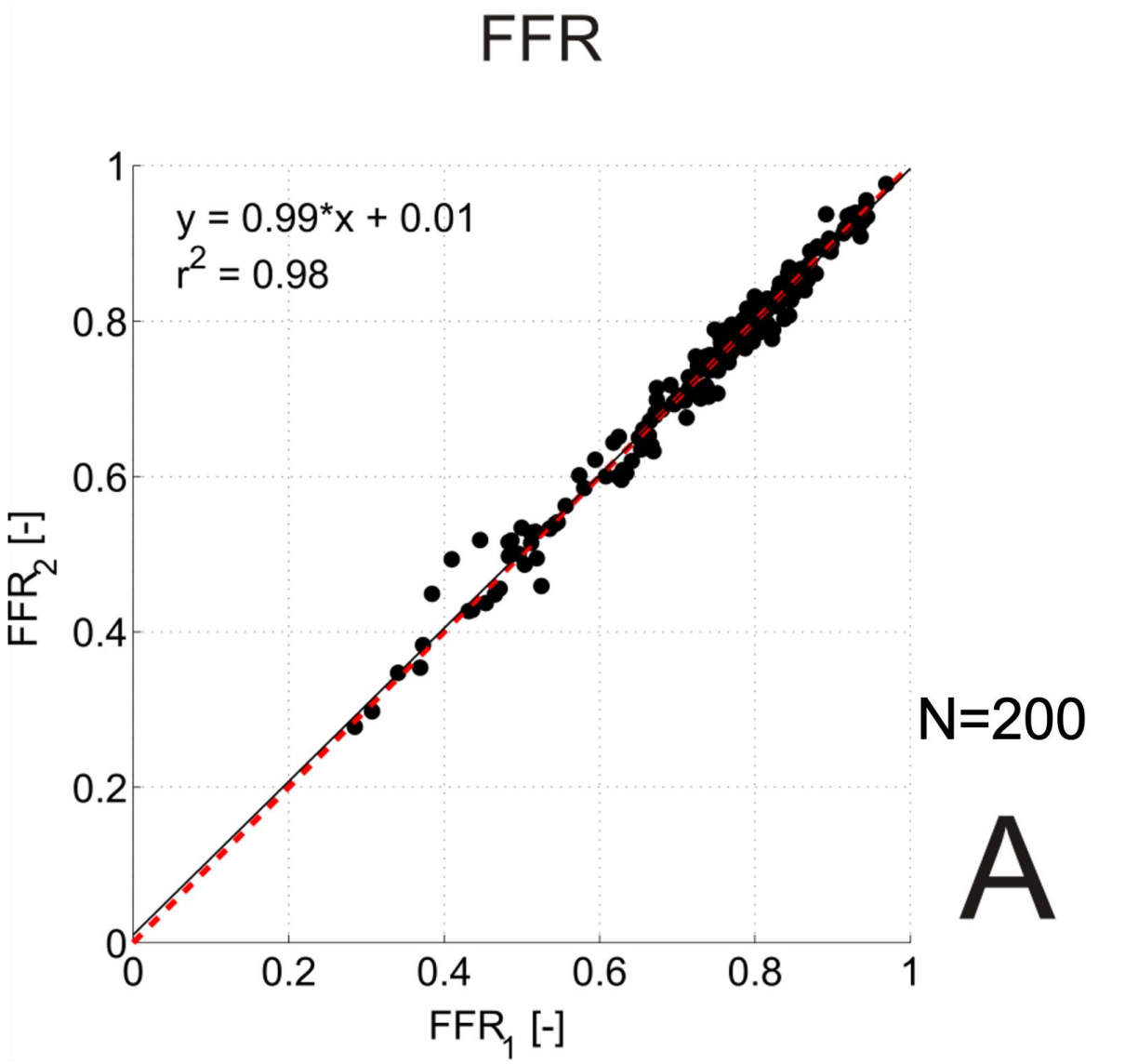
De Bruyne, Circulation 2001; 104:2401-2406

Reproducibility of FFR

VERIFY study, Berry et al, JACC 2013
(published JACC 2012; N=200)

(all-comers during one month in 5 large centers)

There is not any other index in physiology or clinical medicine so reproducible as FFR



Threshold value of FFR to detect significant stenosis in humans

How can you validate a new index if no gold standard exists?

→ **Prospective multi-testing Bayesian approach**

FFR < 0.75 → 100 % certainty for ischemia

FFR > 0.80 → 95 % certainty of “no ischemia”

Pijls et al, New Engl J Med 1996; 334:1703-1708

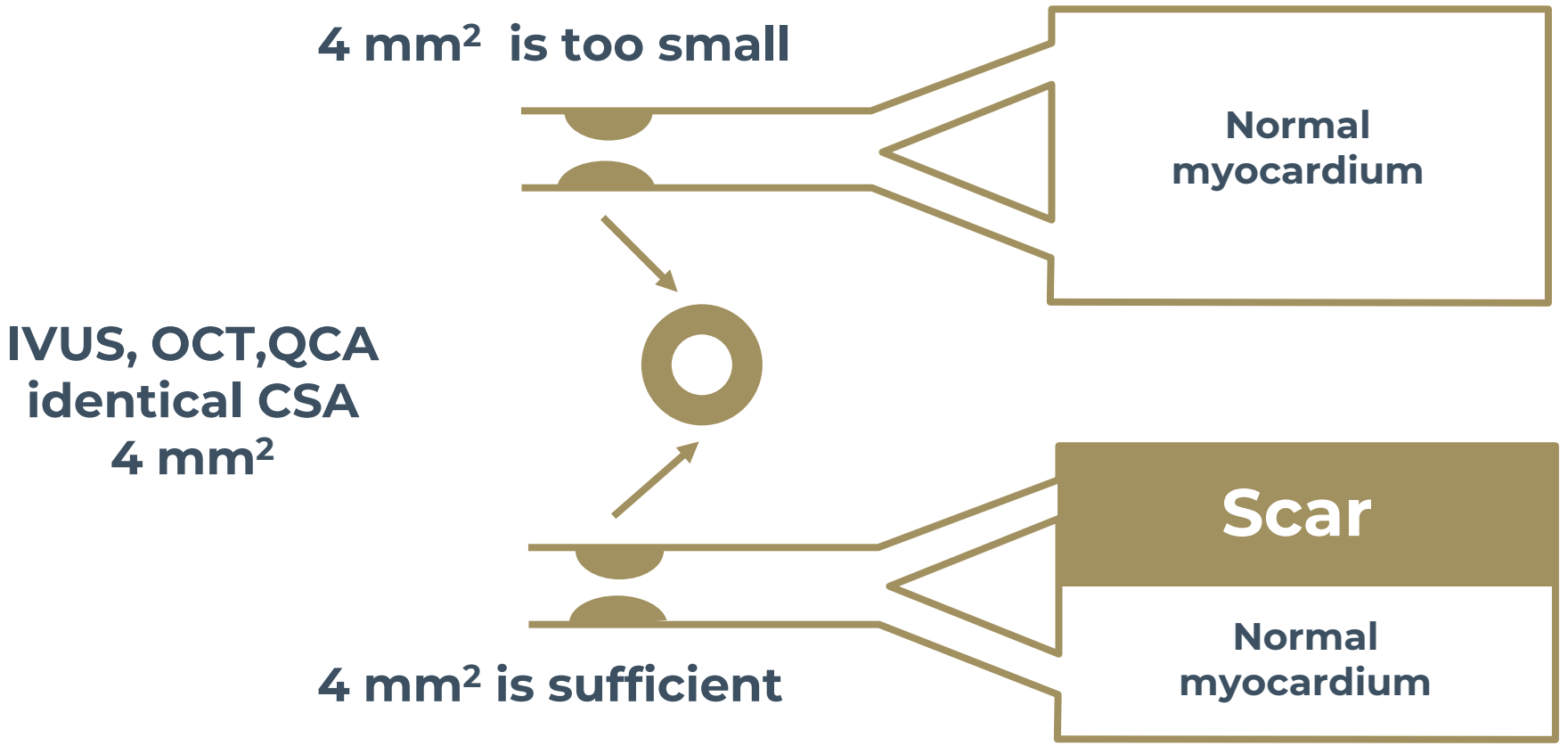
One other special and *unique feature* of FFR…

