Imaging & Physiology Summit

JOURNEY INTO THE DISCOVERY OF CORONARY PHYSIOLOGY: *20 YEARS OF FFR*

Seoul, Korea, december 3rd, 2015

CATHARINA-ZIEKENHUIS

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catharina ziekenhuis

The New England
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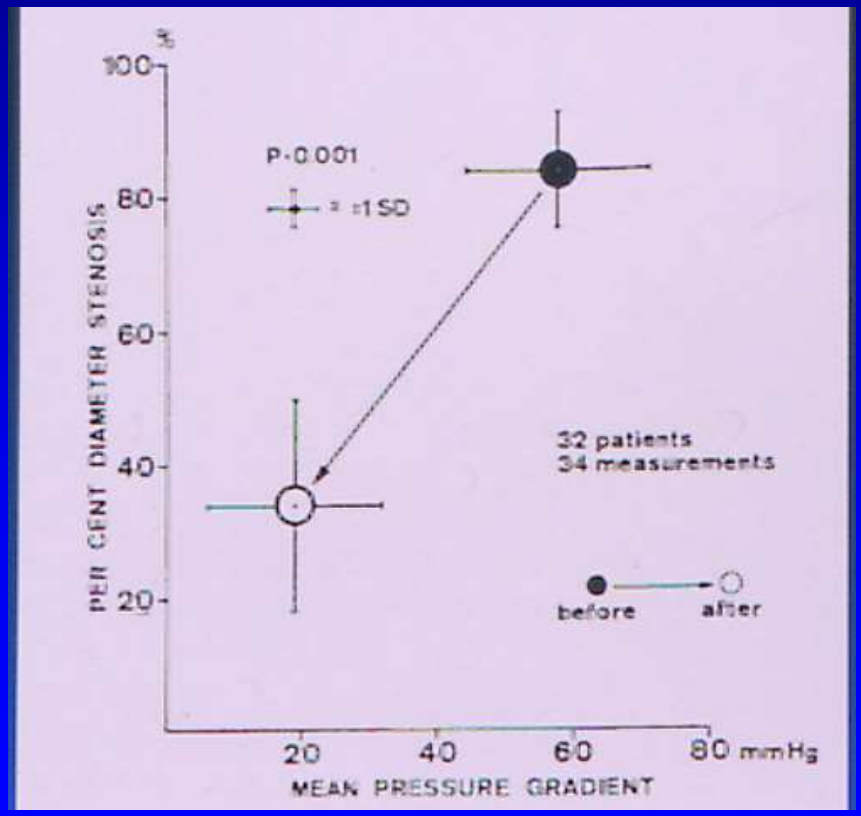
NONOPERATIVE DILATATION OF CORONARY-ARTERY STENOSIS

Percutaneous Transluminal Coronary Angioplasty

ANDREAS R. GRÜNTZIG, M.D., ÅKE SENNING, M.D., AND WALTER E. SIEGENTHALER, M.D.

Gruentzig and other early investigators, intuitively noticed the importance of coronary pressure measurement

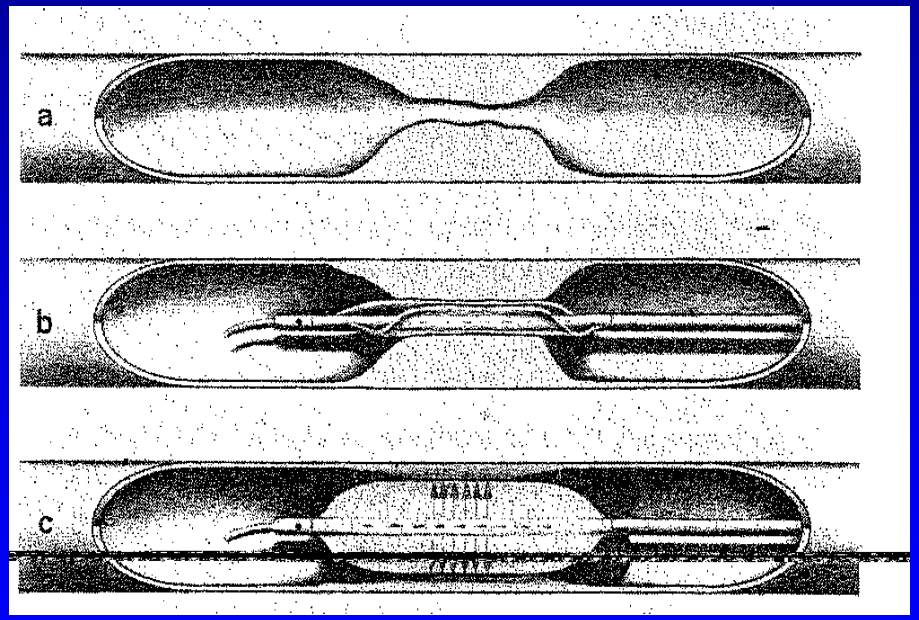


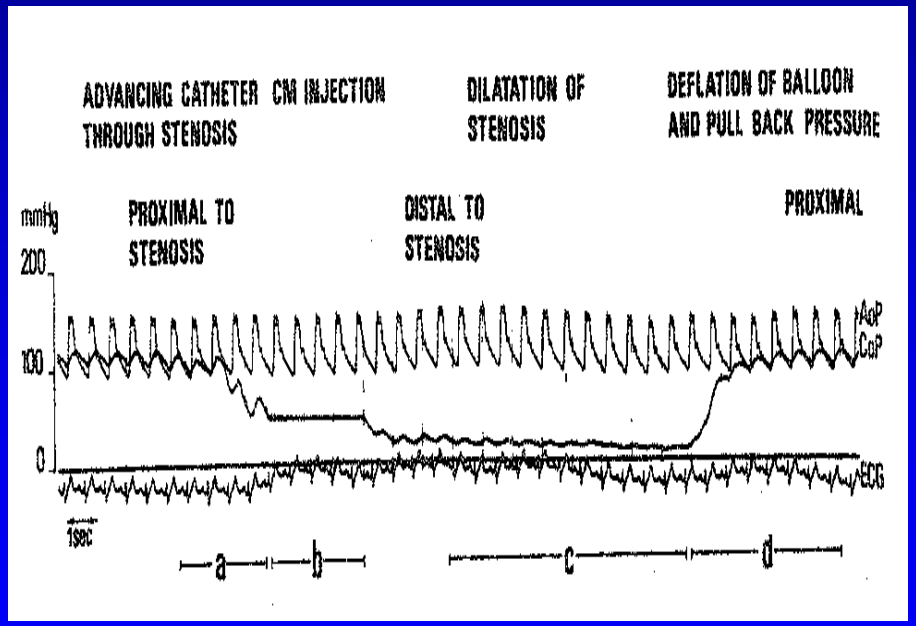
But....they were limited by

- inadequate equipment to measure pressure: *(no Pressure Wire)*
- inadequate hemodynamic measuring conditions (*no hyperemia*)
- inadequate interpretation of pressures *(no FFR)*

