Master of The Masters Award Lecture

50 YEARS OF CORONARY PHYSIOLOGY

A Magnificent Journey

Incheon, April 26th, 2024

CATHARINA-ZIEKENHUIS

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catharina ziekenhuis

Disclosure

- Institutional Research Grants from Abbott
- Consulting relations and fees from Abbott and Coroventis
- Minor equity in Philips, ASML, Heartflow, and General Electric
- Member of the Scientific Advisory Board of Heartflow
- Patents pending in the field of the Coronary Microcirculation and Aortic Valve Stenosis.

50 Years of Coronary Physiology

- In the sixties, awareness arose among scientists that coronary blood flow was regulated by a sophisticated physiologic system and held constant in resting conditions despite changes in perfusion pressure *(Mosher, Ross, Driscol, and others)*

- Similarly, it was observed that blood flow could increase in response to increased demand

- And it was suggested that such **“autoregulation”** could play a role to maintain resting blood flow normal in case of coronary artery stenosis

- These assumptions were experimentally validated and synthesized into a coherent theory by the seminal work of Lance Gould in 1974, who introduced the concept of Coronary Flow Reserve and paved the road for “applied coronary physiology” in the human catheterization laboratory

50 Years of Coronary Physiology

Gould

CFR

1974

videodensitometry

eighties

Pijls & De Bruyne

FFR

1993

Fearon

IMR

bolus thermodilution

1999-2001

Davies

iFR

2011

Pijls & De Bruyne

MRR

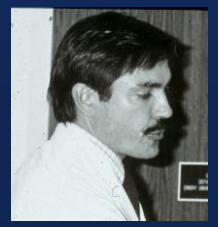
2021

2024

1976

Gruntzig

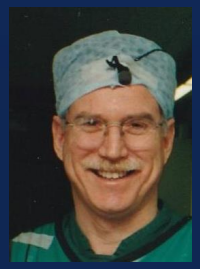
PCI



1990

Kern

Doppler wire



Yock

Mintz

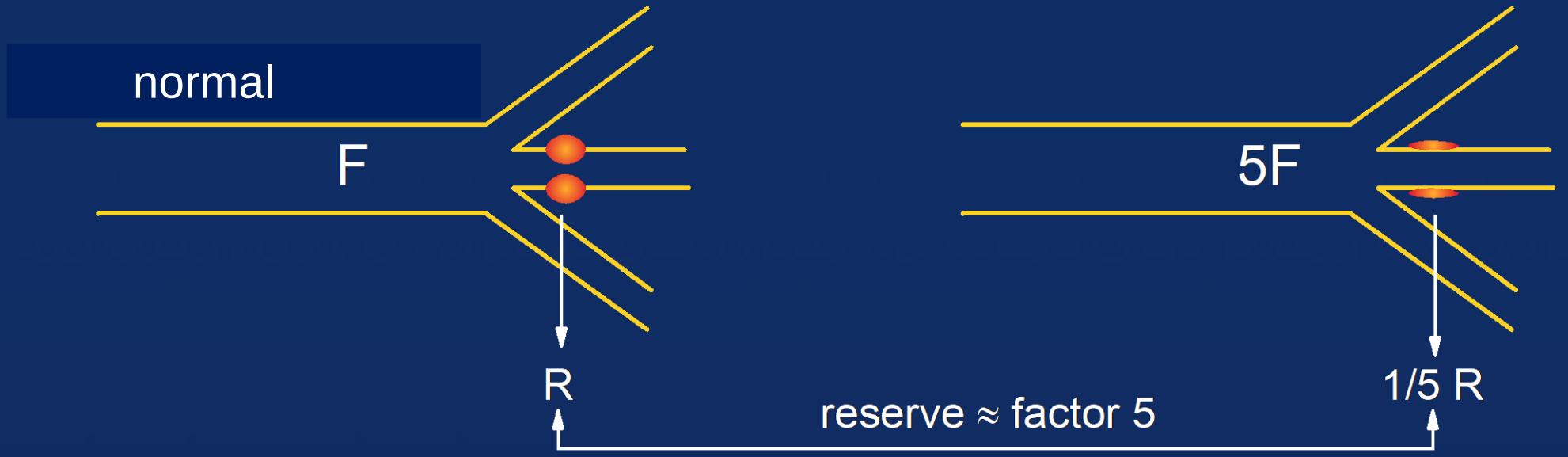
2016

absolute flow by continuous thermodilution

FAME studies

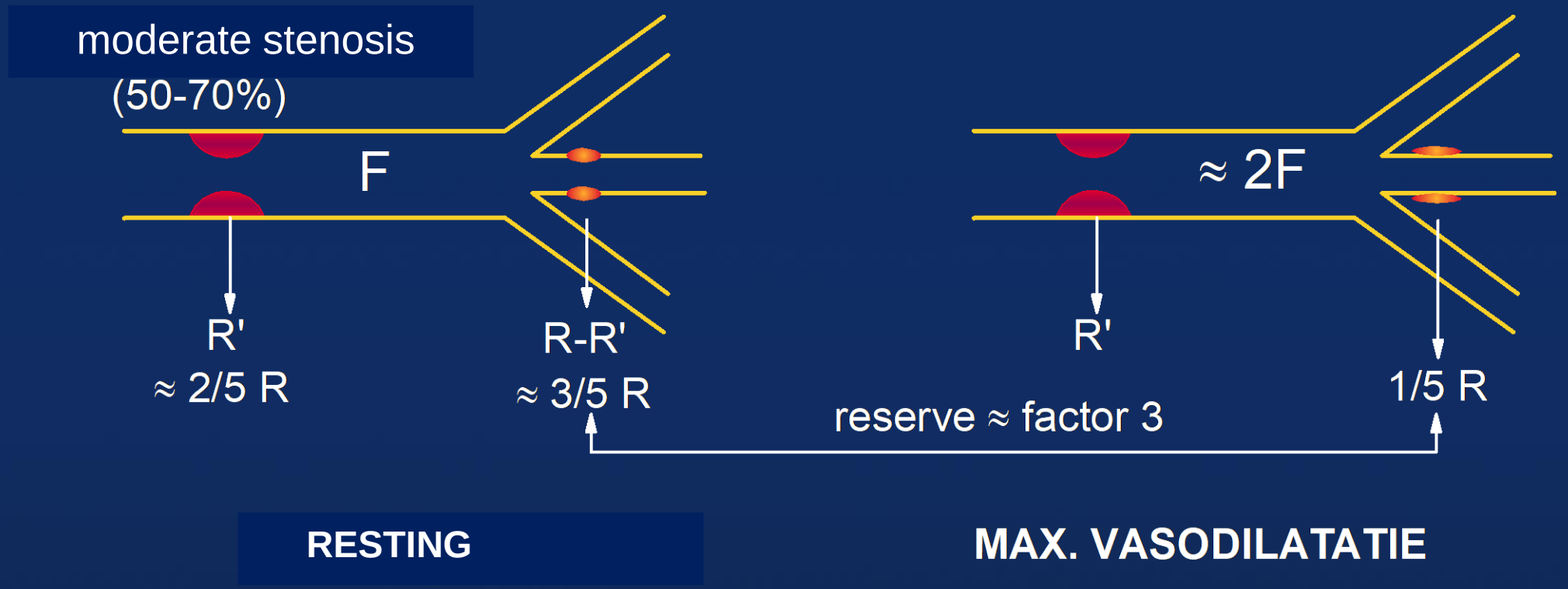
Intracoronary Imaging (IVUS, OCT)

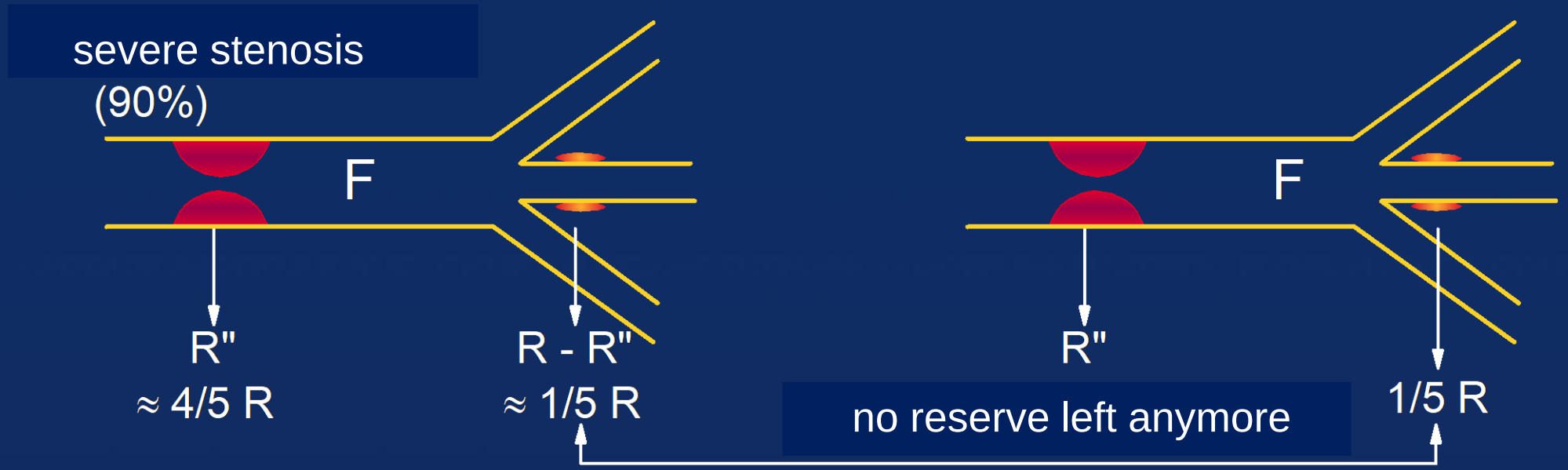
Autoregulation of Coronary Blood Flow



RESTING

MAX. VASODILATATIE


moderate stenosis
(50-70%)
F
R'
≈ 2/5 R
R-R'
≈ 3/5 R
≈ 2F
R'
1/5 R
reserve ≈ factor 3
RESTING
MAX. VASODILATATIE