FFR is in fact the link between:

- Stenosis severity
- Maximal blood flow
- Perfusion territory
- and myocardial ischemia

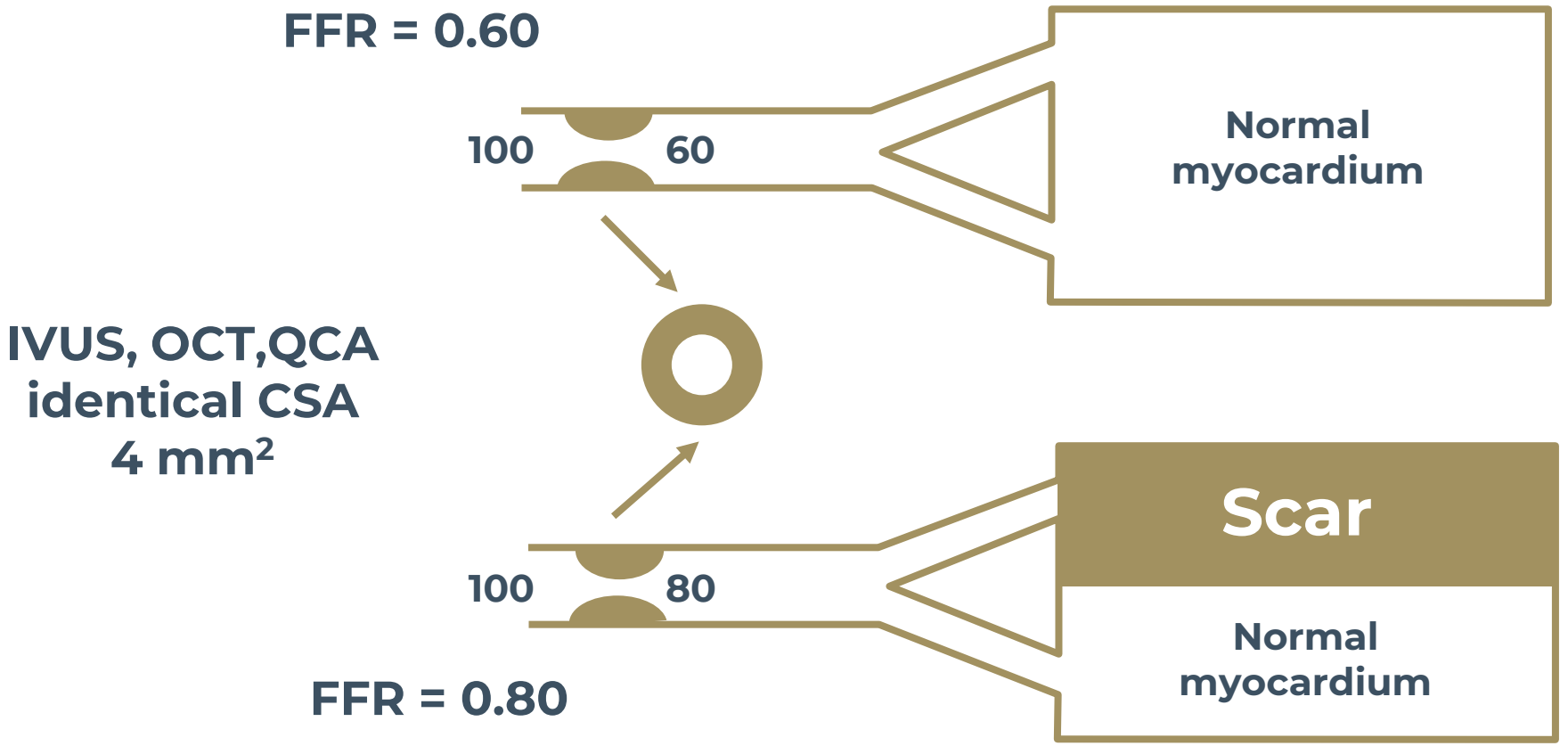
With permission from Dr Haitma Amin, Bahrain

Similar stenosis but different extent of perfusion area



Identical CSA, but different significance of stenosis

Similar stenosis but different extent of perfusion area



Identical CSA, but different significance of stenosis

In many complex angiographic and clinical conditions, FFR has been validated and can be assessed as regular:

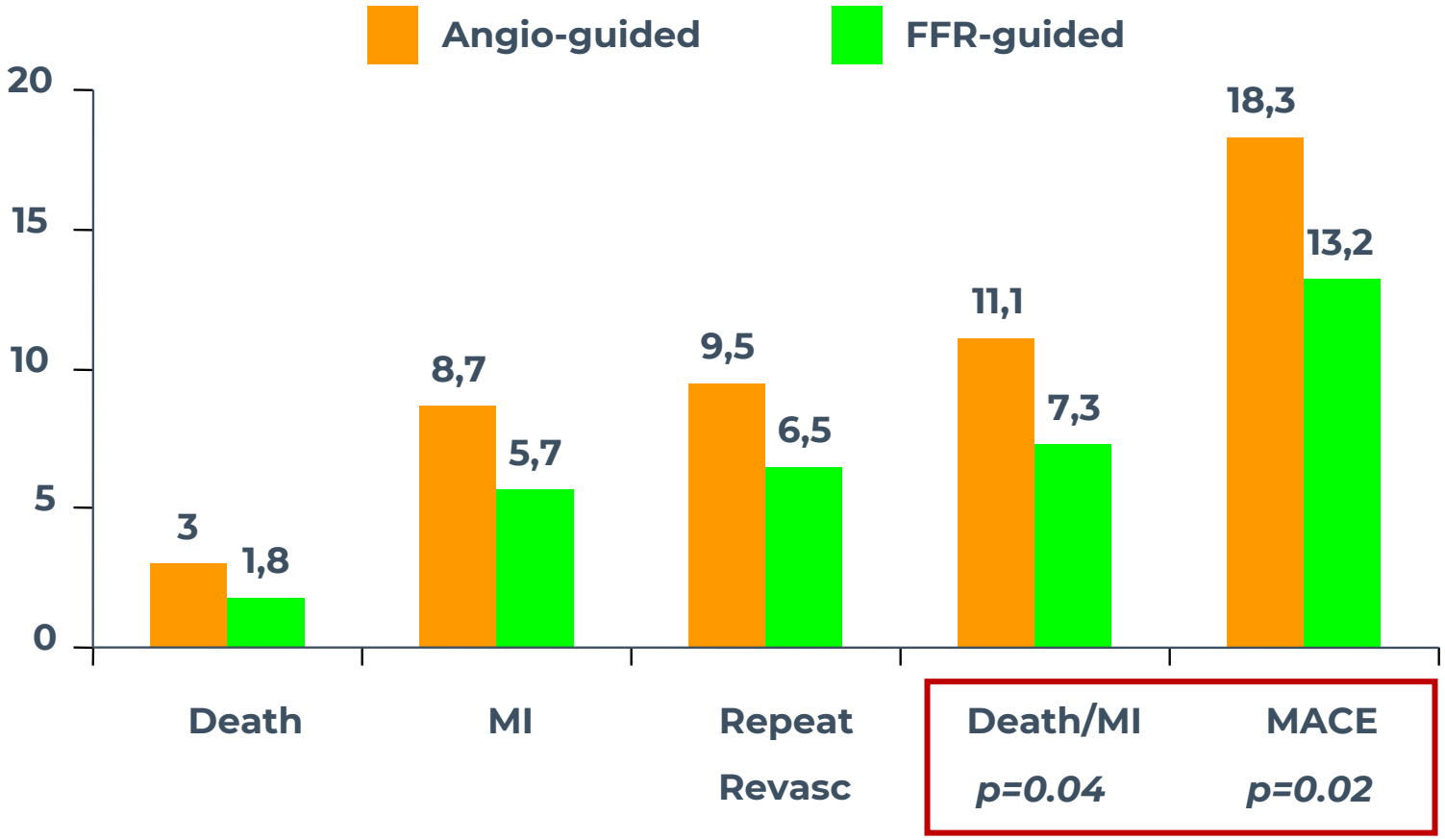
- ostial lesions
- MVD
- left main lesions
- tandem lesions
- diffuse disease
- CTO

- The hyperemic pull-back recording: practical way to guide if and where exactly the stent(s) should be placed and to evaluate the result of PCI.
- Resting pullback useful in serial stenosis

→ Recently refined and made more sophisticated by **PPG –index** *(Collet C, Sonck J, De Bruyne B)*

FFR and clinical outcome

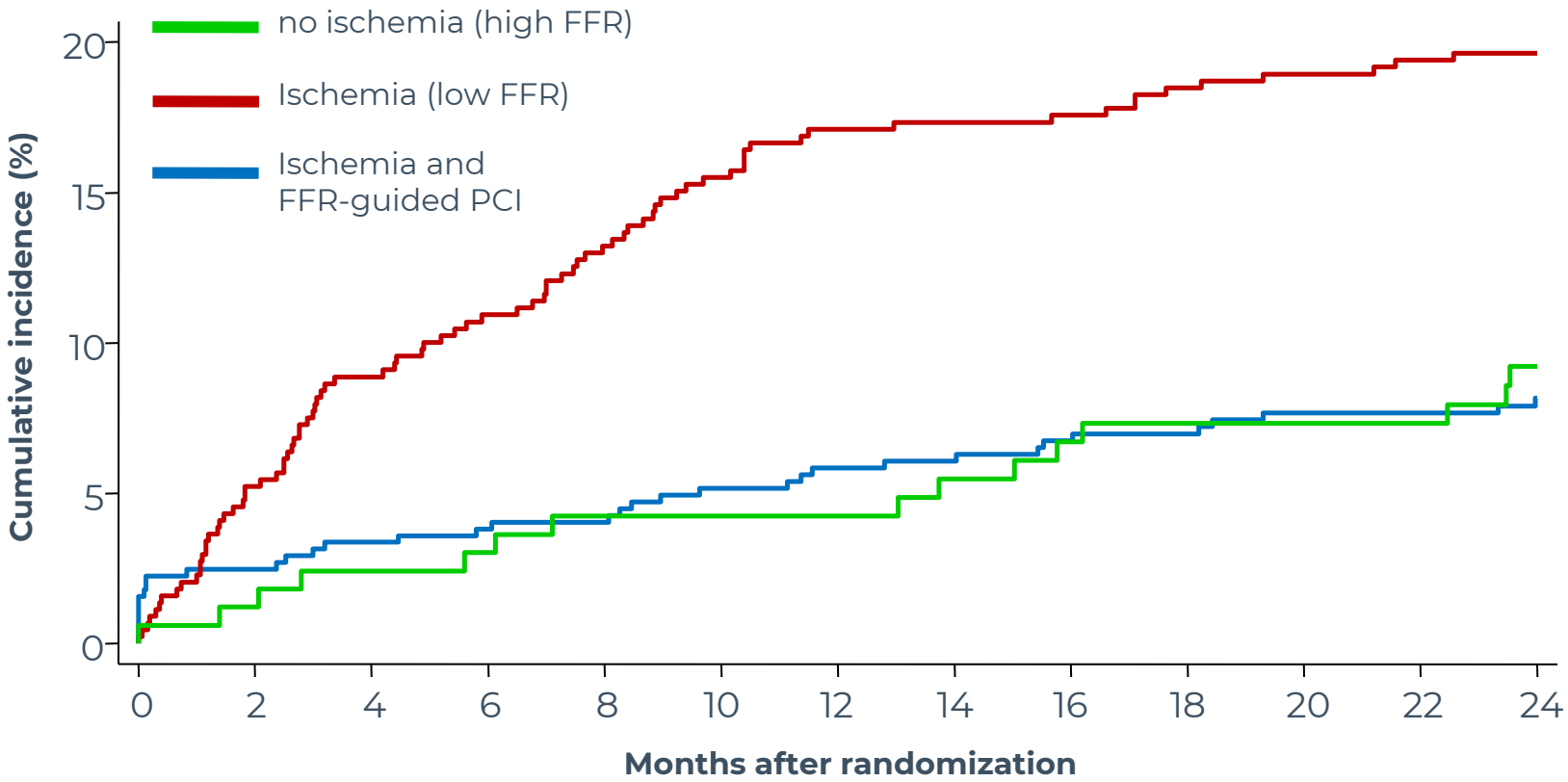
Measuring FFR in multivessel disease: FAME study (N=1005) : *reduction of ALL events by 30% after 1, 2, 5 years*