But....they were limited by

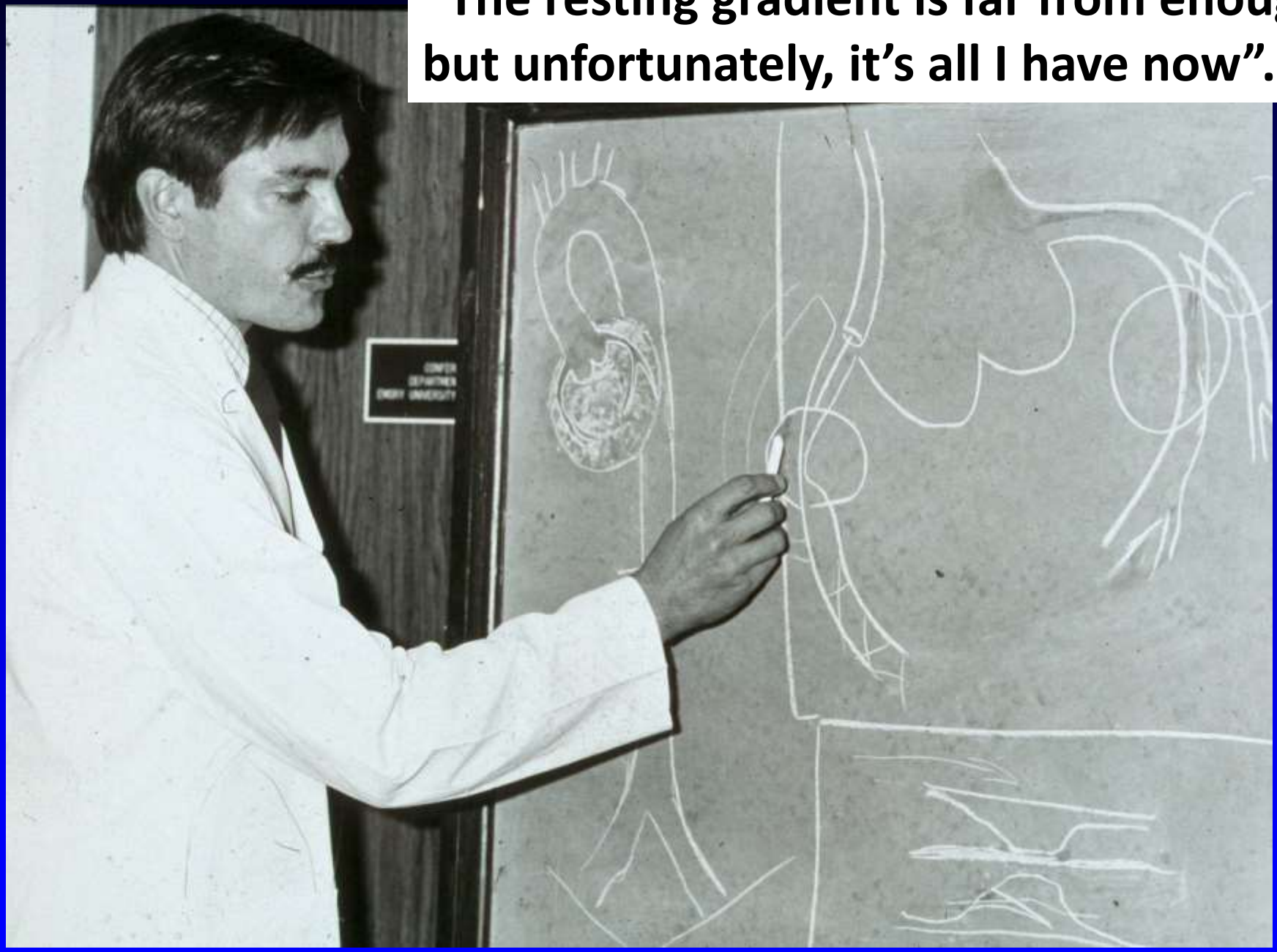
- inadequate equipment to measure pressure:
  → ***balloon catheter instead of 0.014' wire***



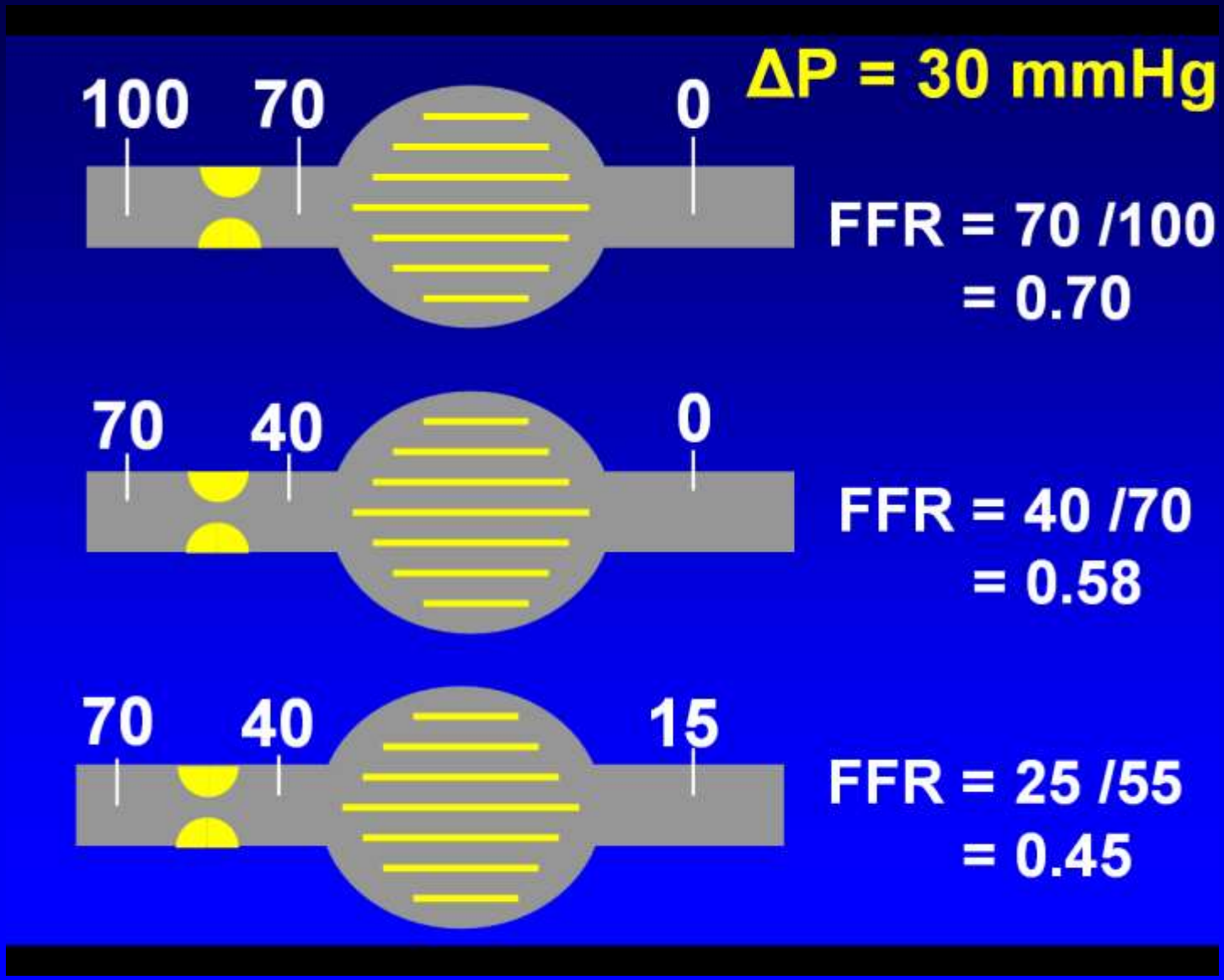


Overestimation of gradients by presence of balloon catheter

“The resting gradient is far from enough but unfortunately, it’s all I have now”.



3 different patients with each hyperemic trans-stenotic gradient of 30 mmHg:



Fortunately, these 3 limitations were overcome:

- *pressure guide wires* were developed (home-made device for first animal studies, followed by high-fidelity guidewires later on)

- *Safe and reproducible hyperemic drugs* were validated for use in the human coronary circulation

- And it was recognized that not gradients in itself are important, but the ratio of perfusion pressures at hyperemia ⟶ ***Fractional Flow Reserve***