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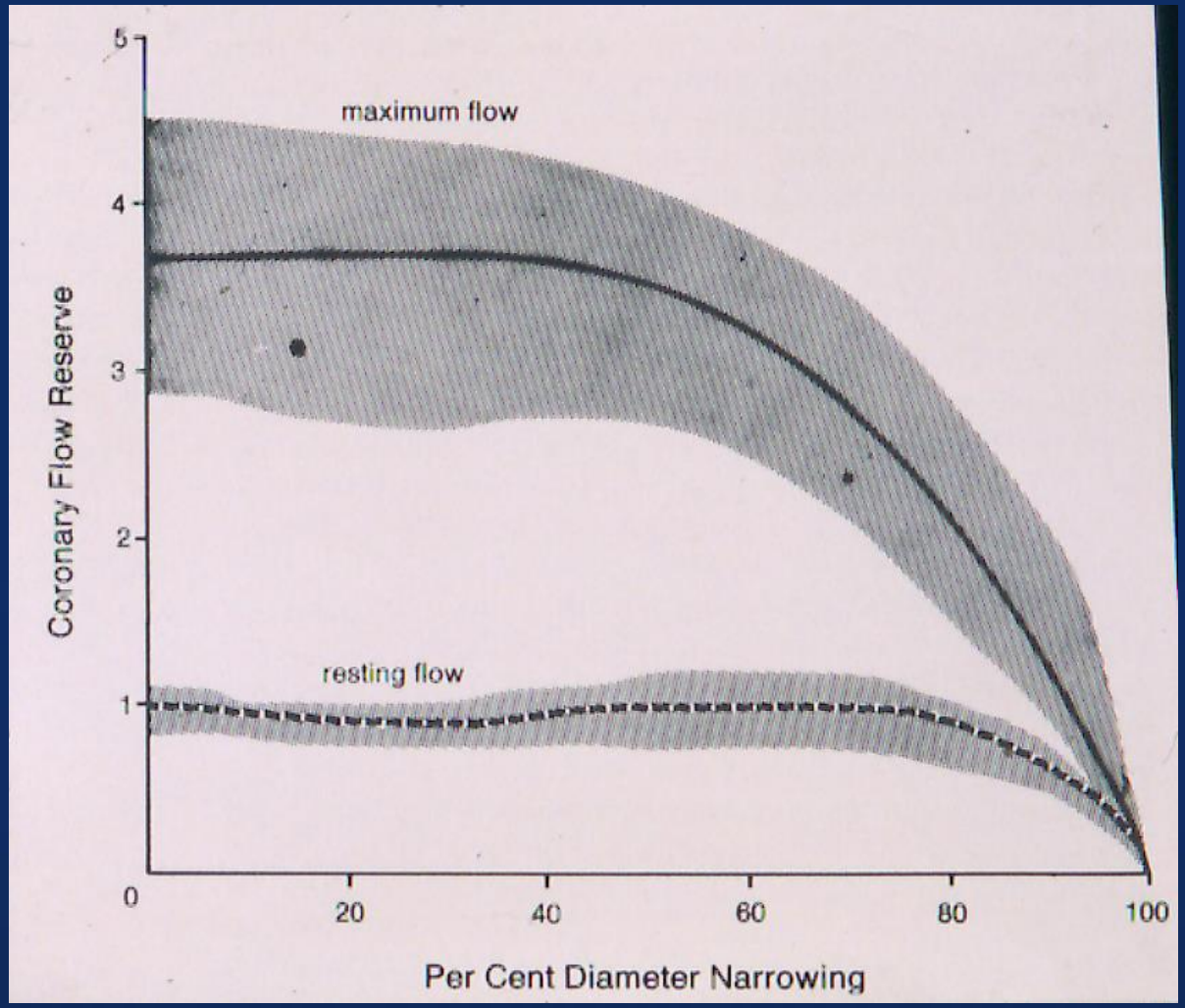
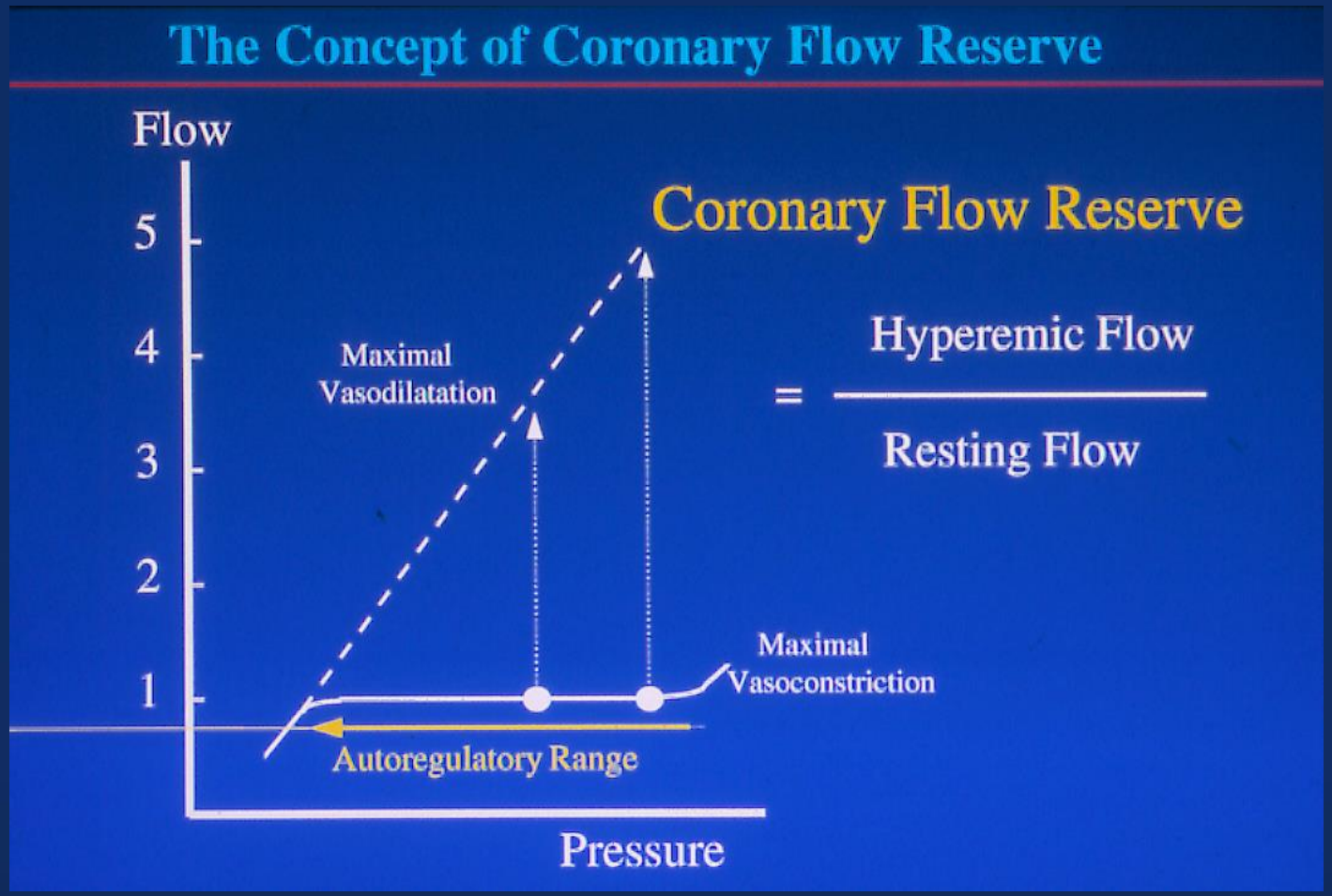


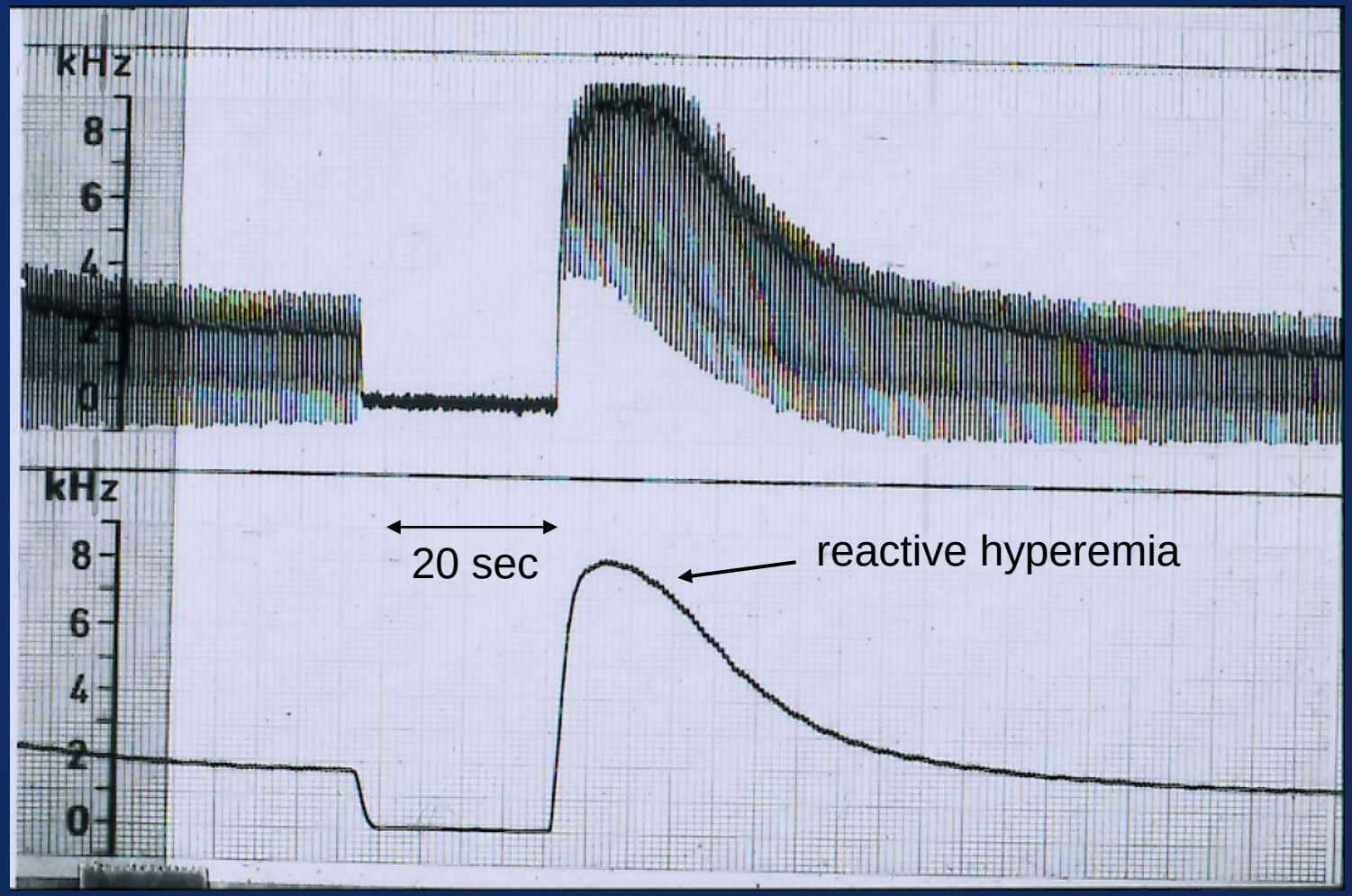
Coronary Flow Reserve (*at any degree of stenosis)*
was defined as maximum blood flow divided by resting blood flow

K.Lance Gould, Circulation 1974



In a similar way, Gould concluded that without a stenosis, resting flow was kept constant over a wide range of driving pressure (Pa) from 50 to 130 mmHg, whereas maximum flow was linearly related to the driving pressure.

Gould, Hoffman, and others, 1974 - `1982



The only way for creating maximum hyperemia in those days, was “reactive” hyperemia after 20” of occlusion. No safe pharmacological hyperemic drugs were available

From Pijls et al, Circulation 1990

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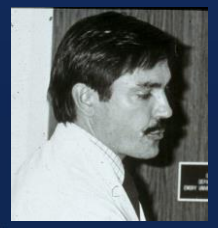

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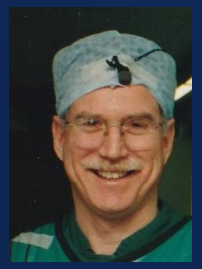

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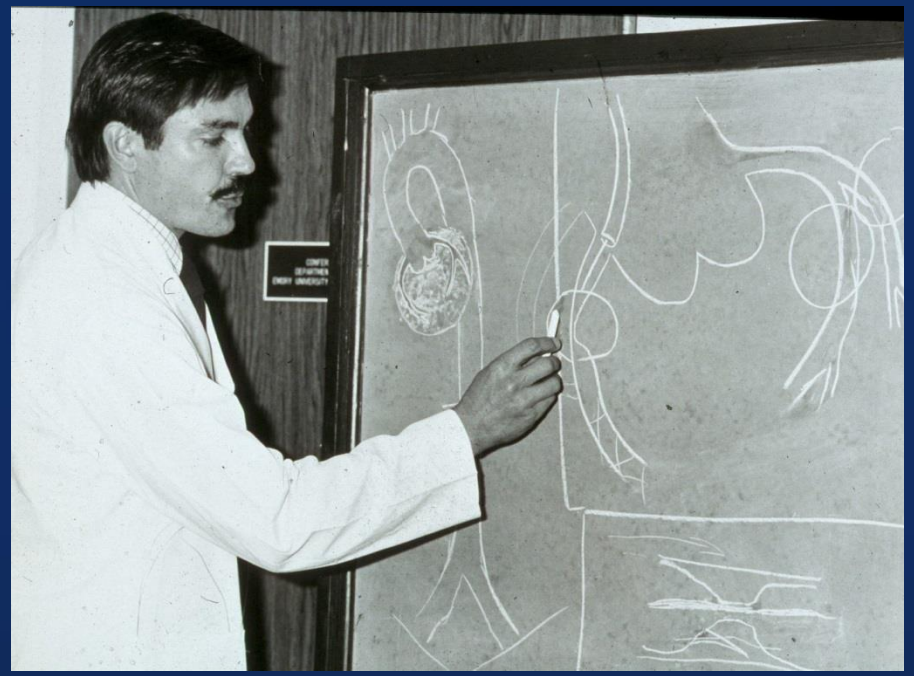
absolute flow by continuous thermodilution

FAME studies

Intracoronary Imaging (IVUS, OCT)

In the late seveties, the world changed by the unsurpassed courage of Gruentzig who opened the gate for applied coronary physiology in conscious humans



Gruentzig was greatly interested in coronary pressure and tried to measure (kind of resting) coronary pressure by his ballon catheter routinely.