Tonino ,NEJM 2009; Pijls, JACC 2011, Zimmermann, EHJ 2015

FAME 2: death, infarction, urgent revascularization

N = 1220



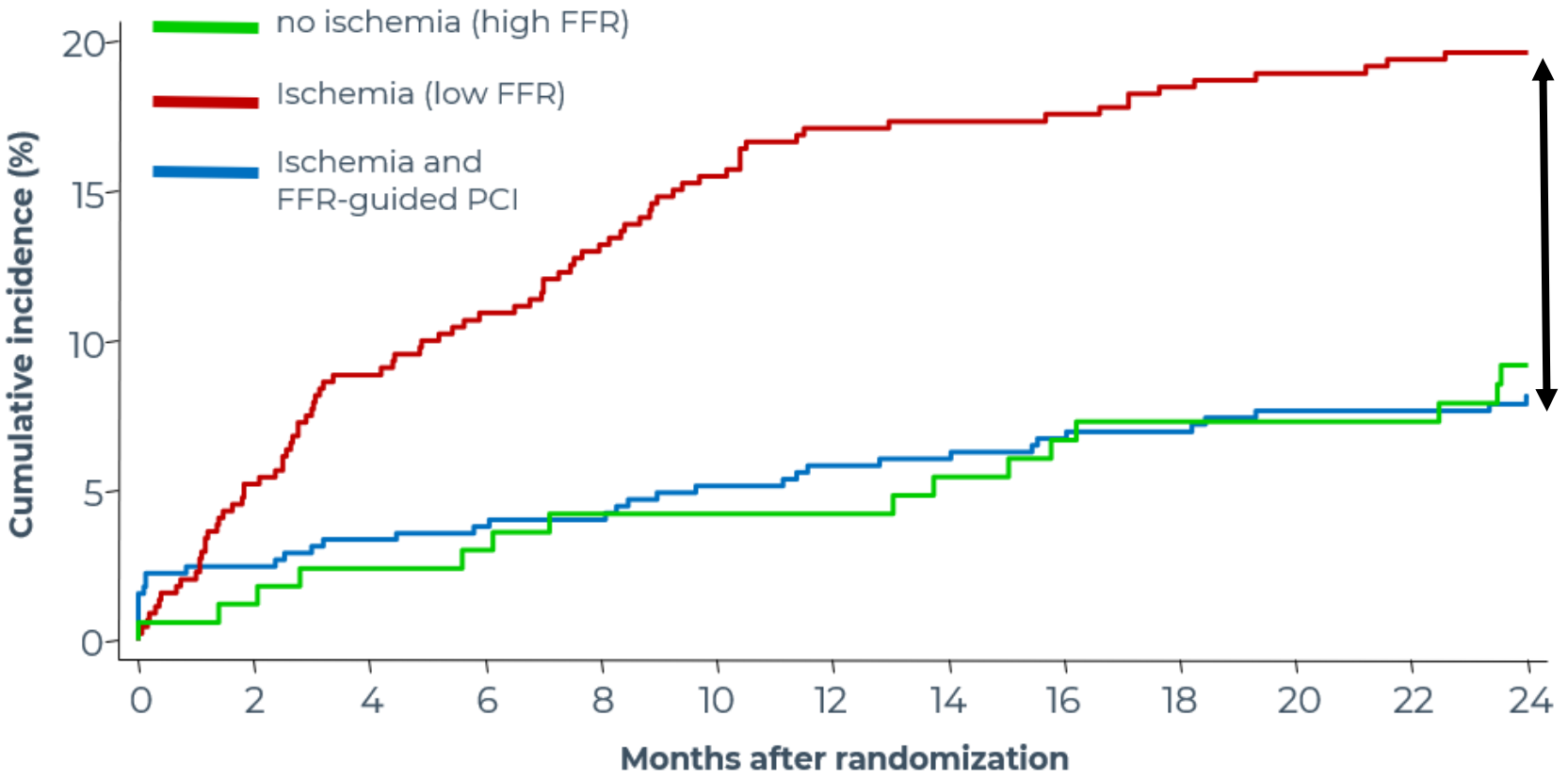
No. at risk

MT	441	417	398	389	379	369	362	360	359	355	353	351	297
PCI+MT	447	434	429	426	425	420	416	414	410	408	405	403	344
Registry	166	164	162	160	157	157	156	153	151	150	150	150	122