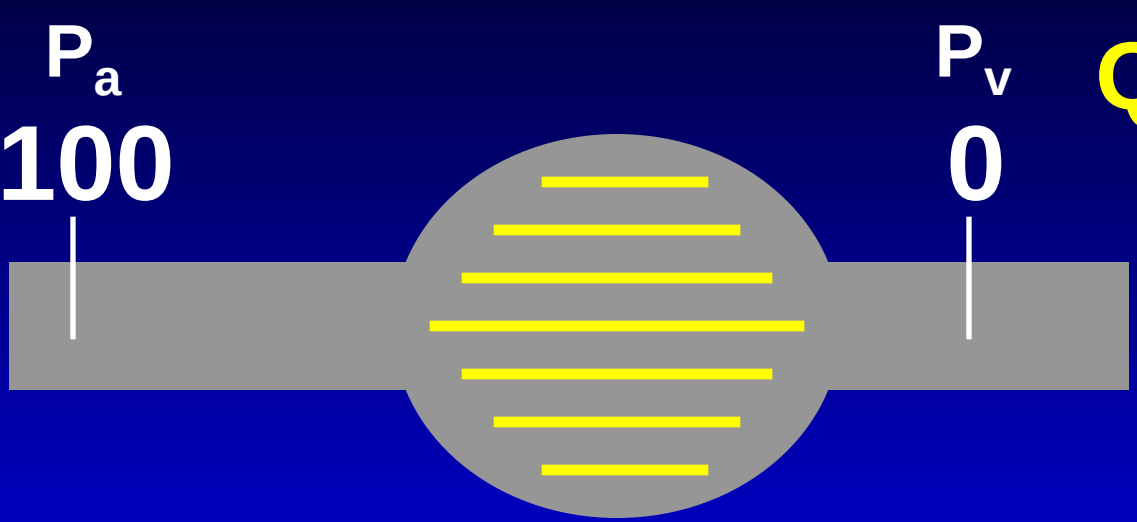
FRACTIONAL FLOW RESERVE:

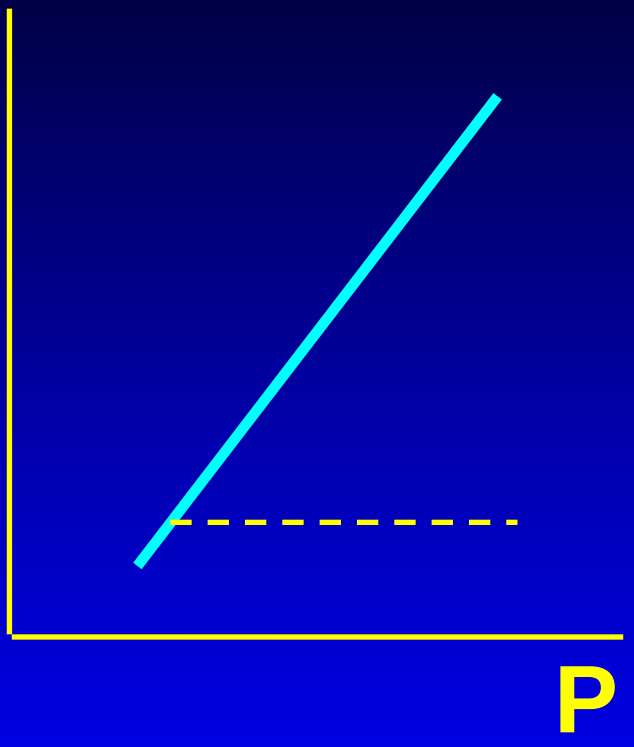
The index FFR (***Fractional Flow Reserve***)
is based upon the two following principles:

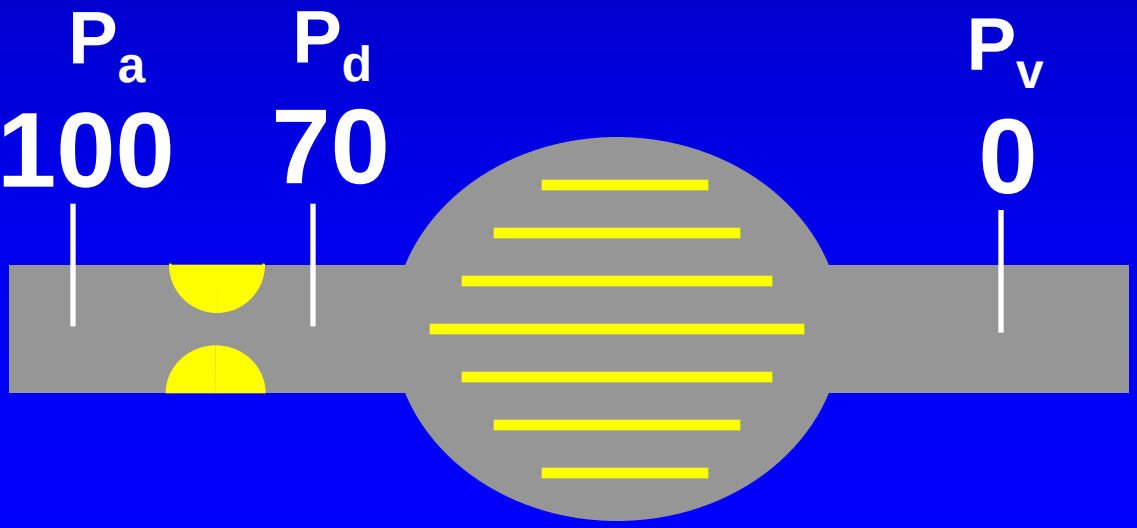
- *It is not resting flow, but **maximum achievable flow** which determines the functional capacity (exercise tolerance) of a patient*