Andreas Gruentzig, Zurich, 1979:
“I wished I could measure hyperemic pressure, but the resting gradient is all I have now”

Next, with the introduction of monorail balloon systems the interest in direct coronary pressure measurements faded away for more than 10 years

By the *introduction of QCA in the eighties*, cardiologists hoped that the shortcomings of coronary angiography to account for physiologic significance of a stenosis, would disappear.

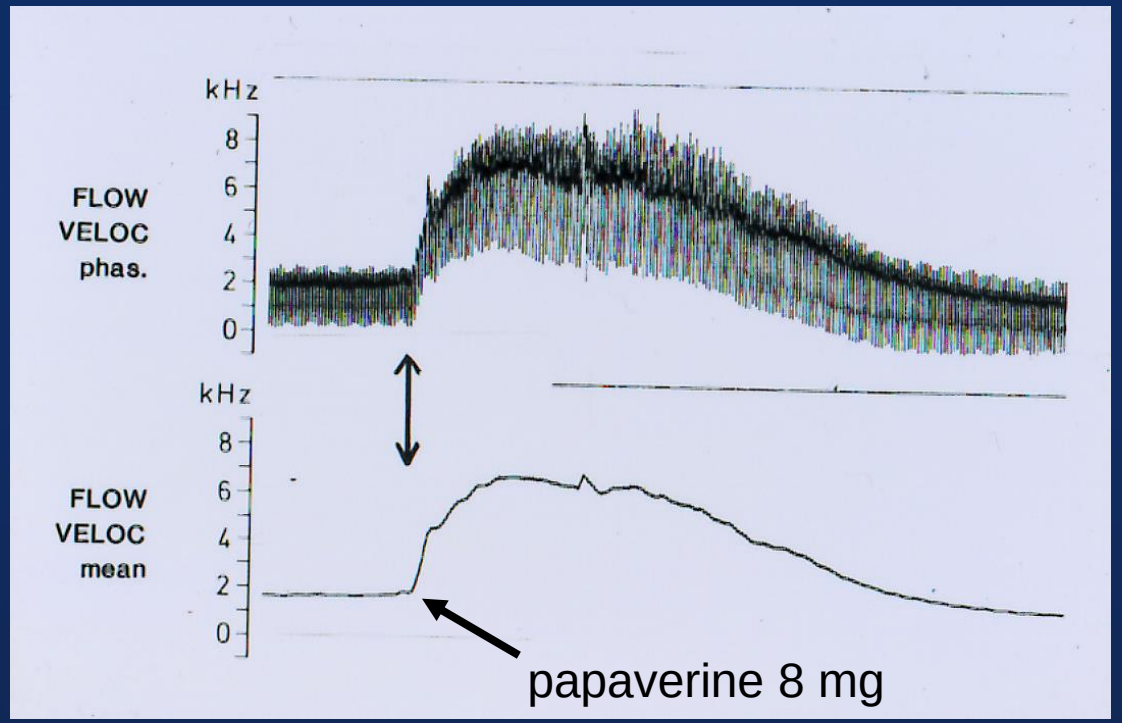
Nothing was less true !!!!

- the mismatch between coronary anatomy and functional significance of a stenosis was *not* improved by QCA
- It became more and more clear that *not the morphology* of the lesion is decisive for having angina, but the decrease of (maximum) blood flow
- coronary autoregulation in humans remained a virtual concept for the time being.

In the late eighties, Bob Wilson and Melvin Marcus in Iowa validated reliable hyperemic agents in humans during cardiac catherization, enabling maximum hyperemia in the cathlab and opening the road to more extensive physiologic investigations in human coronary arteries

Maximum vasodilatory stimuli

- papaverine i.c.
- adenosine i.c.
- adenosine i.v.
- ATP i.v.



Wilson RF, Marcus M, several papers, Circulation, 1985 and 1989; Pijls, Circulation 1990; De Bruyne, Circulation 2002

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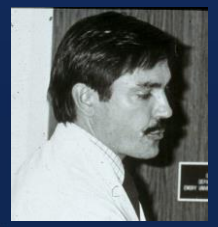

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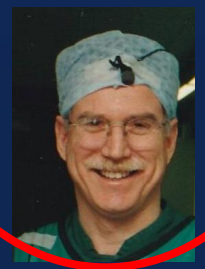

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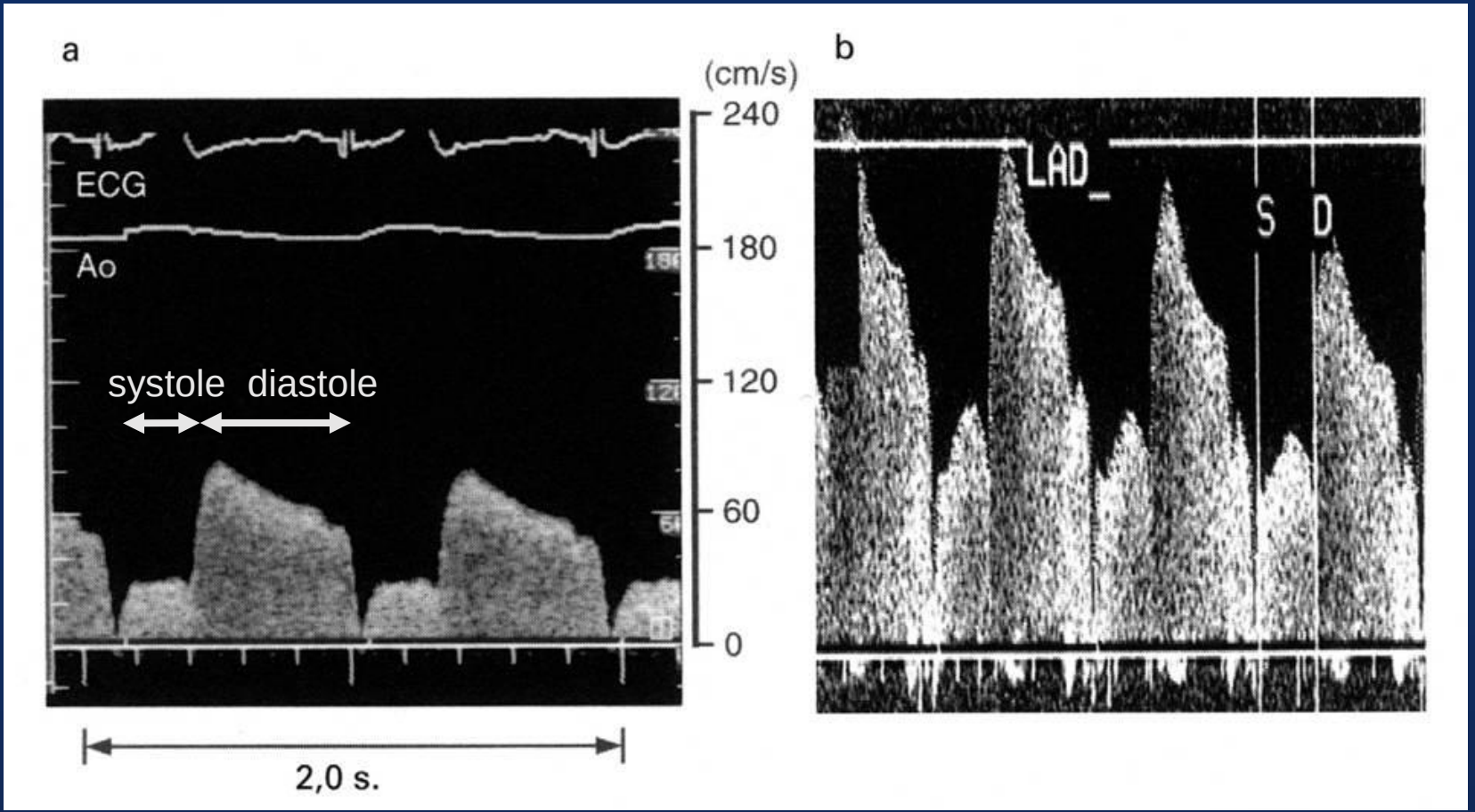
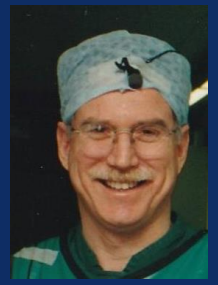
FAME studies

Intracoronary Imaging (IVUS, OCT)

Around 1990, ***Morton Kern*** for the first time measured intracoronary blood flow velocity directly by an 0.014” Doppler guidewire, compatible by contemporay PCI equipment, and investigated CF(V)R in humans as a measure of functional stenosis severity



Flow velocity signals in a coronary artery at resting conditions and at maximum hyperemia (note the difference between systole and diastole)



By the work of Kern and others, knowledge about coronary physiology, the influence of a stenosis, and improvement after PCI rapidly increased and the Doppler wire became the standard tool for a while for “physiology in the cathlab” by measuring CF(V)R

However, in the next years it was realized that…….:

- CFR can vary considerably within one patient due to changes in “resting flow” and blood pressure, making interpretation of CFR rather difficult.
- CF(V)R is not a specific index for the epicardial stenosis but is also influenced by the microcirculation
- CFR by Doppler is often difficult to measure reliably: in at least 30% of patients no reliable tracing could be obtained *(“week 22 study”)*

……...and the necessity was felt to have an index which is specific for the epicardial disease and easy to measure in 99% of all patients

→ **FFR**

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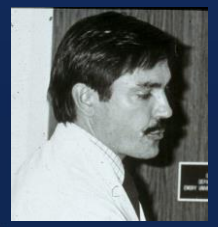

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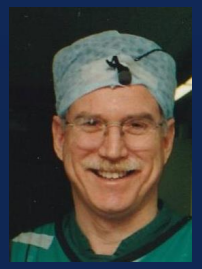


Yock

Mintz

Intracoronary Imaging (IVUS, OCT)

Basic Principles of Fractional flow reserve

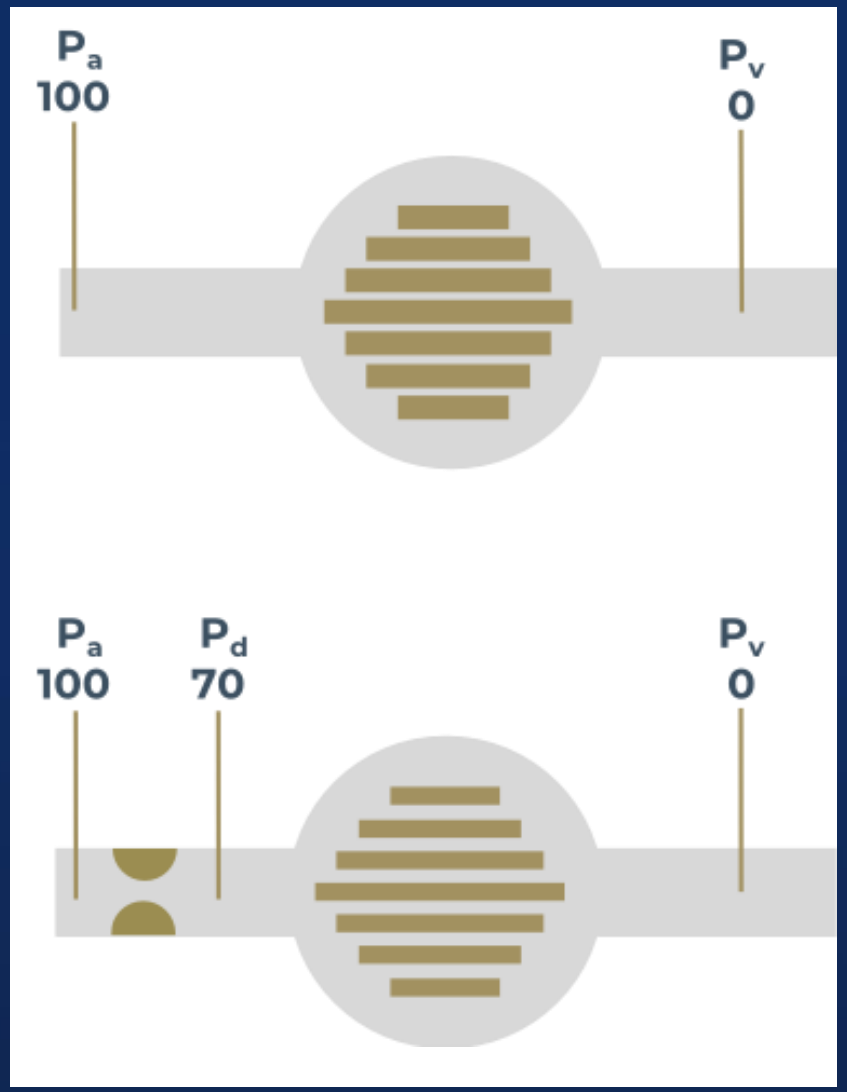
- It is not resting flow, but ***maximum achievable flow*** which determines the functional capacity (exercise tolerance) of a patient