De Bruyne et al, NEJM 2012, NEJM 2015; Xaplanteris et al, NEJM 2018

FAME 2: death, infarction, urgent revascularization

N = 1220



Benefit of FFR-guided PCI

No. at risk

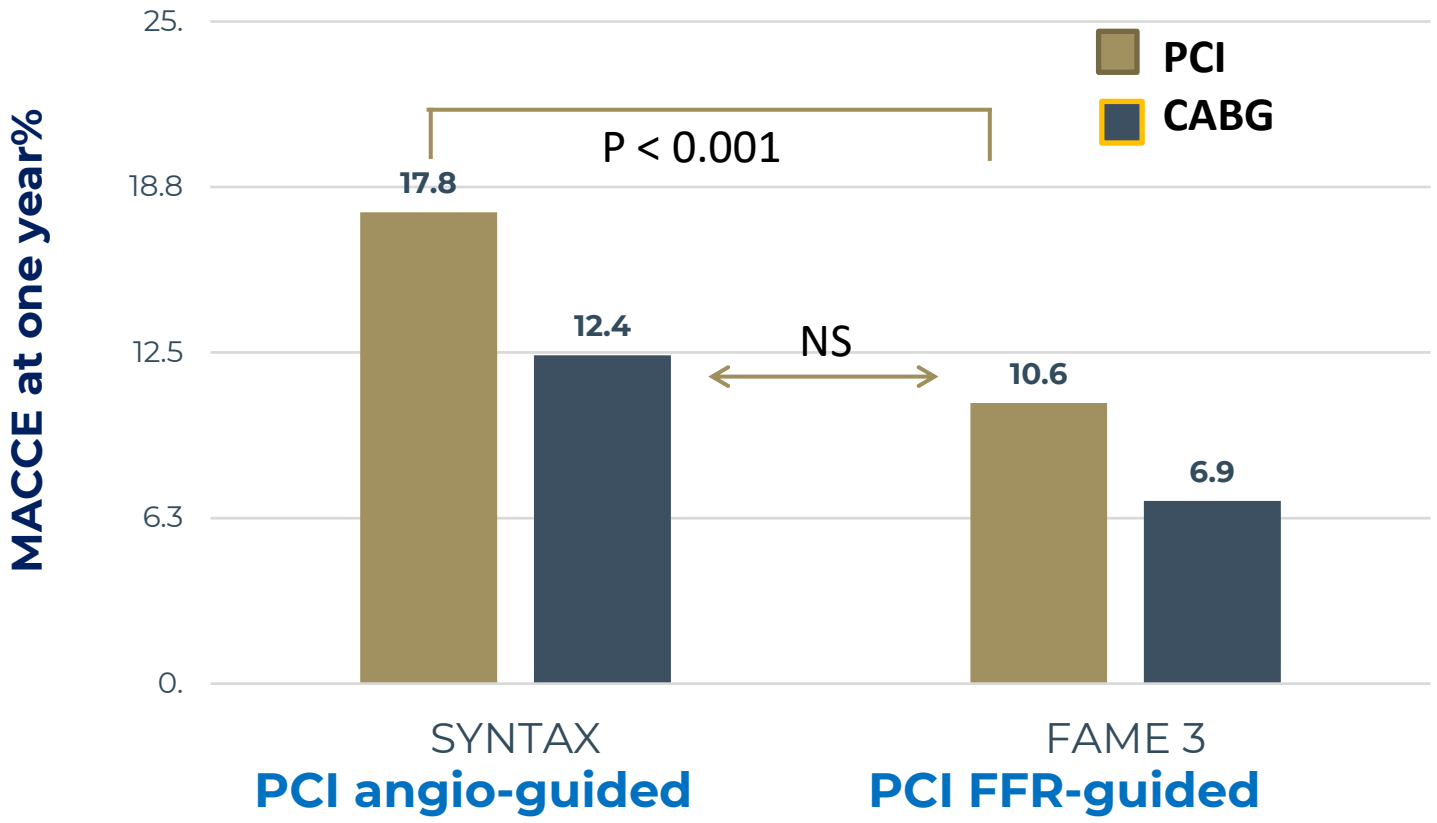
MT	441	417	398	389	379	369	362	360	359	355	353	351	297
PCI+MT	447	434	429	426	425	420	416	414	410	408	405	403	344
Registry	166	164	162	160	157	157	156	153	151	150	150	150	122

De Bruyne et al, NEJM 2012, NEJM 2015; Xaplanteris et al, NEJM 2018

SYNTAX and FAME-3 studies (N = 1500)
(optimal revascularisation in 3-VD)

MACCE at 1 year

(Death, MI, stroke, or repeat revascularization)



Fearon et al. NEJM 2021 Serruys et al. NEJM 2009

FFR and clinical outcome

Similar results are corroborated in hundreds of RCT's and large Registries, e.g very systematic

IRIS Registry from Korea (Jung-Min Ahn, SJ Park , et al, Circulation 2017; 135: 2241-2251

Spin-Off of FFR And Future Perspectives

- Resting indices *(Pd/Pa, iFR, dPR, RFR, etc)*
  (no hyperemia mandatory, but more often false-negatives: focal lesions in large coronary arteries)

- IMR *(Index of Microvascular Resistance)*

- Angio-Derived FFR *(to be further validated, no outcome data yet)*

- FFR by CT *(truly non-invasive FFR, well validated, positive clinical outcome data, also in terms of triage and cost-efficiency)*

…..and more recently a new paradigm …….!

- Absolute Flow and Microvascular Resistance, Absolute CFR, and ***MRR (Microvascular Resistance Reserve),*** the new standard for quantifying microvascular disease

→ Symposium ***"Opening The Black Box of The Microcirculation"***
Tomorrow (Monday) 4.30-5.50 pm Coronary Theater (*including live case from Aalst, B*)

Take Home Messages from 30 years of FFR:

- **Anatomy alone is insufficient to understand the physiologic significance of coronary artery disease**
- **FFR (and derived indices) provide superior insights in coronary pathophysiology and greatly improve the correct diagnosis of coronary artery disease**
- **There is incontrovertable evidence for improved outcome of coronary disease and revascularisation by dedicated use of FFR**