- *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



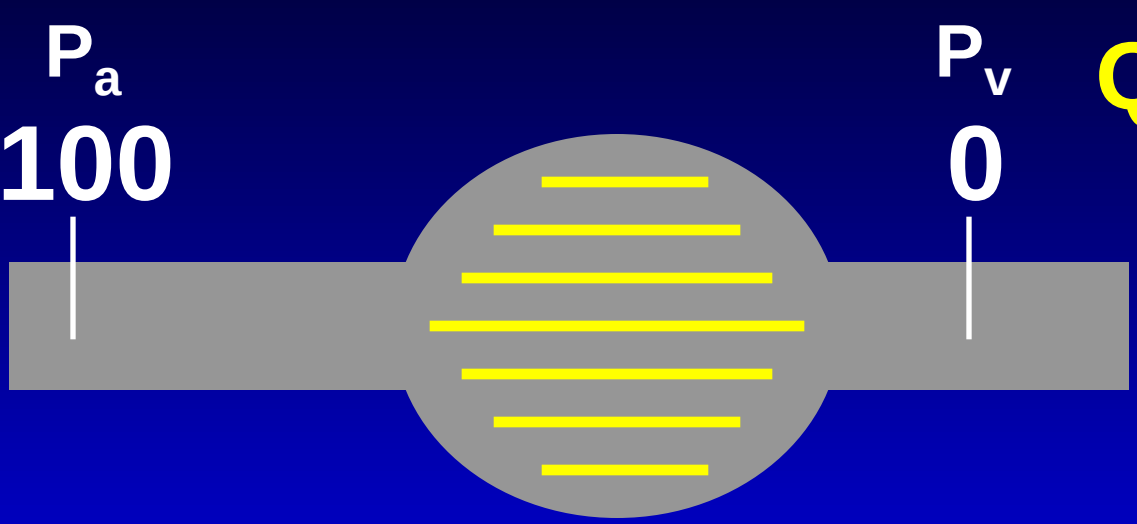


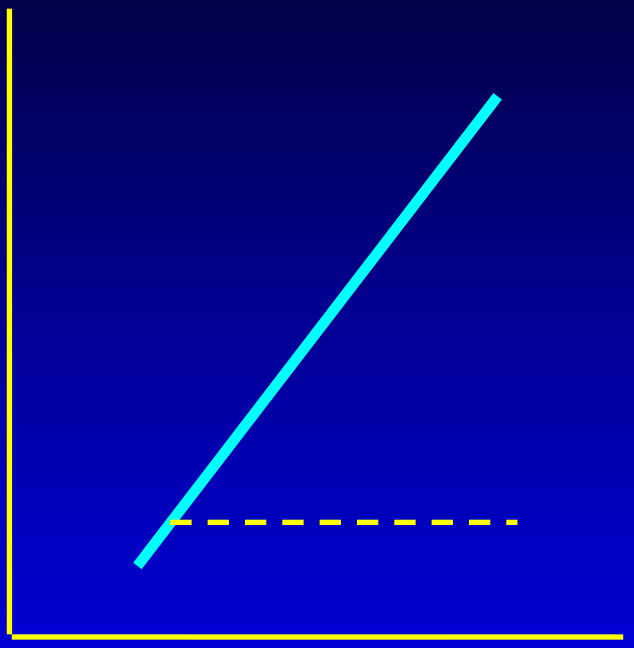


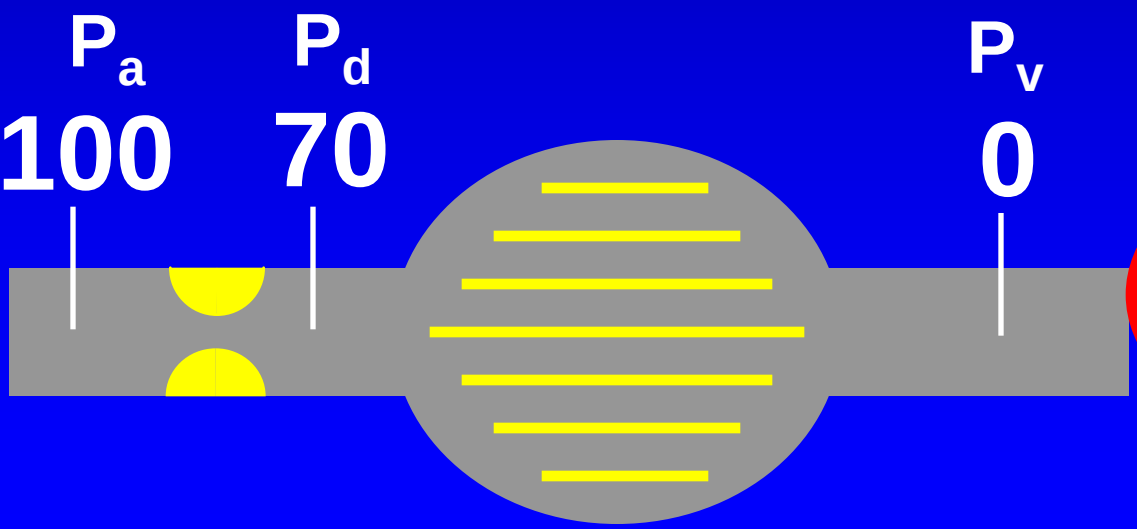
$$FFR_{myo} = \frac{P_d - P_v}{P_a - P_v}$$

$$= 0.70$$

During Maximal Vasodilatation



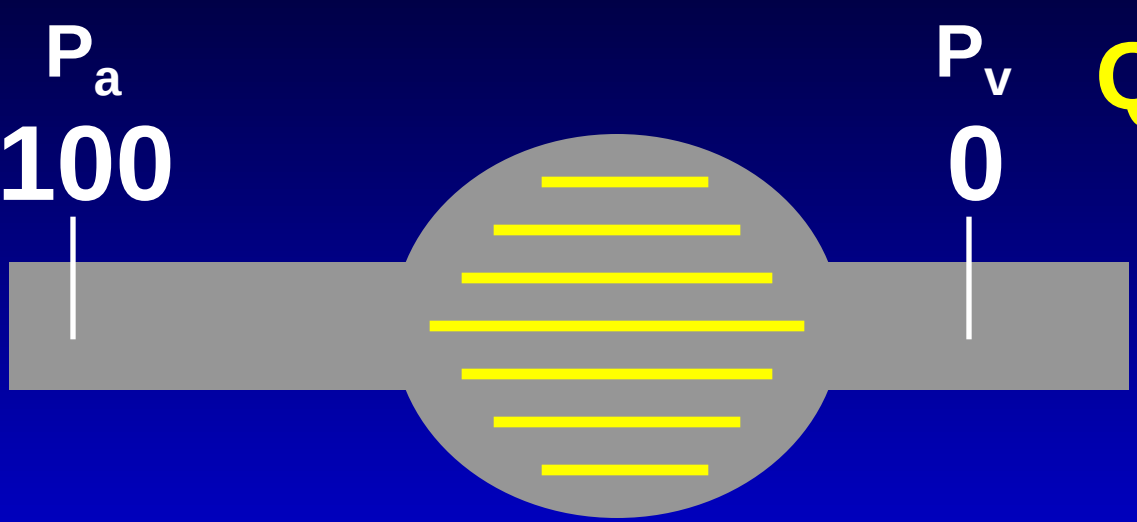


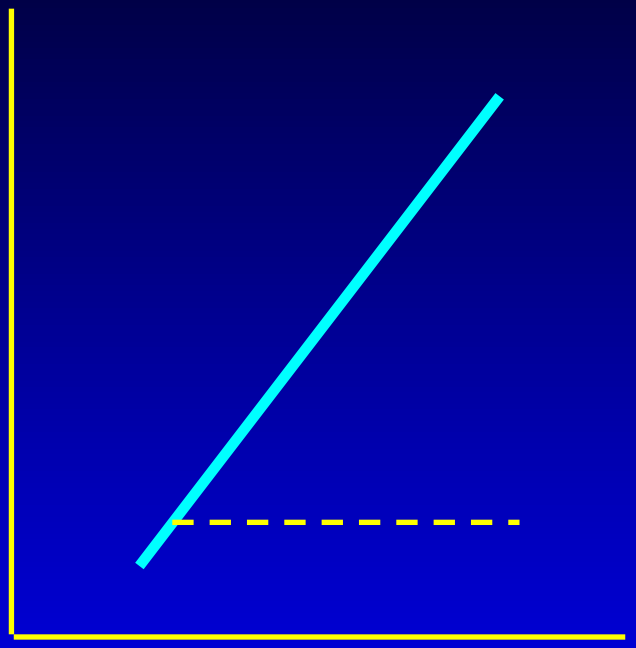


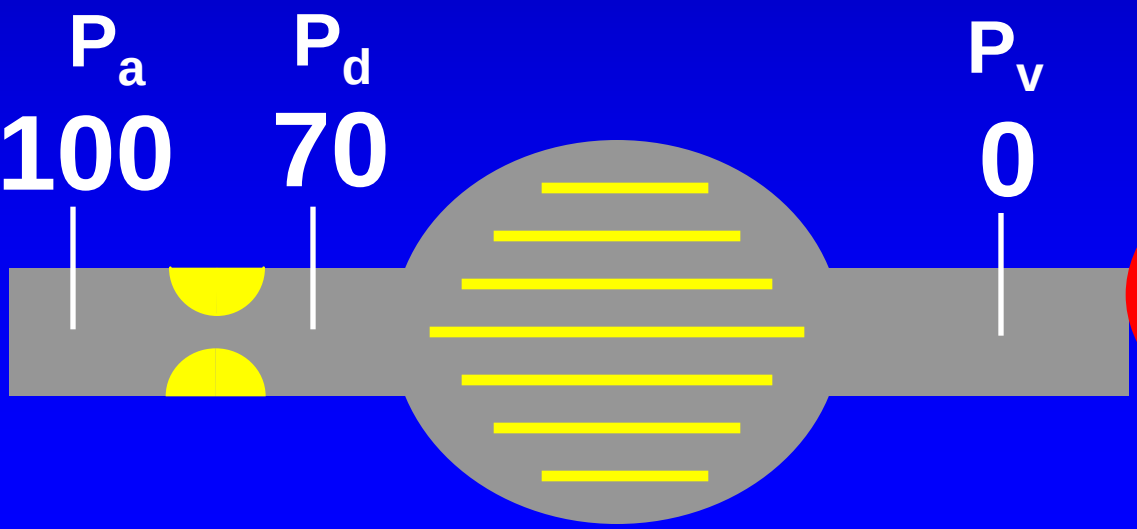
$$FFR_{myo} = \frac{P_d - P_v}{P_a - P_v}$$