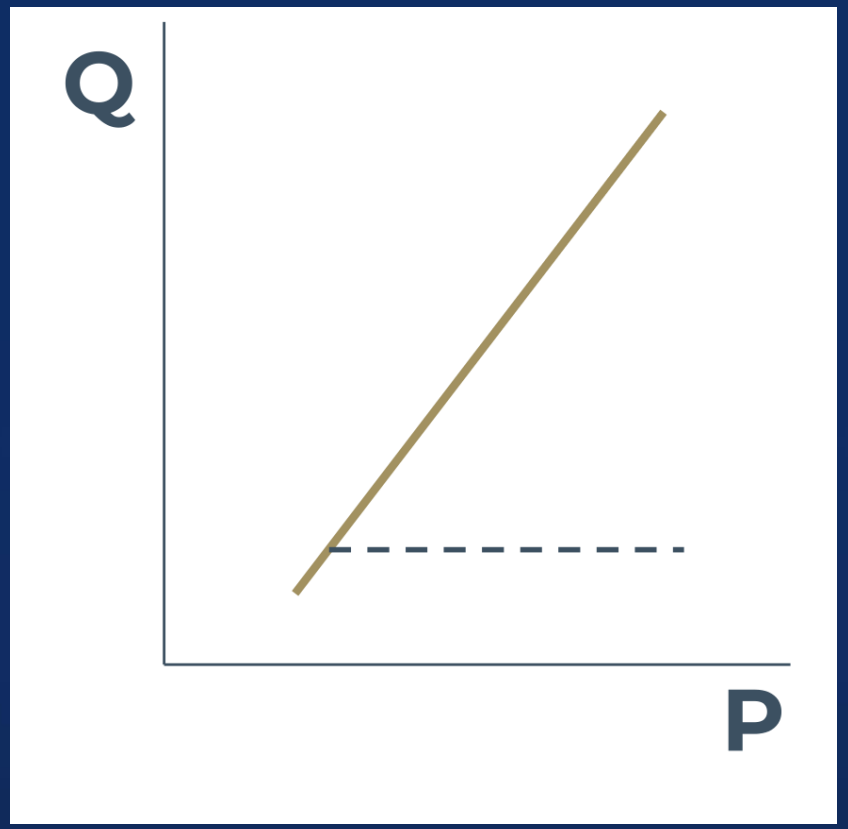
- At maximum vasodilation (corresponding with maximum hyperemia or with maximum exercise), blood flow to the myocardium is linearly proportional to *myocardial perfusion pressure (~hyperemic distal coronary pressure)*

Consequently:

Fractional Flow Reserve is defined as maximum achievable blood flow in the presence of a coronary stenosis as a ratio to normal maximum flow
(i.e maximum flow in the hypothetical case that the artery were completely normal)

During maximal hyperemia:



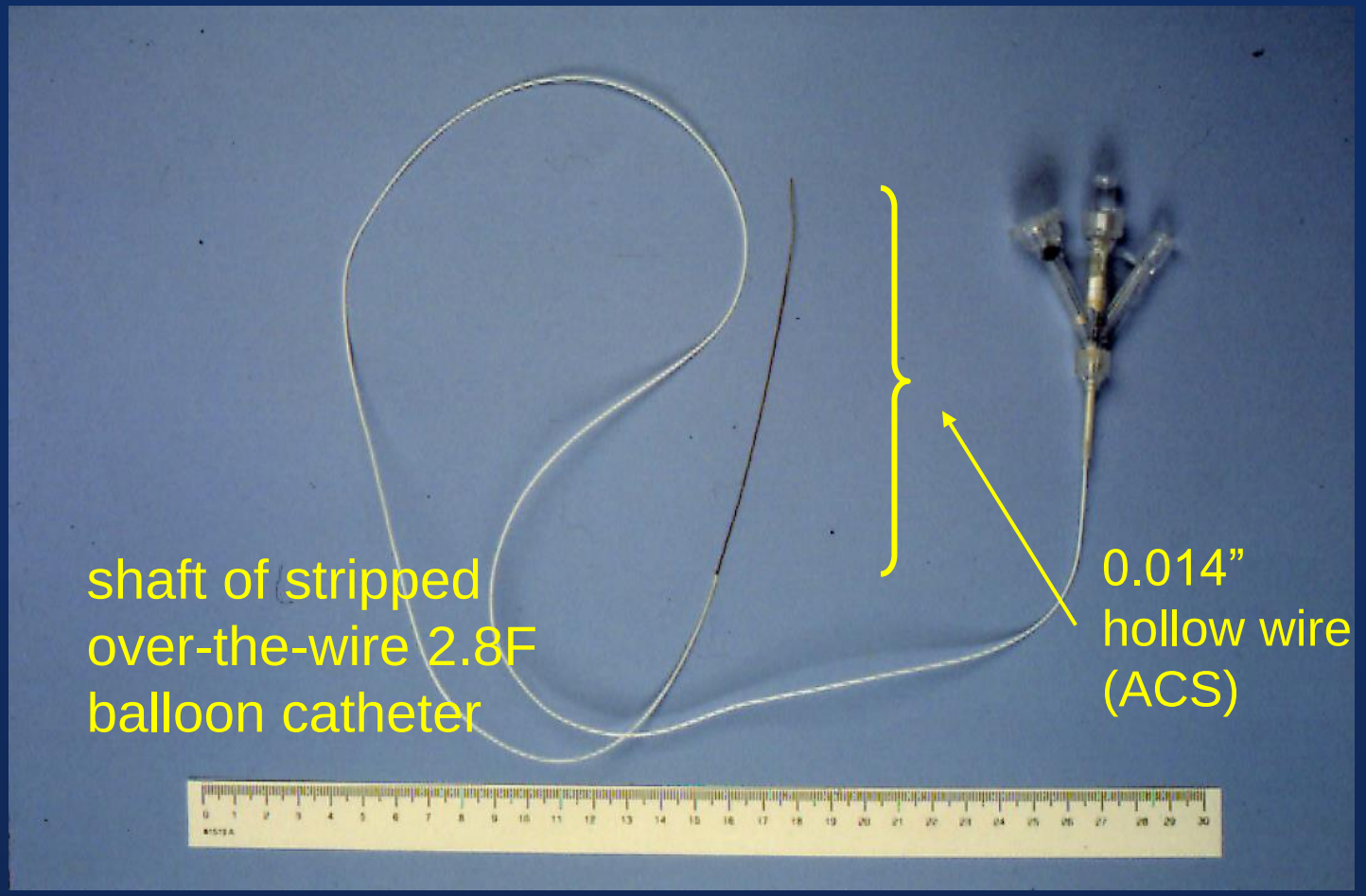


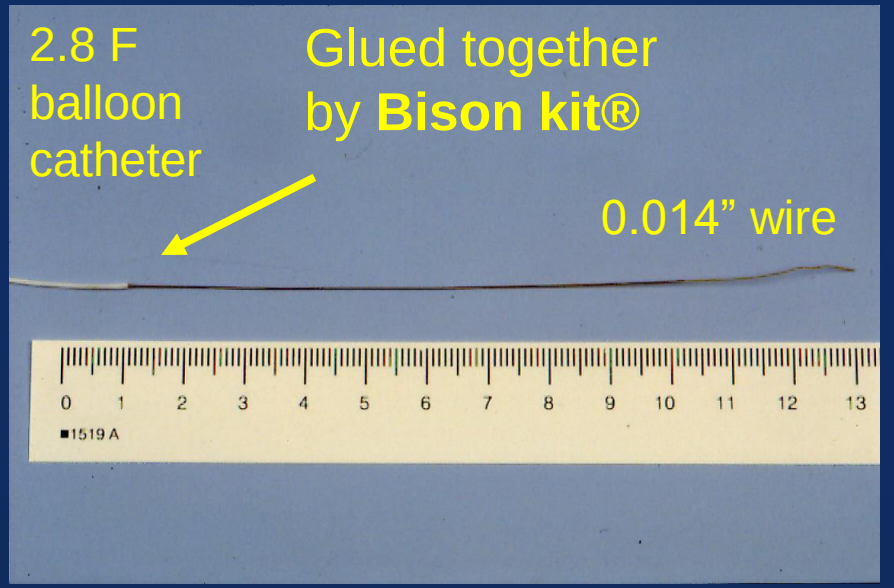
$$FFR_{myo} = \frac{P_d}{P_a} = 0.70$$

Major limitations in the first years:

- Few people believed it
- No commercial pressure wire available

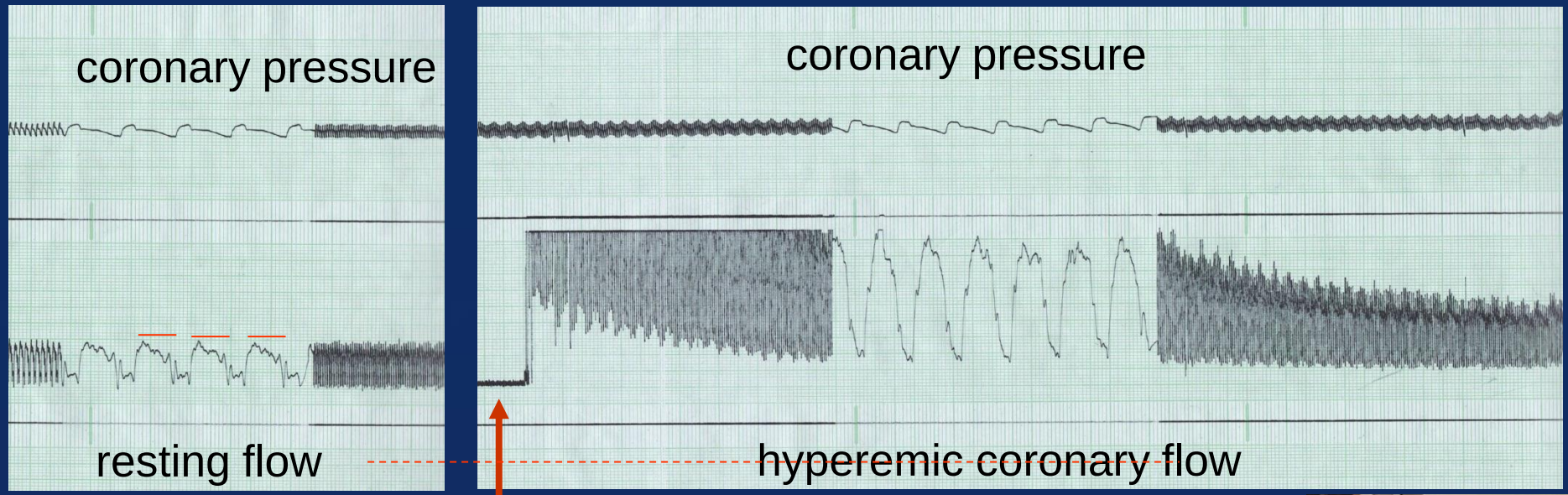
→ *First studies with home-made deviced “pressure wire”*