Catharina Hospital, Eindhoven, NL

1600 FFR cases per year…

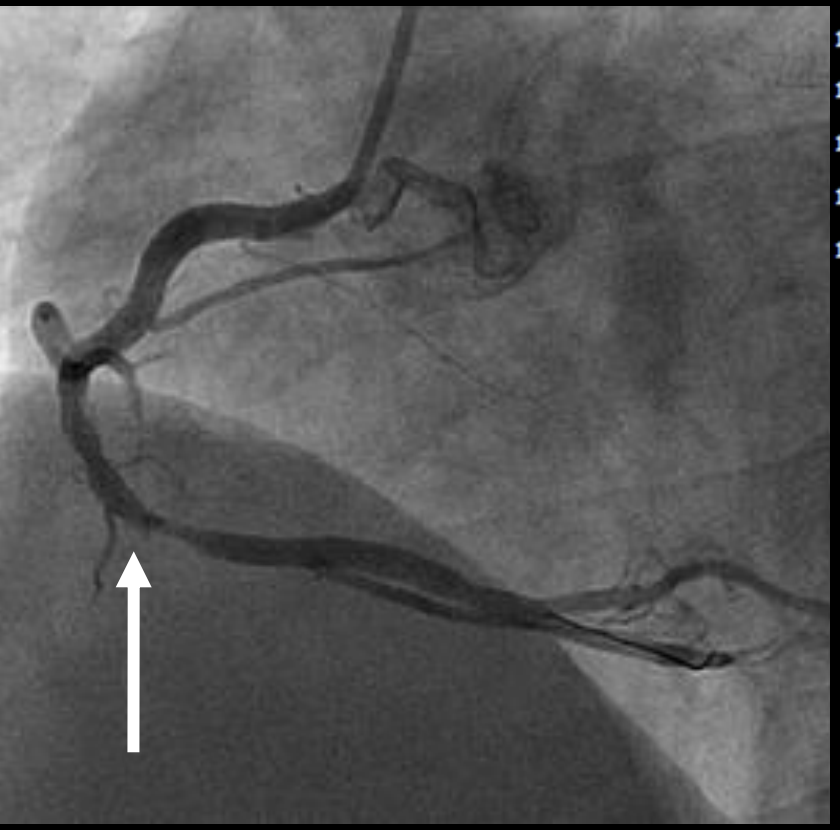
It’s a pleasure to measure pressure

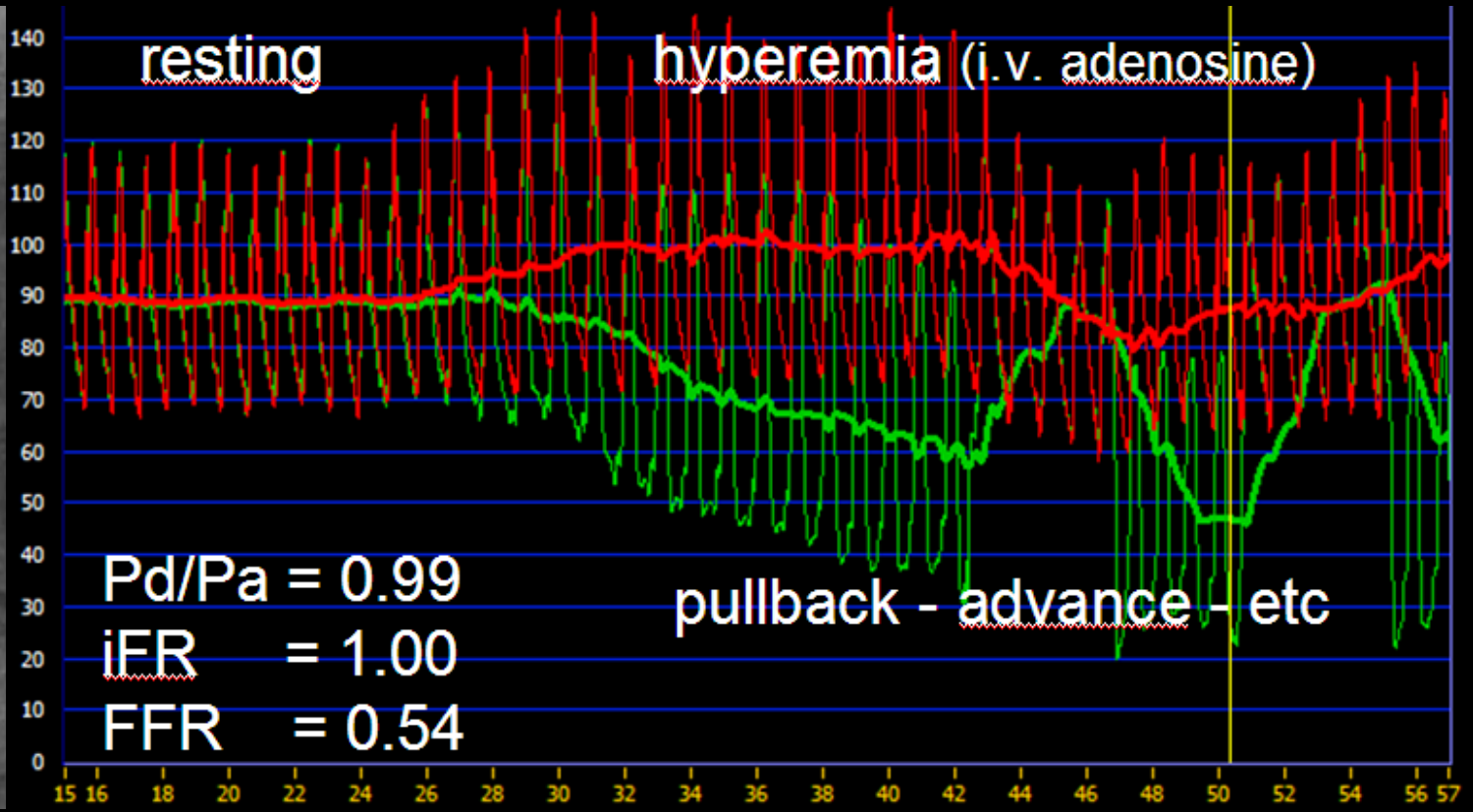
Is hyperemia mandatory?

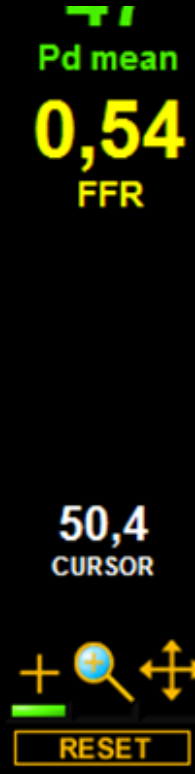
- In low-risk groups of patients, leaving out hyperemia may be non-inferior to FFR
  (diagnostic accuracy ~ 85% versus 95% for FFR)

- But in particular in **proximal lesions** in **large coronary arteries** in rather **young patients**, missing a significant stenosis by iFR is not uncommon *(and increases mortality!)*.