$$= 0.70$$

During Maximal Vasodilatation







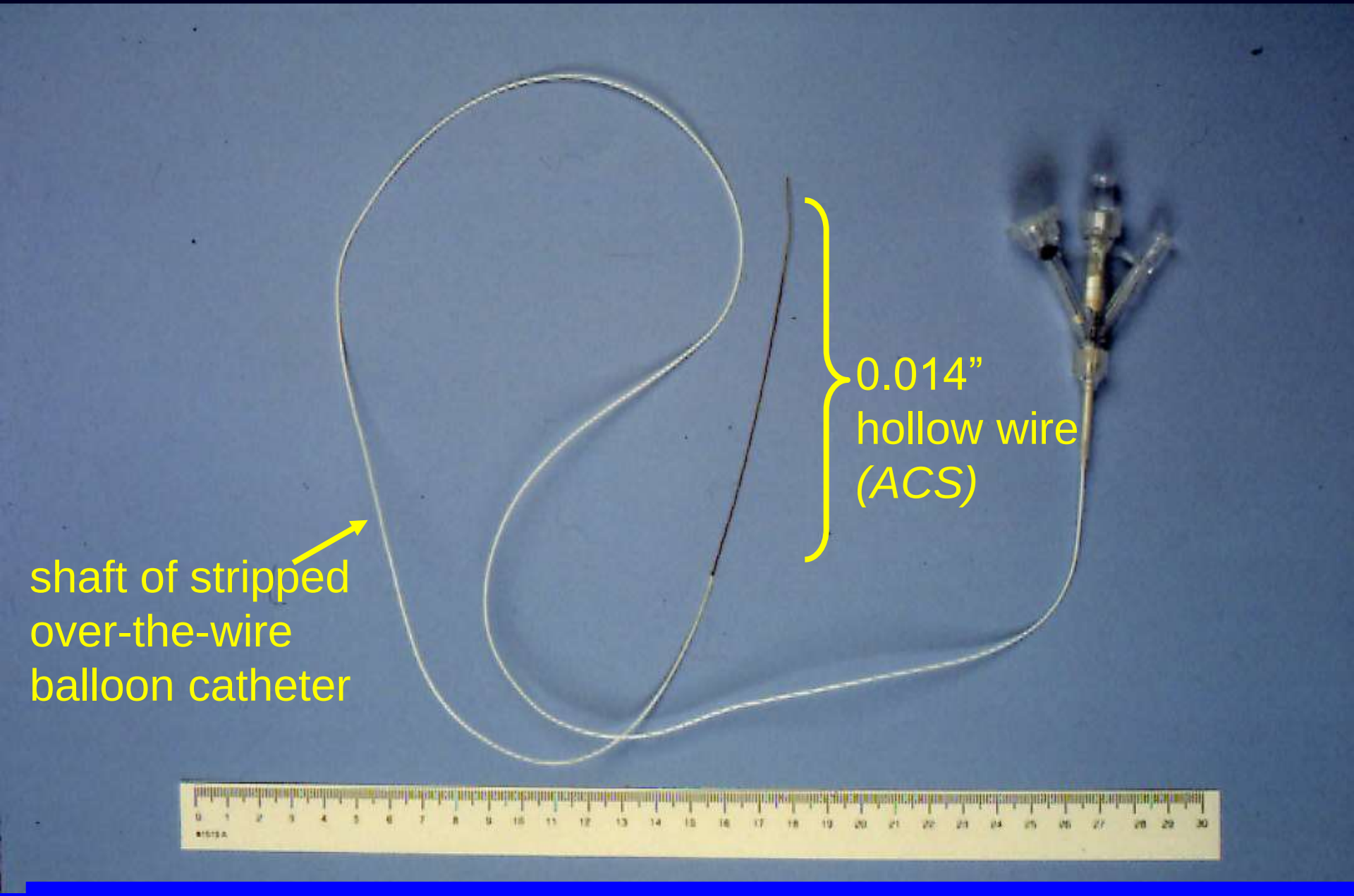
$$FFR_{myo} = \frac{P_d}{P_a} = 0.70$$

During ACC in New Orleans in 1990 →

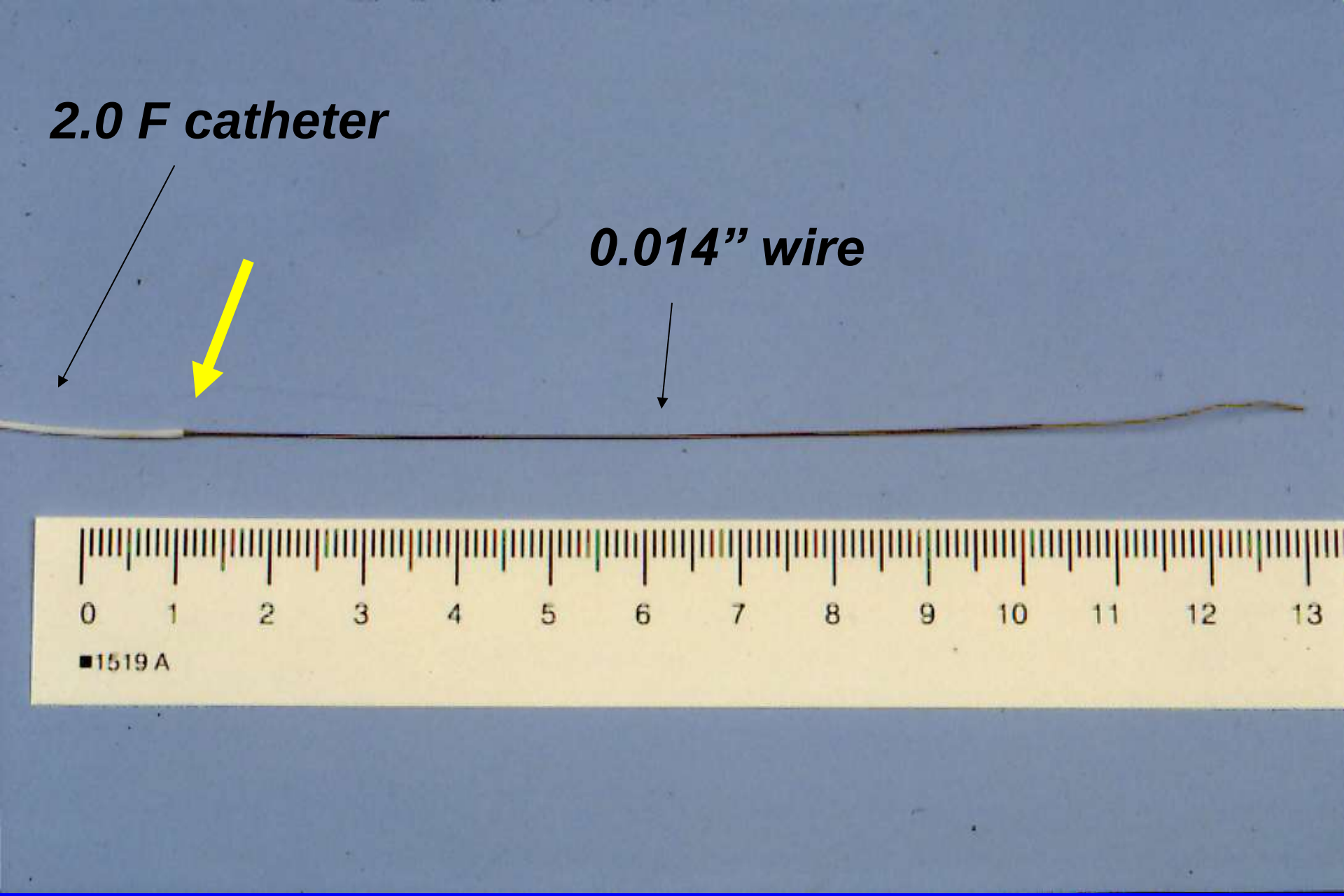
I had a completely accidental meeting with Dr De Bruyne from Aalst, Belgium