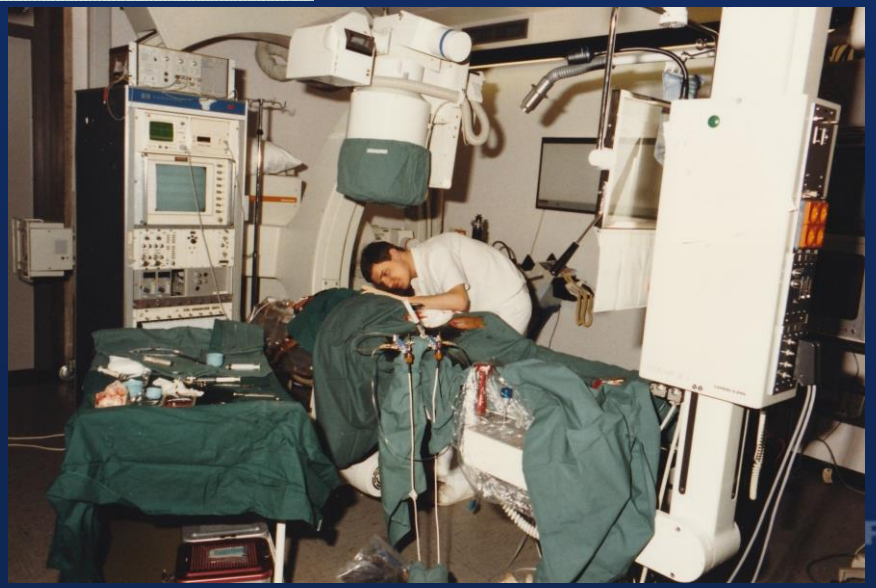




Produced on the kitchen table of the Pijls family in Malden, NL)
(Sterilized by Ethylene-Oxyde)

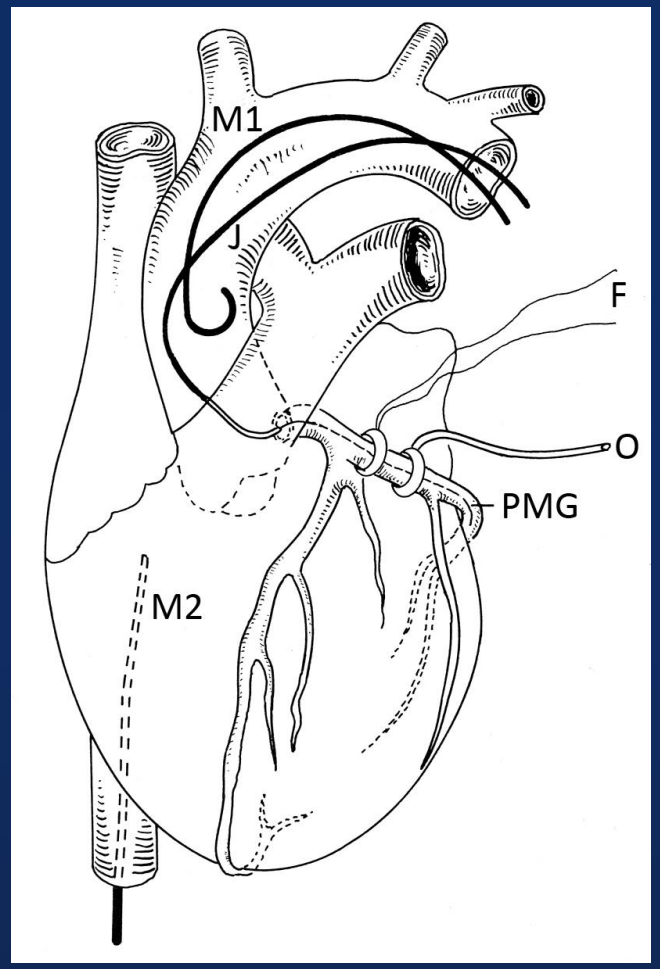
First measurement of truly phasic coronary pressure
by a (home-made) guidewire during rest and during hyperemia

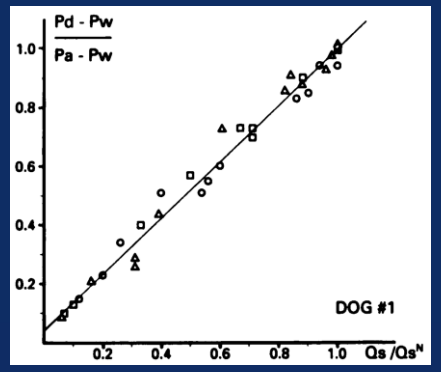


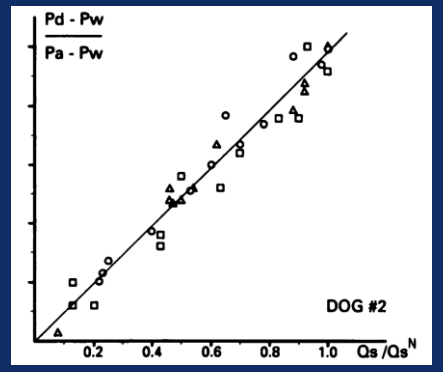


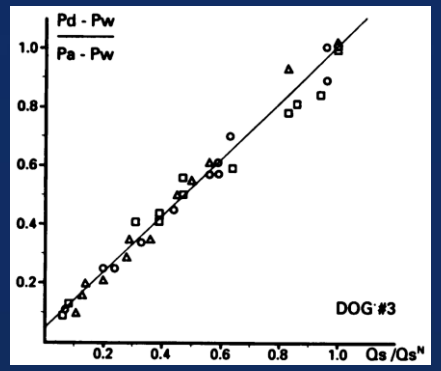
Pijls and De Bruyne, Circulation 1993

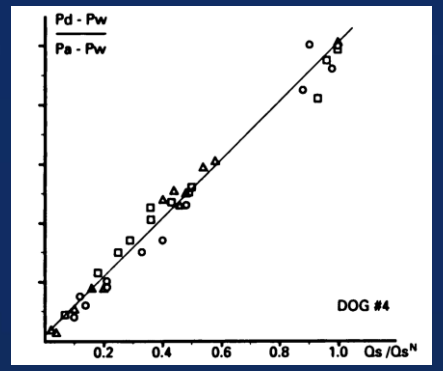
FFR: Experimental validation in experimental studies in dogs

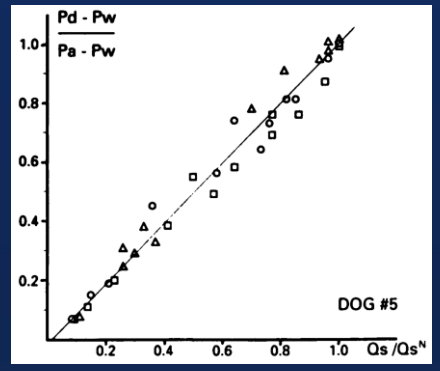












o = no medic.
Δ = phenylephr
□ = nipride

One – to – one relation between FFR calculated by pressure and FFR measured directly by flow, in all dogs

ánd FFR independant of changes in blood pressure, heart rate, and contractility

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

- Soon, *commercial* ***0.014"sensor-tipped Pressure wires*** came on the market
- (Pioneered by RADI Medical Systems)

- Over the years, these wires have been greatly improved and can be *used as primary PCI wires* in > 95 % of all cases

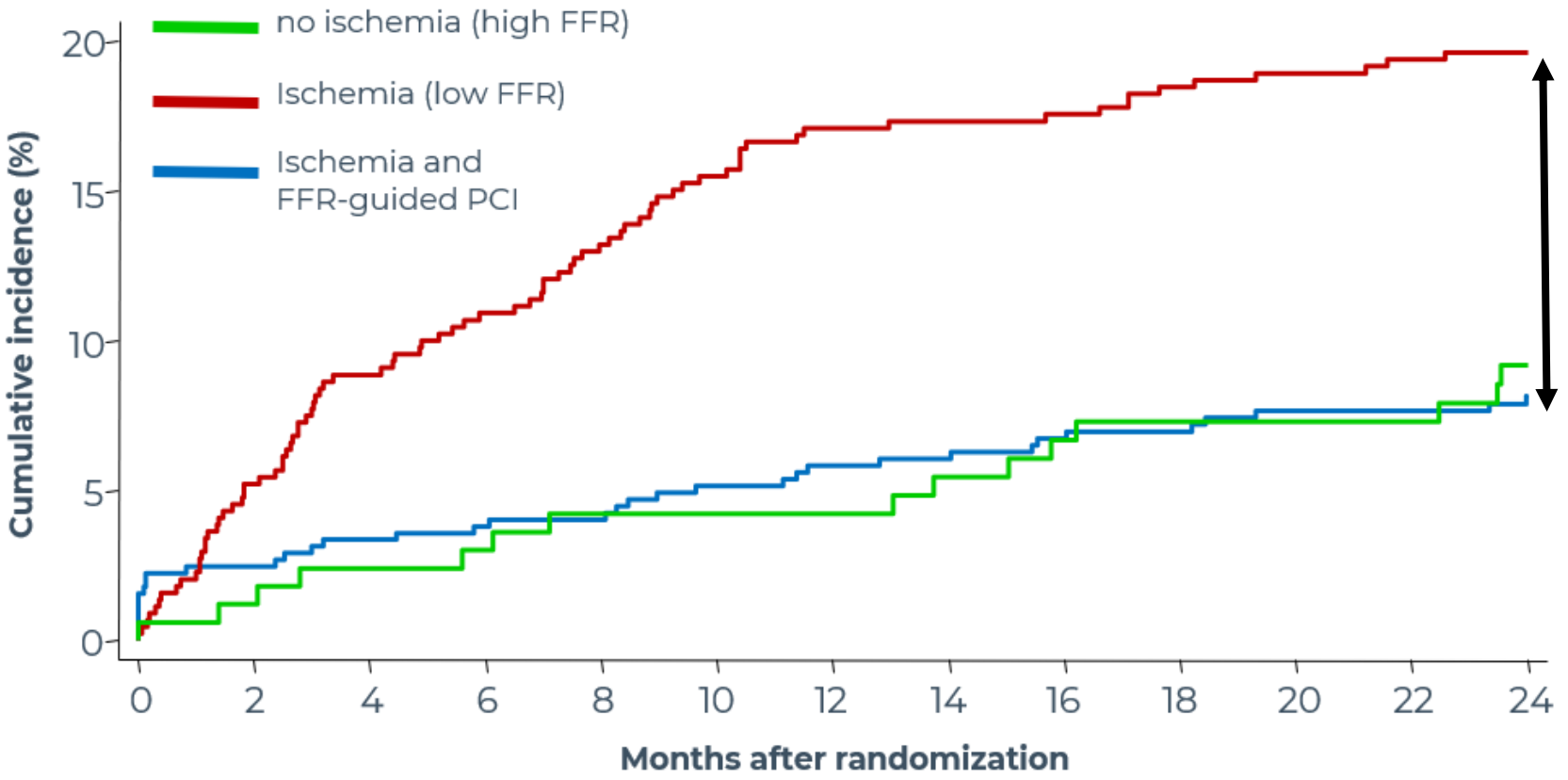
- All aspects of FFR have been *extensively validated* in hundreds of studies in humans

- *FFR is applicable in almost all clinical and angiographic conditions:*
  - multivessel disease
  - left main disease
  - bifurcations
  - ostial lesions
  - CTO
  - diffuse disease and tandem lesions (→ PPG index)

- And *FFR is the gold standard* for decisions with respect to presence of inducible ischemia and need for revascularization with *important consequences for outcome* (DEFER study, FAME 1,2,3 studies and numerous other RCT's

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

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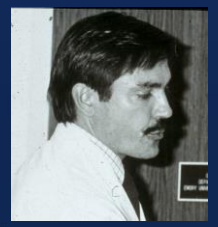

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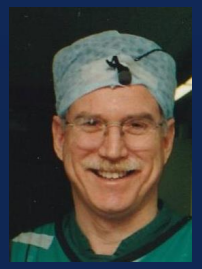

Paul Yock *Gary Mintz*

Intracoronary Imaging (IVUS, OCT)