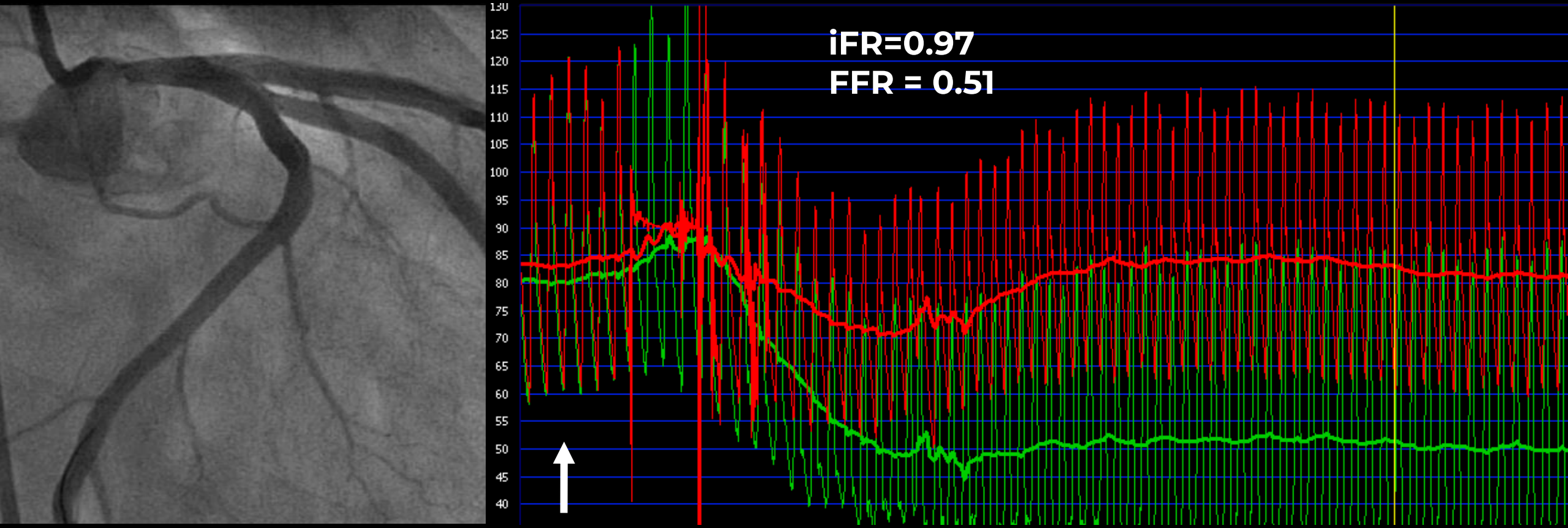
Young male, large RCA, 70%





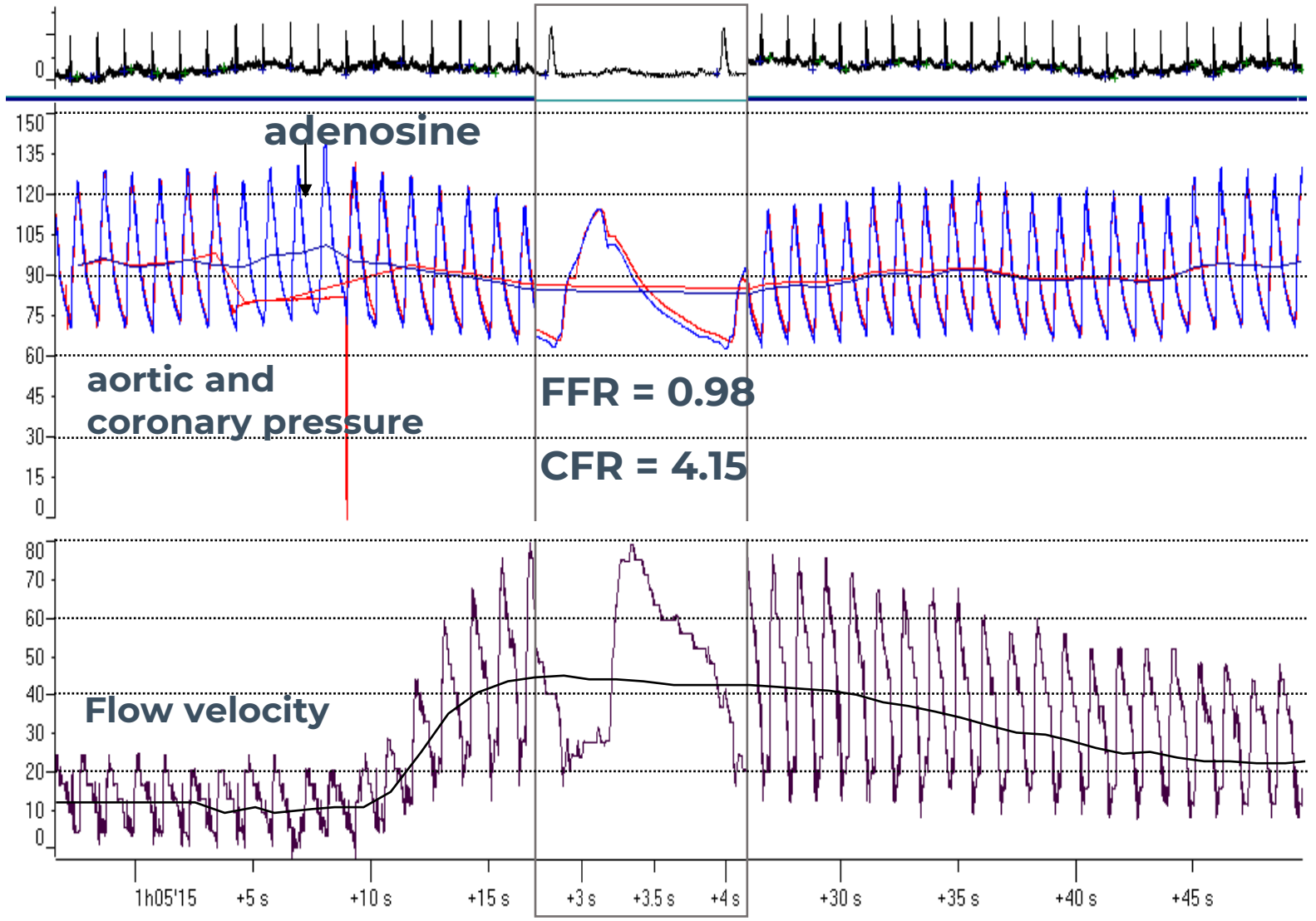


Middle-aged woman, 50% LM

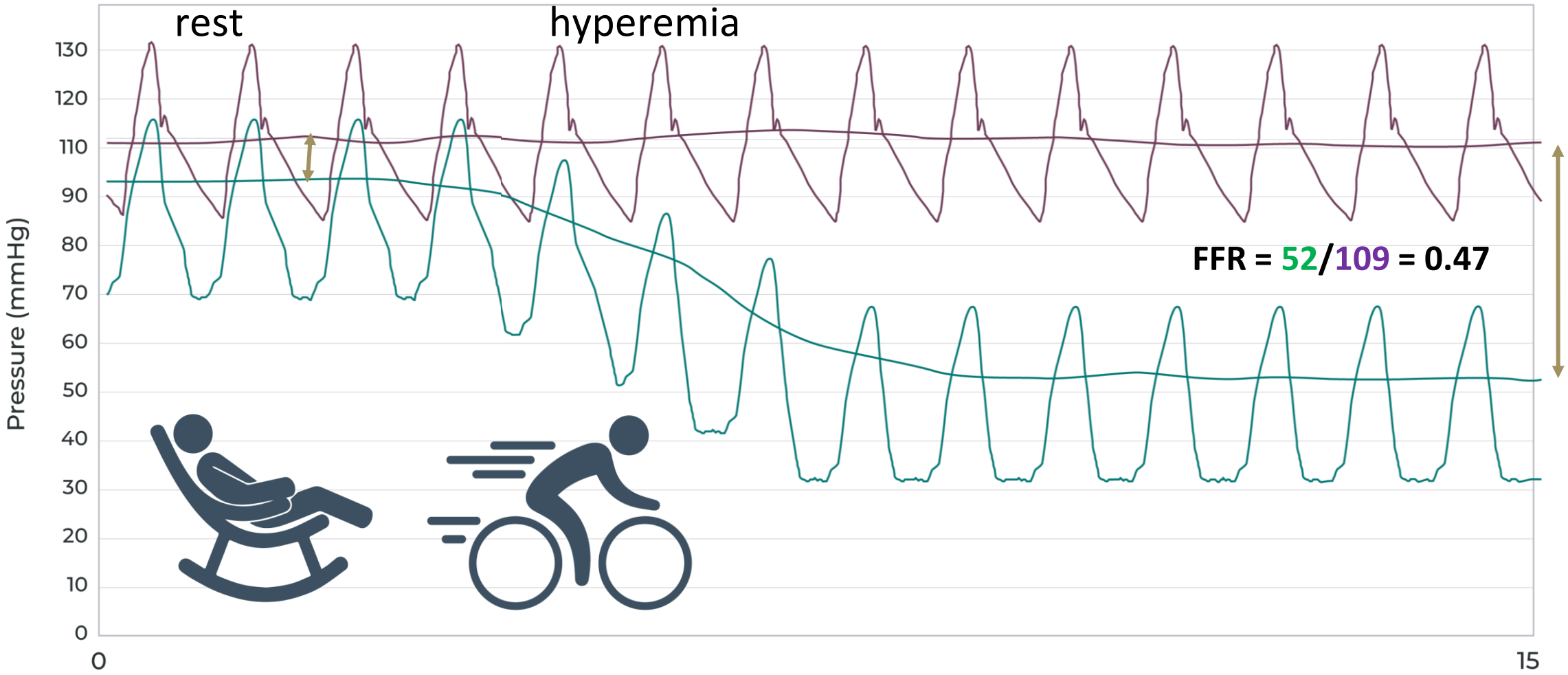


Normal coronary artery (young woman with PFO)