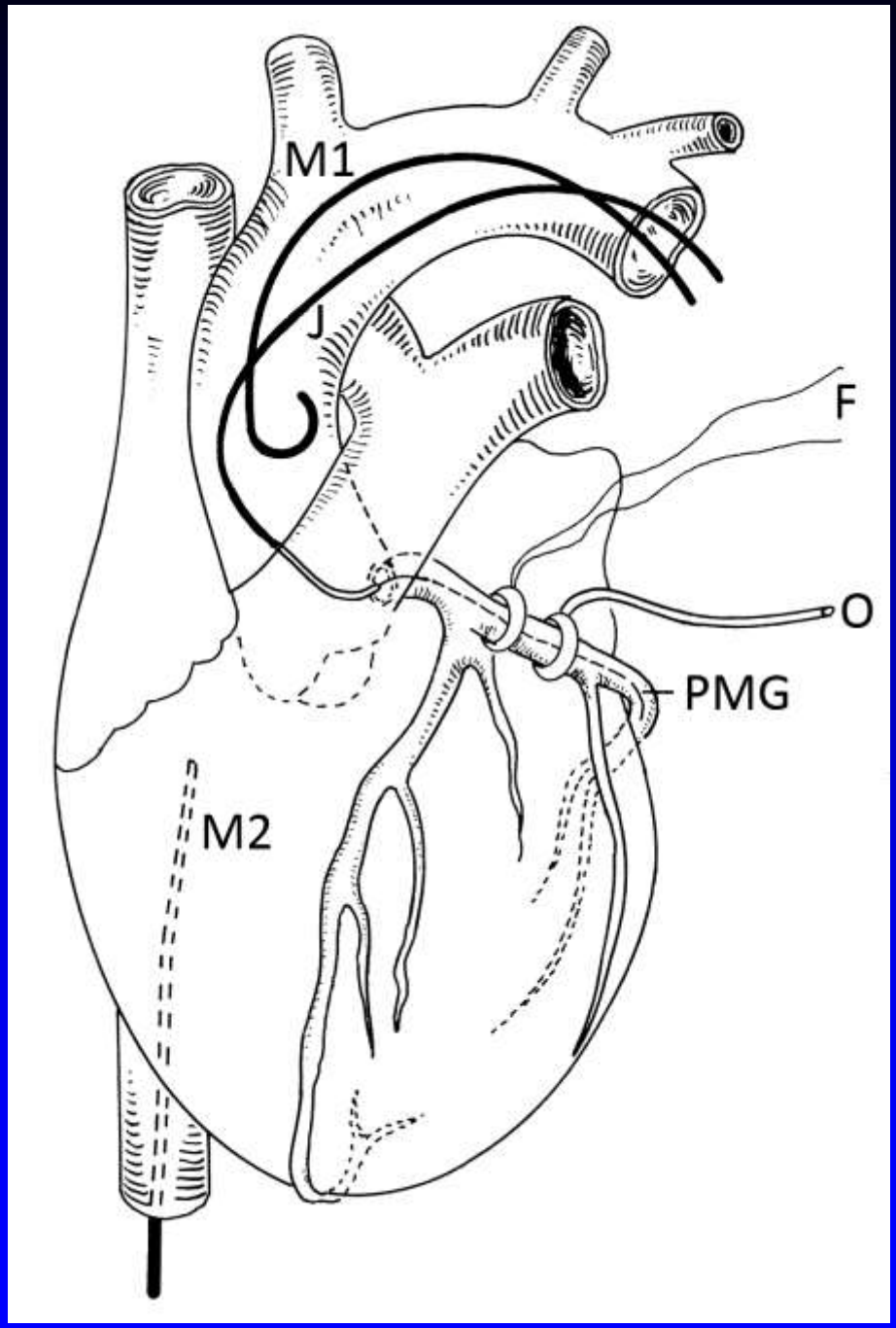
we shared similar ideas and decided to cooperate……..

……and we still cooperate 25 years later and became close friends



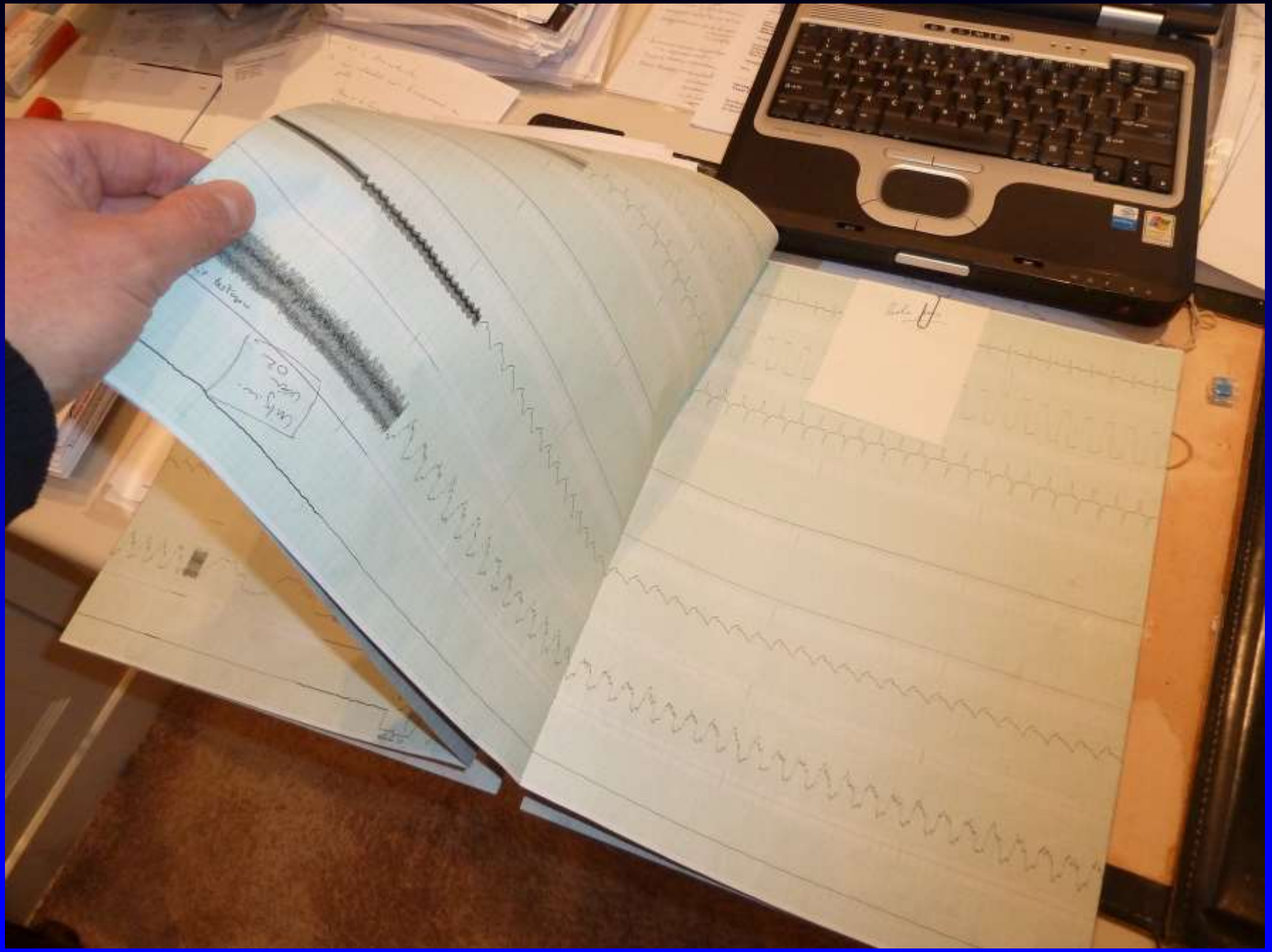
(Produced on the kitchen table of the Pijls family in Malden, NL)