1980 - 2010

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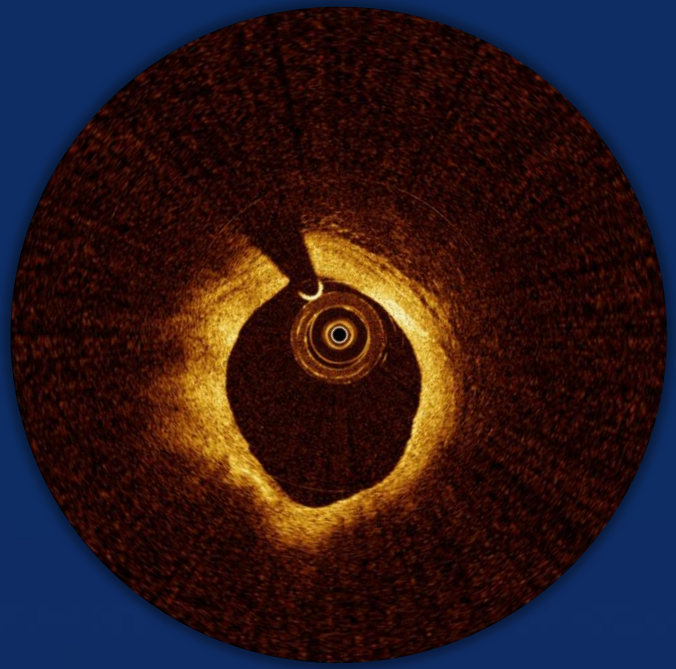
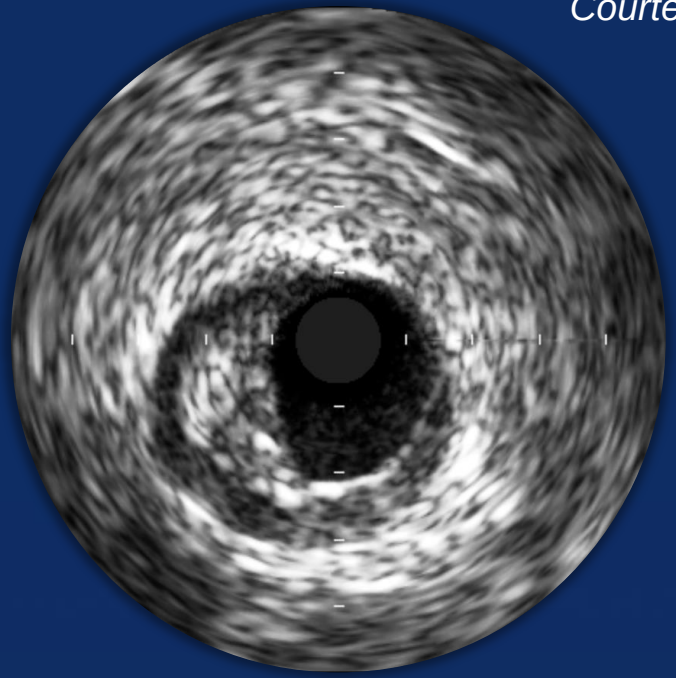
FAME studies

Courtesy of Dr Andersan, Gainesvill, FL





Although strictly spoken, ***IVUS and OCT*** are anatomic imaging methods, these techniques also taught us about structure and evolution of plaques, enhanced insight in what PCI does in coronary arteries, and were useful to optimize coronary intervention .

Recently published ***PREVENT study*** *is milestone:*
Discrimination of vulnerable plaques makes sense and PCI of such plaques improves outcome *(Park SJ, Ahn J-M, et al. Lancet April 8th 2024)*

The coronary microcirculation:

- In the last 20 years, awareness arose that - *in particular in women* – angina pectoris and coronary ischemia are not the exclusive domain of the epicardial arteries, but that also disease of the coronary microcirculation may play an important role

- Presently, it is believed that this may be the case in at least 25% of all patients.

- Microcirculatory disease can be structural (generalized atherosclerosis, post-MI, micro-emboli, LVH, etc), or functional (microcirculatory spasm or blunted dilatation in response to physiologic intrinsic transmitters) or a combination of both

How to assess microvascular disease ??

- CFR is decreased both with epicardial ánd microvascular disease → non-specific
- FFR is specific for epicardial disease and gives no info about the microcirculation

Are there "more specific" indices for the microcirculation ??

⟶ ***Principles of Bolus Thermodiltion and IMR***

CVRF

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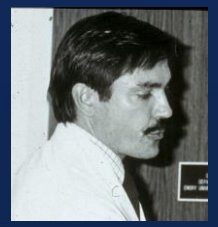

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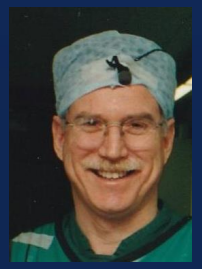

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50 Years of Coronary Physiology

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CFR

1974

Pijls & De Bruyne

FFR

videodensitometry

eighties

1993

Fearon

IMR

bolus thermodilution

1999-2001

2003

Davies

iFR

2011

Pijls & De Bruyne

MRR

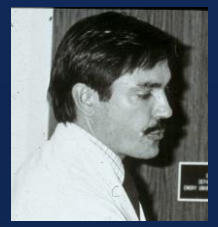
2021

2024

1976

Gruntzig

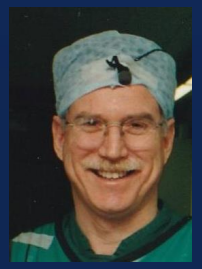
PCI



1990

Kern

Doppler wire



Yock

Mintz

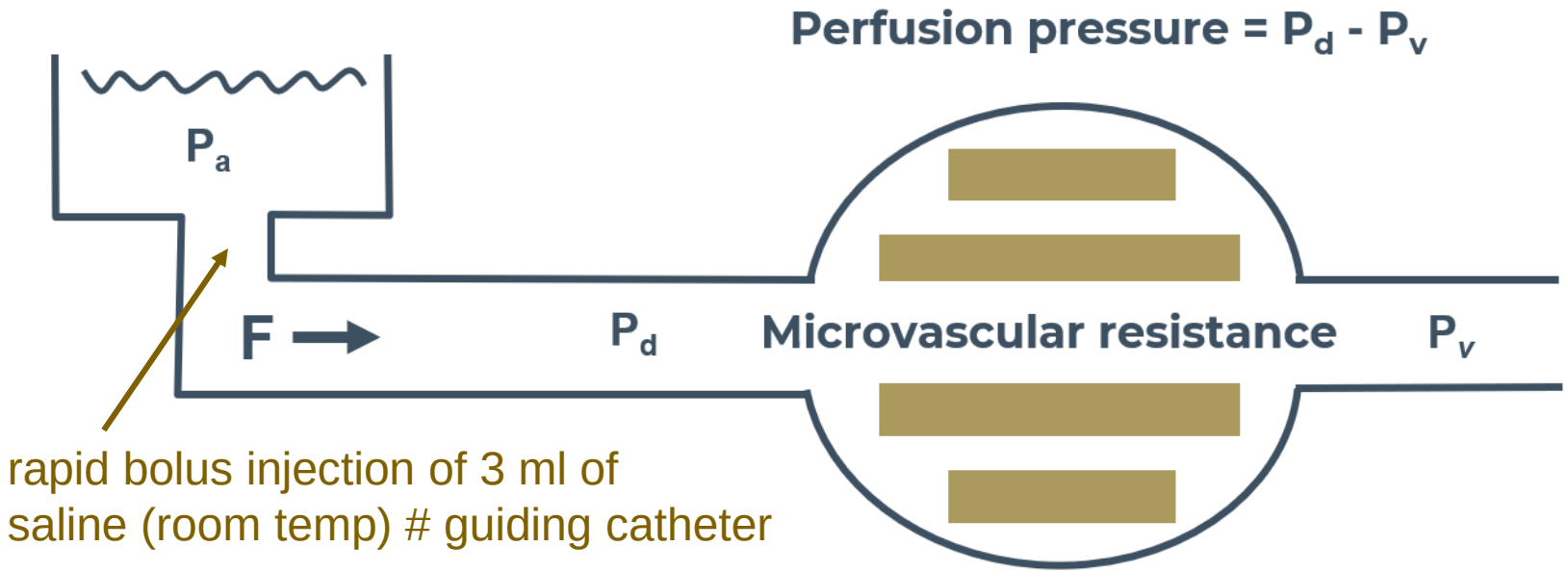
2016

absolute flow by continuous thermodilution

FAME studies

Intracoronary Imaging (IVUS, OCT)

Concept of index of microcirculatory resistance (IMR)



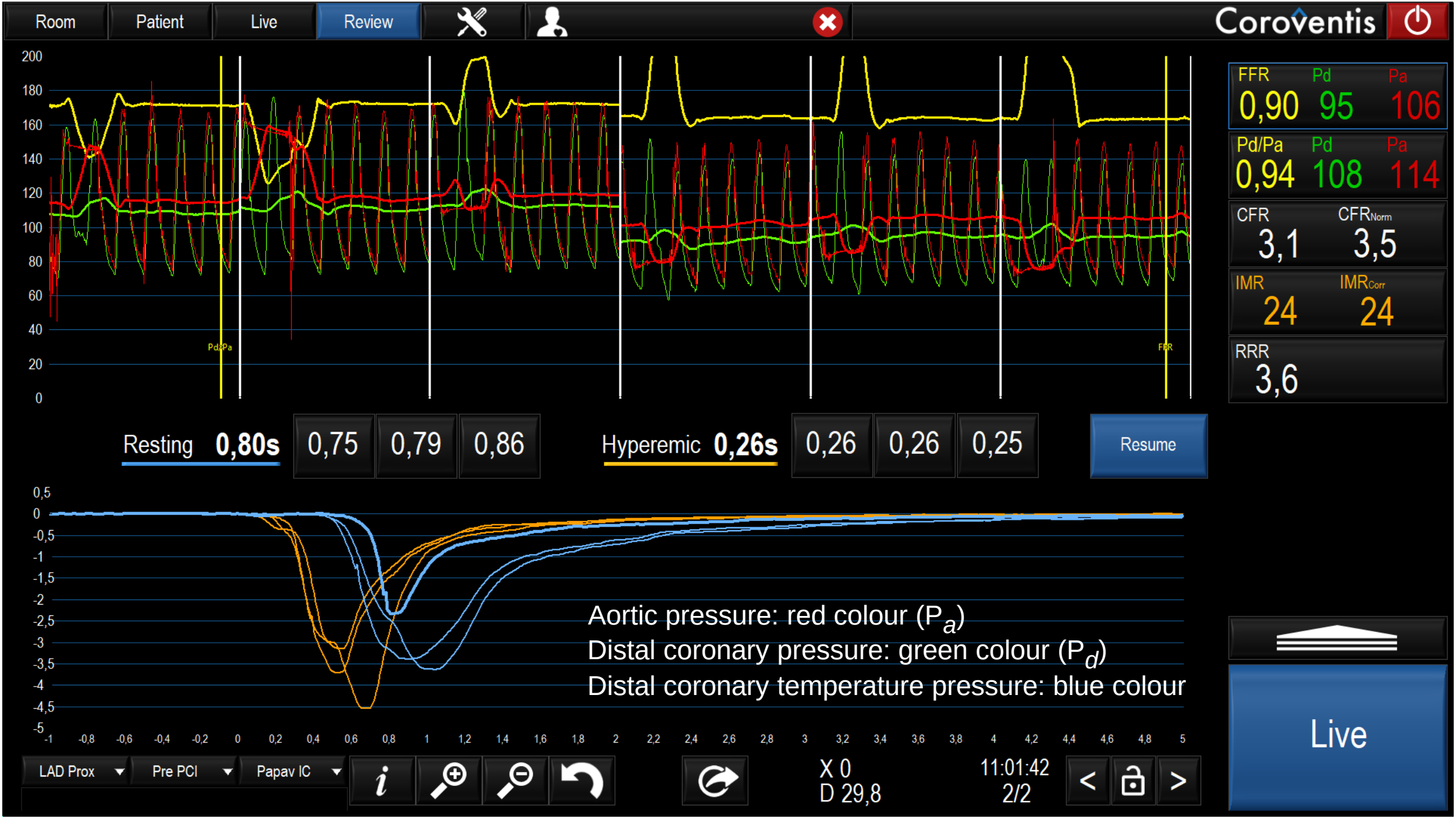
IMR

Microvascular resistance ≈ distal pressure / flow

at maximumhyperemia: **≈ distal pressure x hyperemic T_{mn}**

≈ P_d x T_{mn} ≈ IMR

Fearon WF et al. Circulation. 2003;107:3129–3132


Room
Patient
Live
Review
Coroventis
FFR 0,90
Pd 95
Pa 106
Pd/Pa 0,94
Pd 108
Pa 114
CFR 3,1
CFRNorm 3,5
IMR 24
IMRCorr 24
RRR 3,6
Resting 0,80s
0,75
0,79
0,86
Hyperemic 0,26s
0,26
0,26
0,25
Resume
Aortic pressure: red colour (Pa)
Distal coronary pressure: green colour (Pd)
Distal coronary temperature pressure: blue colour
LAD Prox
Pre PCI
Papav IC
X 0
D 29,8
11:01:42
2/2
Live

Index of Microcirculatory resistance (IMR):

- Is rather specific for the microcirculation
- but needs correction at higher degree of coronary stenosis *(Aarnoudse, Yong)*
- has been shown to have *prognostic significance, both in stable angina and post- STEMI*
- was the best we had during almost 20 years, but….