FFR ~ 1.0



Fractional flow reserve in clinical practice



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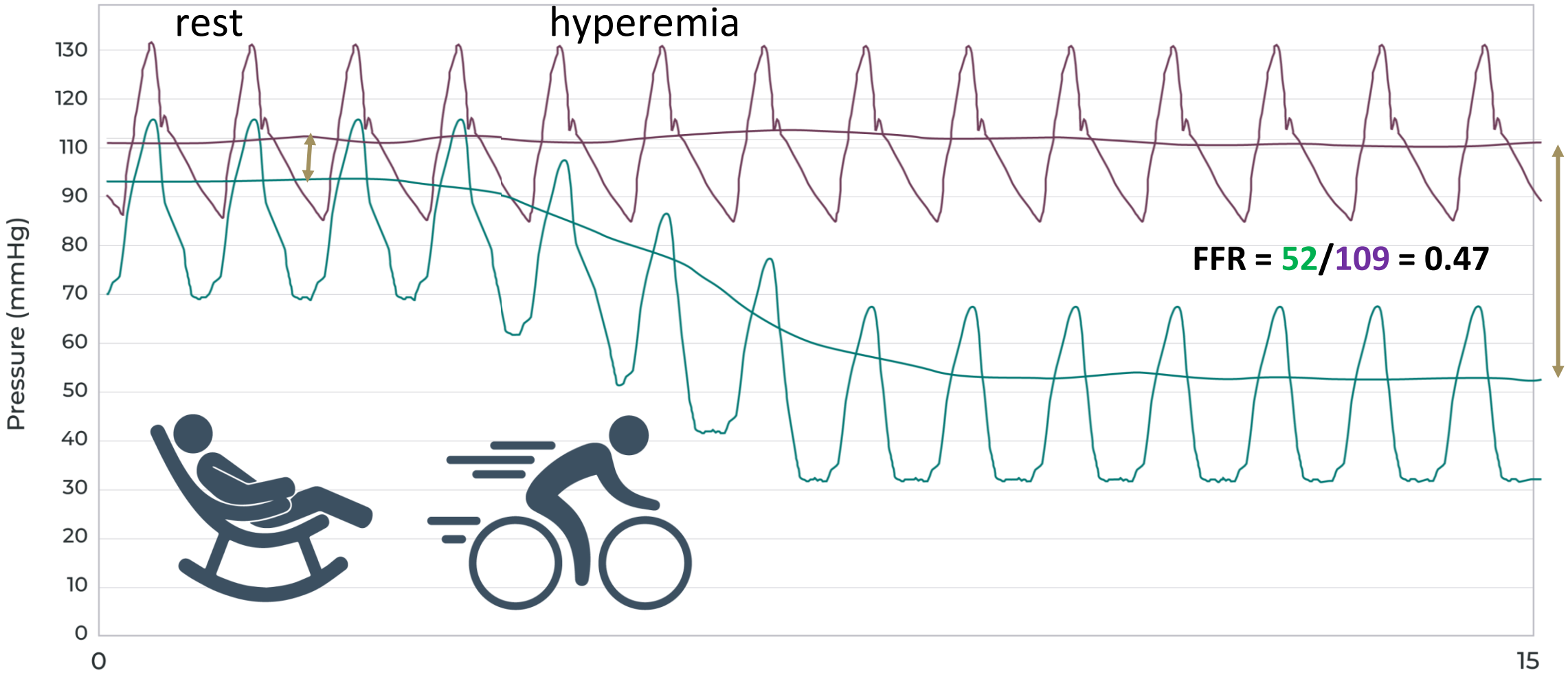

Noem bij clinical outcomne IRIS en FRAME (beide Korea)