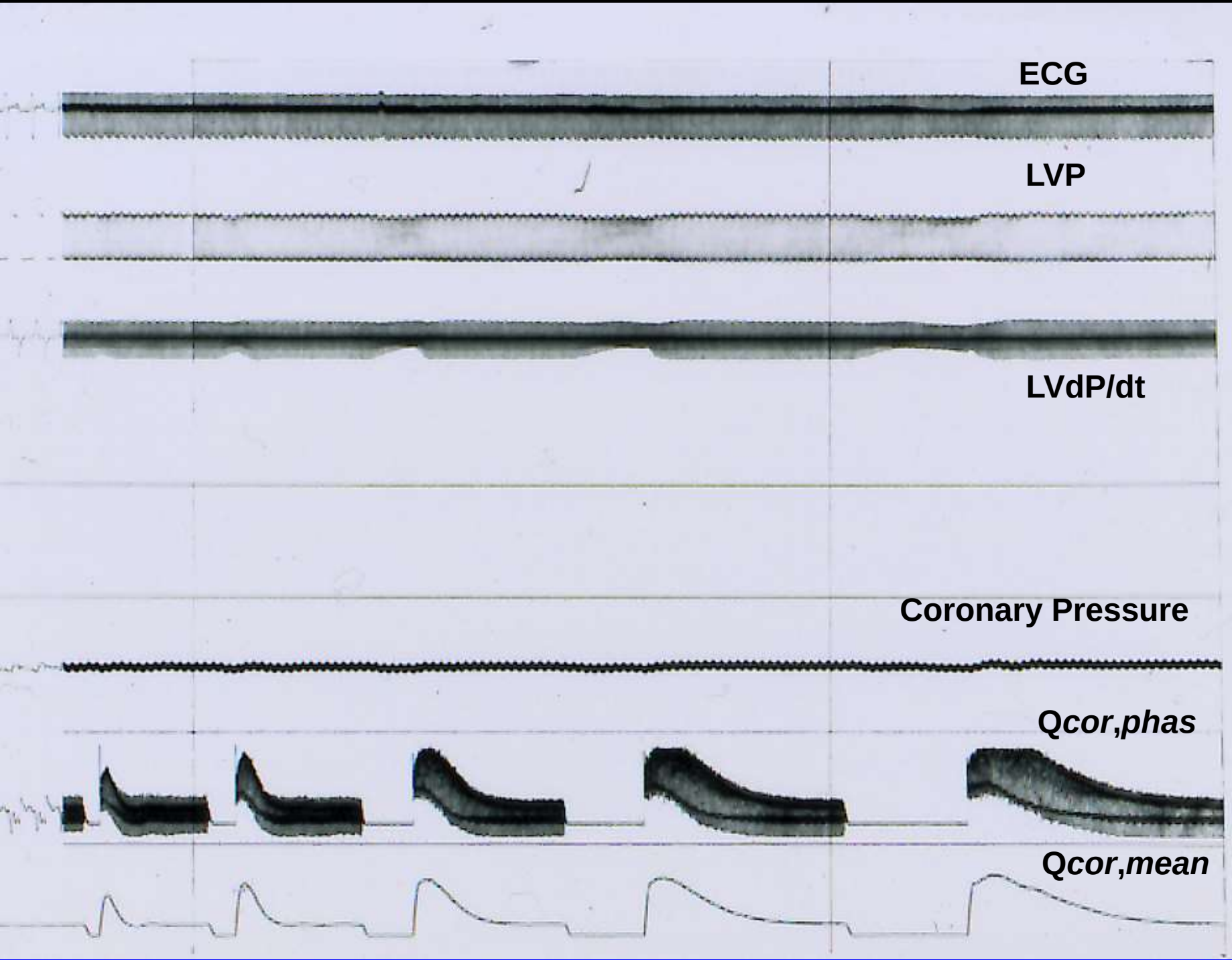

2.0 F catheter
0.014” wire
0 1 2 3 4 5 6 7 8 9 10 11 12 13
■1519 A

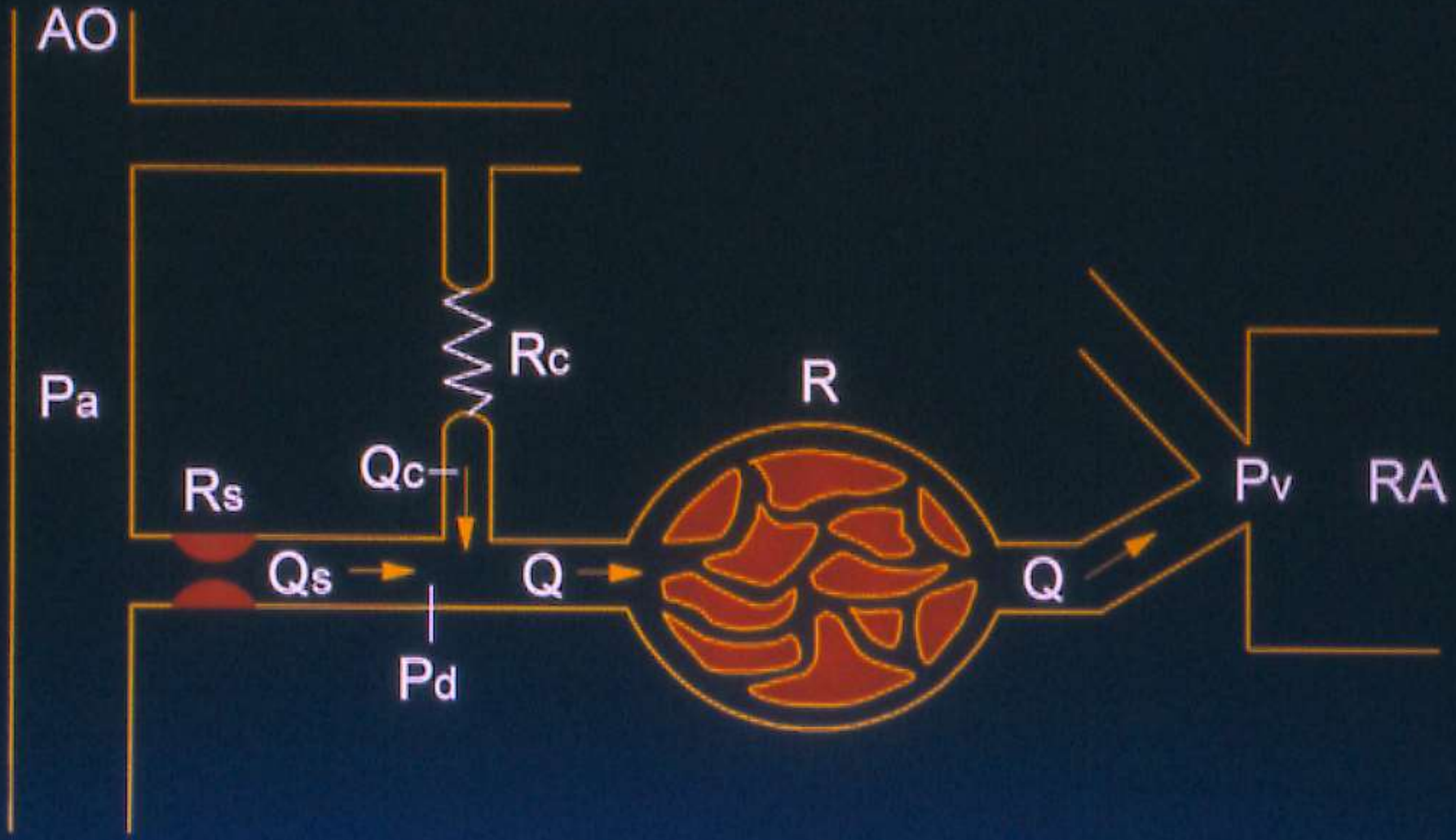


FFR:
experimental validation in chronic dog studies

(first animal study started summer of 1990)




ECG
LVP
LVdP/dt
Coronary Pressure
Qcor,phas
Qcor,mean



Including collaterals in the model…….