- *it reproducibility is far from optimal*
- *not always easy to determine (multiple repeated injections of saline)*
- *no direct measurement of microvascular resistance (R_μ)*

→ ***Volumetric measurent of absolute flow and resistance (R_μ) and Microvascular Resistance Reserve***

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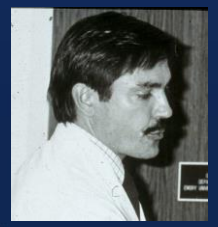

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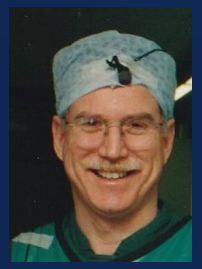

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Intracoronary Imaging (IVUS, OCT)

- Because FFR needs an hyperemic stimulus (adenosine or others),attempts have been made to make such measurements easier by trying to avoid the necessity of adenosine

- It was claimed in 2011 by Davies et al that during a so-called Wave-free Period during diastole, resting distal-to-proximal pressure ratio ***(called iFR***) would be equal to FFR over the complete heart cycle and could replace FFR

- The physiologic basis for such wave free period was lacking.

- Two large (almost) identical trials were started to demonstrate non-inferiority of iFR compared to FFR (*Define-Flair and SwedeHeart)*

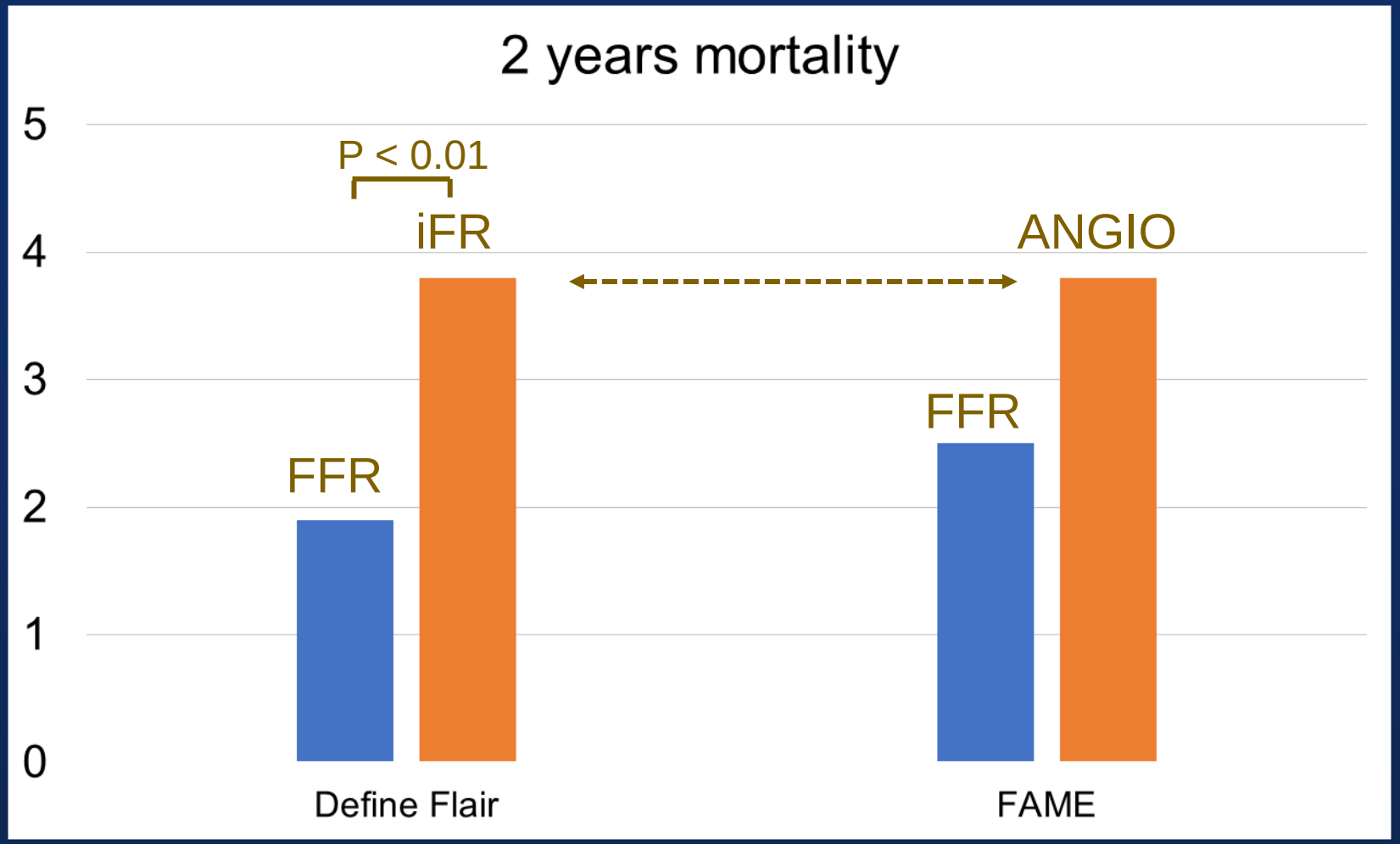
- In these 2 trials, *only low risk patients were included*, and *false-negative iFR was actually excluded by design*, *This bias was not recognized by the investigators, nor the NEJM, nor some guideline committees.* In those study populations, non-inferiority of iFR at one year of FU, was demonstrated

- *Whereafter*, without any additional study or evidence, the *results were extrapolated to all patients*, including more complex anatomy.

- *However*, at 2-year and at 5-y FU, ***mortality was significantly increased when using iFR*** and subsequently, both in JACC and EHJ it was actually recommended to abandon use of iFR for decision making

Lecture today at 3.30 pm in presentation room 2

2-year-mortality with iFR- guidance in low-risk DEFINE-FLAIR population, was as high as in angio-guided group in complex FAME population.
The difference even further increased at 5-year FU



from Davies J, TCT 2019; Escaned X, PCR 2023, Van Nunen, Lancet 2015

AMERICAN COLLEGE of CARDIOLOGY

Instantaneous Wave Free Ratio vs. Fractional Flow Reserve

Nov 06, 2023

Quick Takes

- iFR-guided revascularization is associated with an increase in the composite of MACE (all-cause mortality, MI, or unplanned revascularization) and all-cause mortality alone compared to FFR-guided revascularization.
- Based on the current data, FFR-guided strategy should be the preferred option in proximal lesions in large coronary arteries with a large perfusion territory.
- Pending additional data, it is prudent to use nonhyperemic pressure indices judiciously and consider FFR-guided revascularization the gold standard strategy for intracoronary pressure measurement.

Both JACC and EHJ recommendations 2023 *discourage* use of iFR:

"Be cautious with iFR"

"Use FFR as gold standard"

Lecture today at 3.30 pm in presentation room 2

Finally:

The Coronary Microcirculation again:
can the black box be opened ?

→ *Lecture today at 5.02 pm in presentation room 2*

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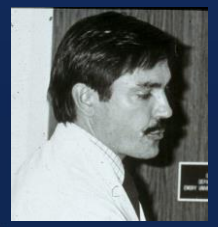

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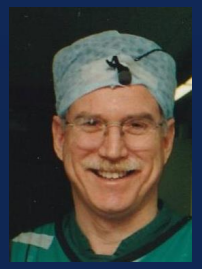

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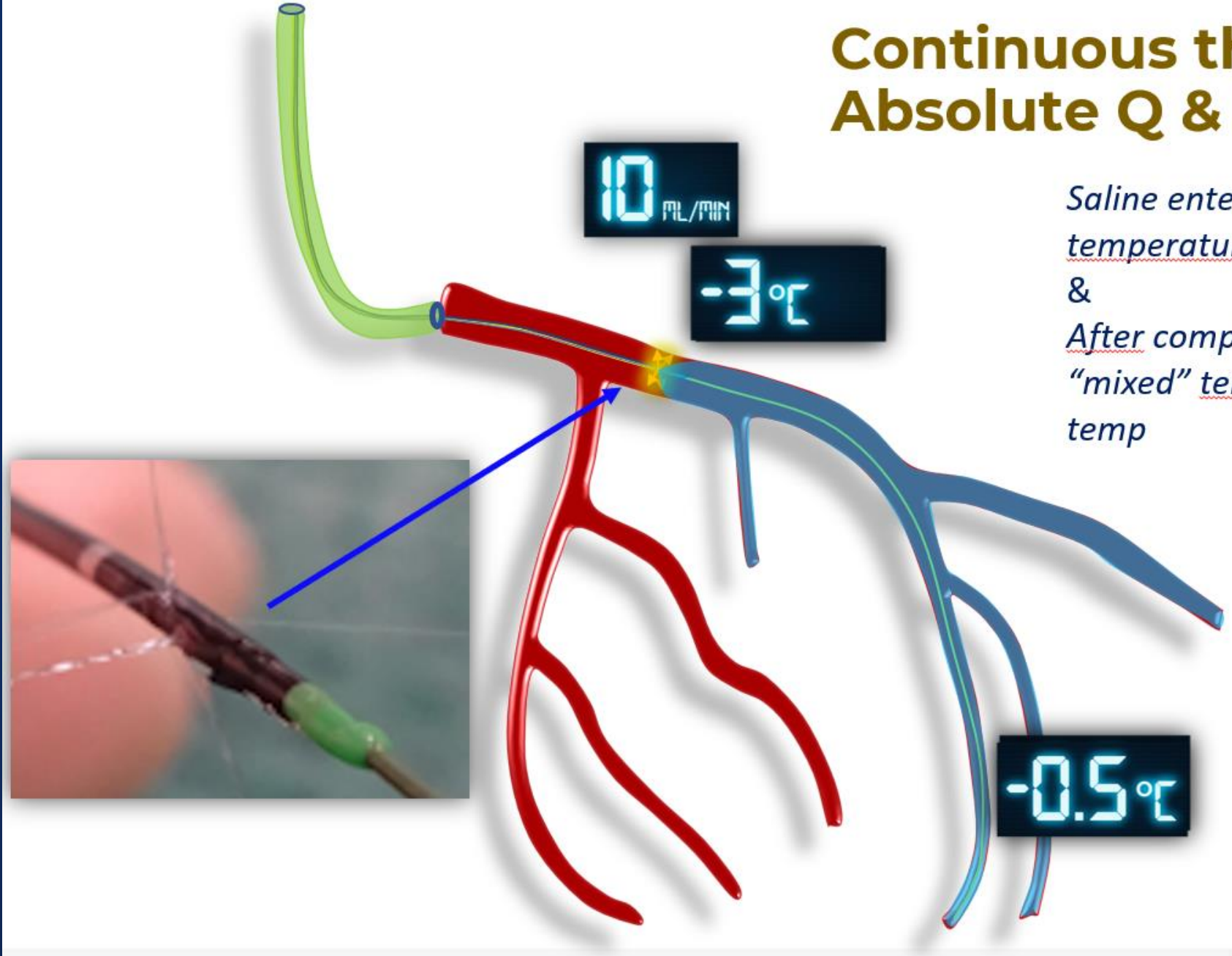
Intracoronary Imaging (IVUS, OCT)

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

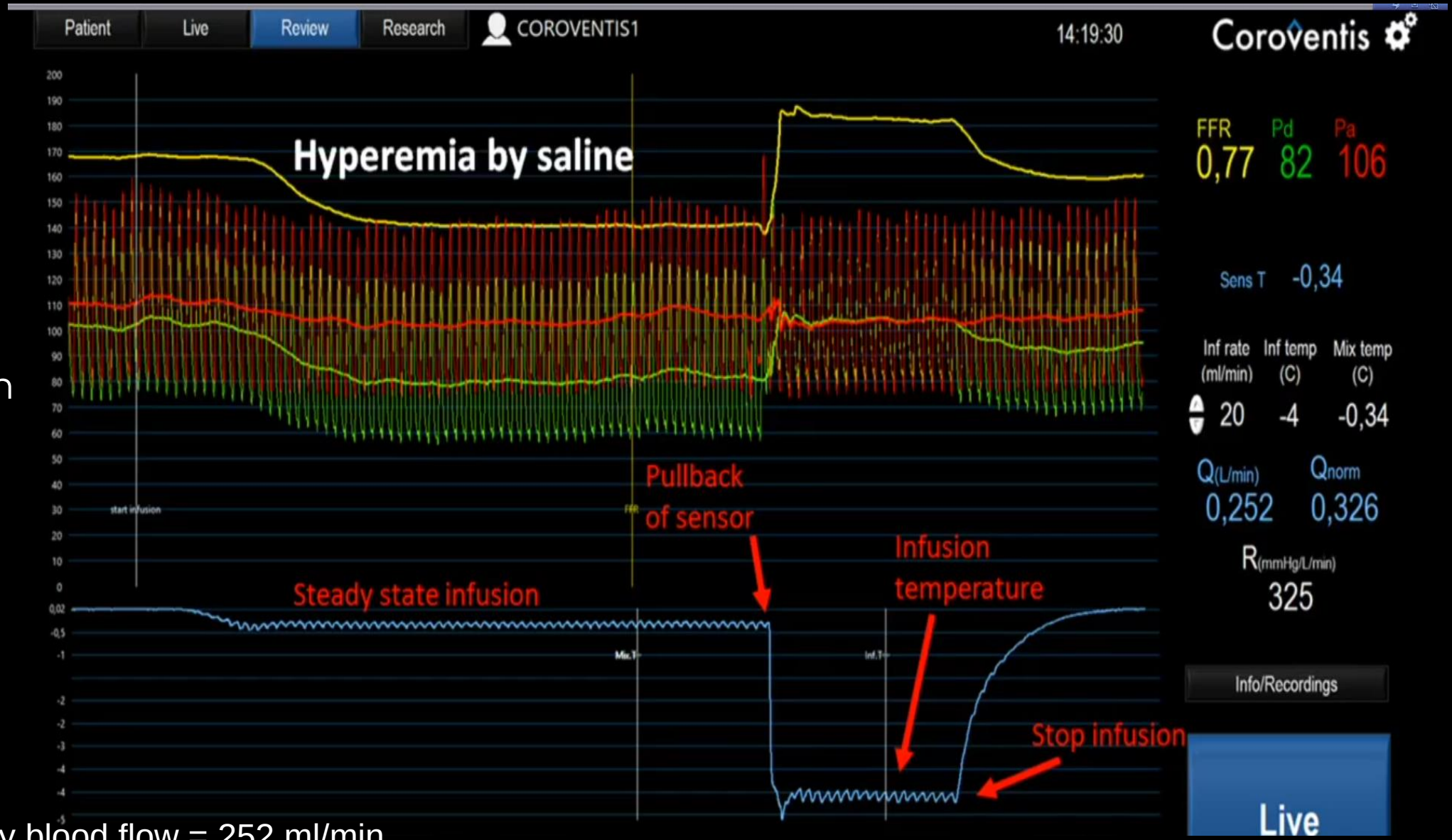
Blood flow must be 6 x infusion flow of saline

60 ml/min

Lecture today at 5.02 pm in presentation room 2

Example of one hyperemic run (20ml/min)

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



FFR = 0.77
maximum coronary blood flow = 252 ml/min
minimal microvascular resistance = 325 WU

Absolute coronary Flow Measurement and Microvascular Resistance Reserve:

The Holy Grail of Coronary Physiology ?

- Can be measured at rest (Q_{rest}, $R_{\mu,rest}$) and at hyperemia (Q_{max} , $R_{\mu,hyper}$)
- No hyperemic drug needed because 20 ml/min of saline in itself creates maximum hyperemia
- ***FFR*** is automatically measured at the same time
- And therefore, also *normal reference values for Q and R* are known
- For the first time in history, invasive measurement of ***absolute CFR*** is possible
- And finally, also ***Microvascular Resistance Reserve (MRR)*** can be calculated, which is the most accurate, reproducible, and super-specific index of the coronary microcirculation,

  MRR is not affected by mass or epicardial disease and *operator-independent*

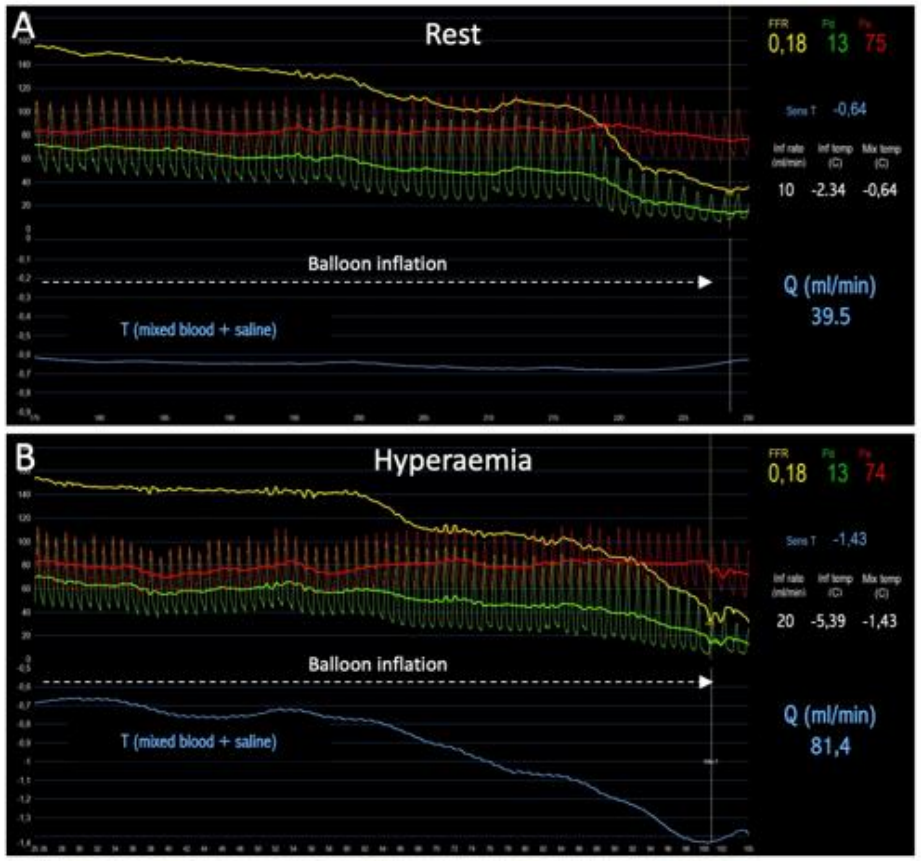
$$MRR = CFR / FFR \times P_{a,rest} / P_{a,hyp}$$

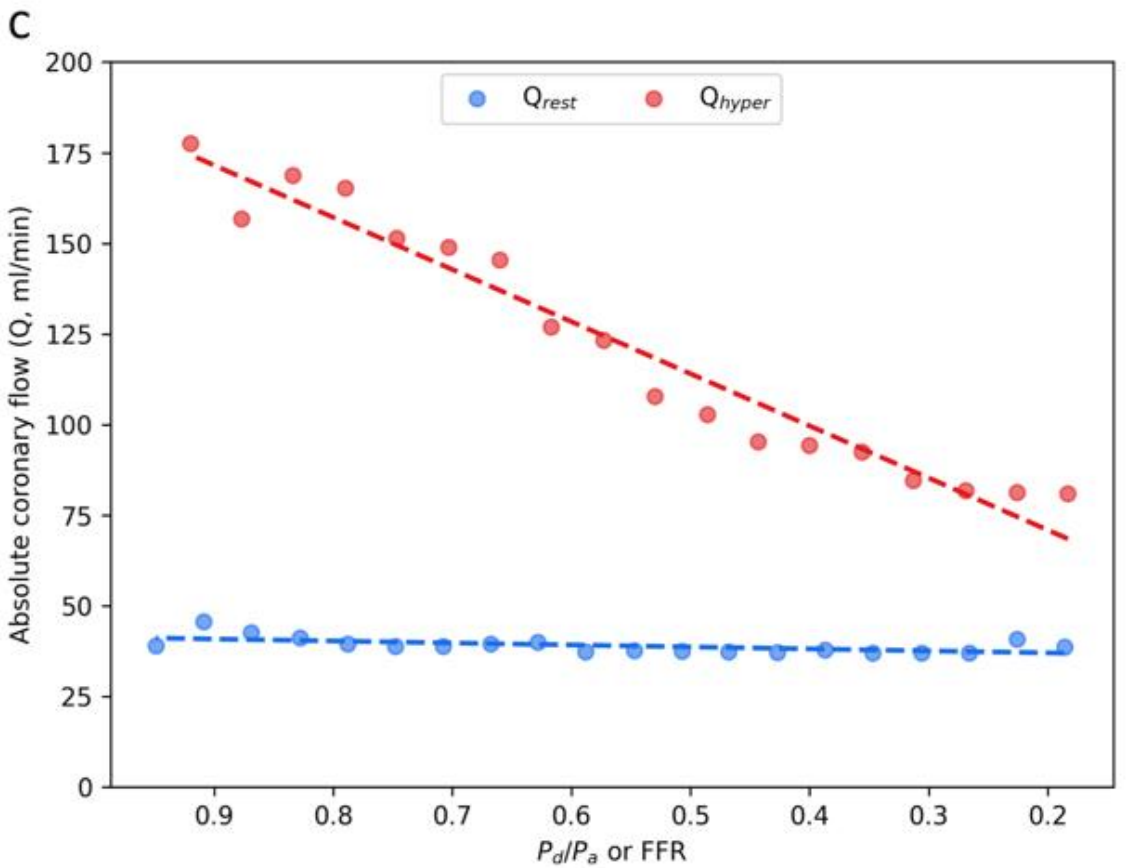
(unifying equation of coronary physiology)

Lecture about this methodology: today at 5.02 pm in presentation room 2

Finally: Coronary Autoregulation 50 years later:

From Gould's experimental animals to conscious humans in the cathlab





increasing stenosis

- *Patient after stenting of prox LAD stenosis*
- *Empty balloon in stent which is slowly inflated*
- *While absolute flow is continuously recorded*

Mahendiran et al, New England Journal of Medicine (in press)

50 Years of Coronary Physiology: Conclusions From a Magnificant Journey

- Interventional cardiology is a dynamic and rapidly evolving world facilitated by great meetings spreading out knowledge and great persons: ***Founders of TCT, EuroPCR, TCTAP***





…….And many others !!

- After the first angiograms by Sones, need for a better physiologic understanding of the coronary circulation arose quickly
- Between 1977 and today, we not only learned sophisticated interventional techniques but also learned how and when to apply these, based upon ***sound physiological principles (FFR)***
- In 50 years, we came from the experimental dogs of Gould to a complete understanding of coronary (patho)physiology and its routine application in the human catheterization laboratory
- Presently, ***FFR, CFR, Absolute flow and Resistance, and MRR*** provide a complete and accurate description of both the epicardial arteries and the microcirculation of the heart