I $$\frac{P_a - P_v}{P_w - P_v} = 1 + \frac{R_c}{R} = \text{constant}$$

IIa $$\mathrm{FFR}_{cor} = \frac{P_d - P_w}{P_a - P_w} = 1 - \frac{\Delta P}{P_a - P_w}$$

IIIa $$\mathrm{FFR}_{myo} = \frac{P_d - P_v}{P_a - P_v} = 1 - \frac{\Delta P}{P_a - P_v}$$

IVa $$Q_c = (\mathrm{FFR}_{myo} - \mathrm{FFR}_{cor}) \cdot Q^N$$

I $$\frac{P_a - P_v}{P_w - P_v} = 1 + \frac{R_c}{R} = \text{constant}$$

IIa $$\mathrm{FFR}_{cor} = \frac{P_d - P_w}{P_a - P_w} = 1 - \frac{\Delta P}{P_a - P_w}$$

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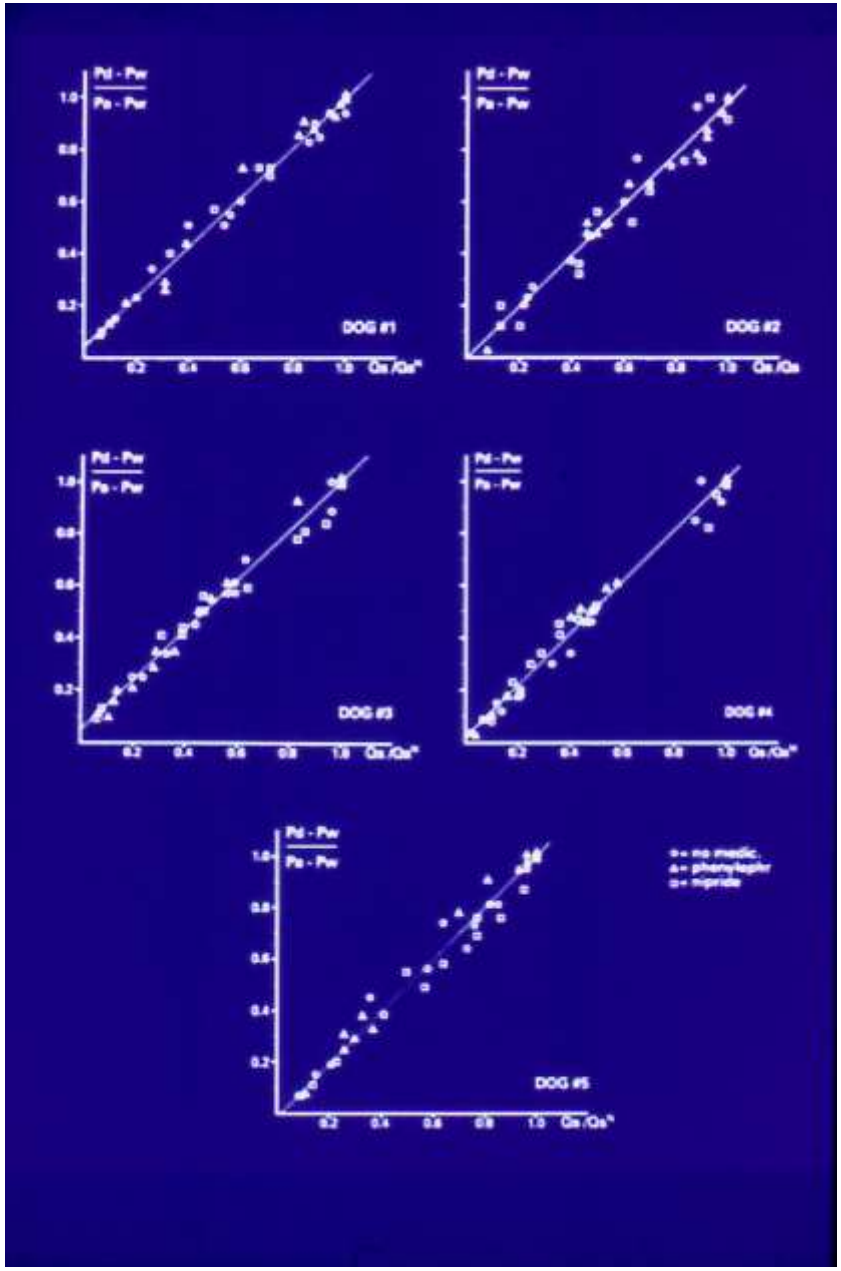
IVa $$Q_c = (\mathrm{FFR}_{myo} - \mathrm{FFR}_{cor}) \cdot Q^N$$



Experimental basis of FFR

<u>Horizontal axis</u>:
FFR measured by true flow

<u>Vertical axis</u>:
FFR measured by
Hyperemic pressure ratio

I $$\frac{P_a - P_v}{P_w - P_v} = 1 + \frac{R_c}{R} = \text{constant}$$

IIa $$\mathrm{FFR}_{cor} = \frac{P_d - P_w}{P_a - P_w} = 1 - \frac{\Delta P}{P_a - P_w}$$

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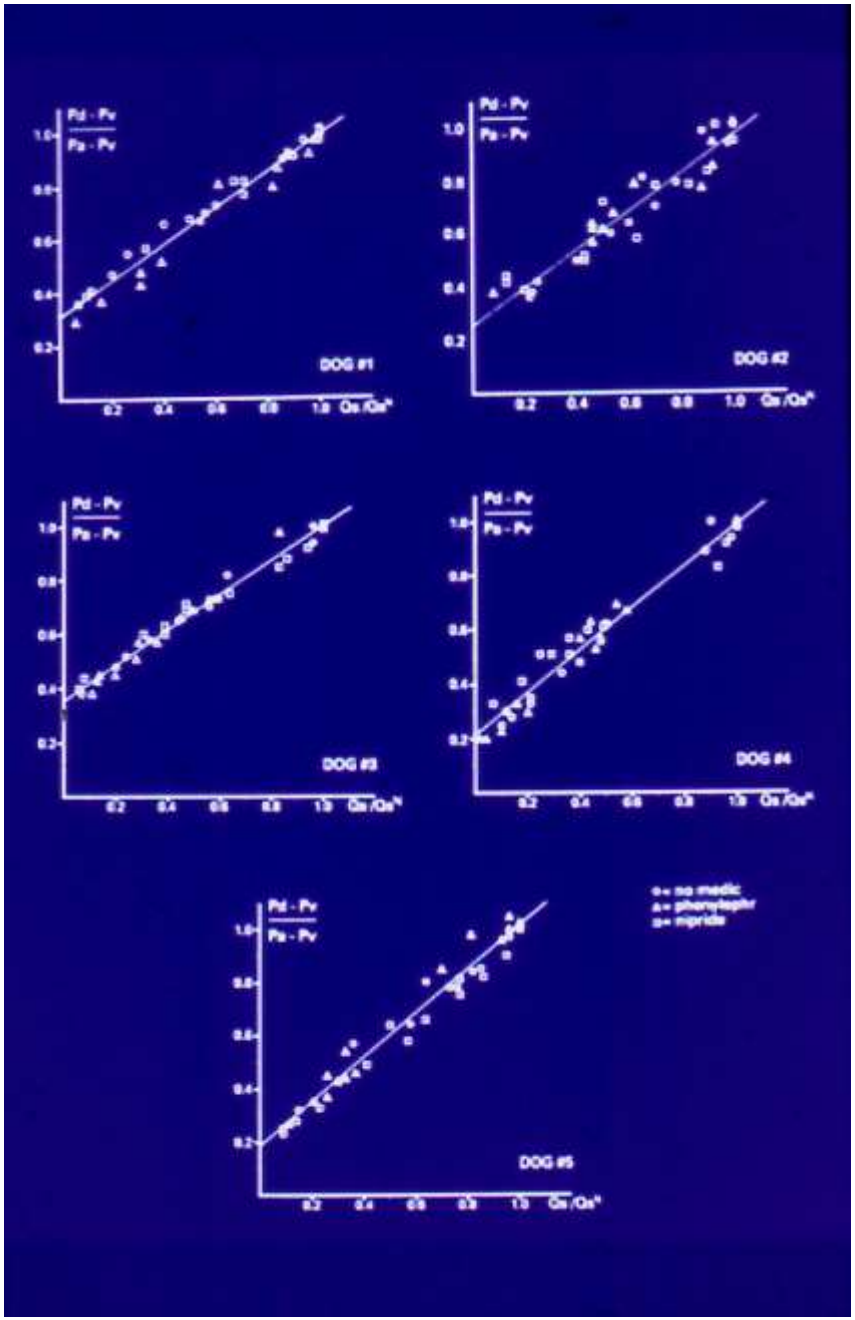


Strange correlation ??

⟶ not anymore !

<u>Horizontal axis:</u>

FFR_{cor} measured by true flow

<u>Vertical axis:</u>

FFR_{myo} measured by Hyperemic pressure ratio

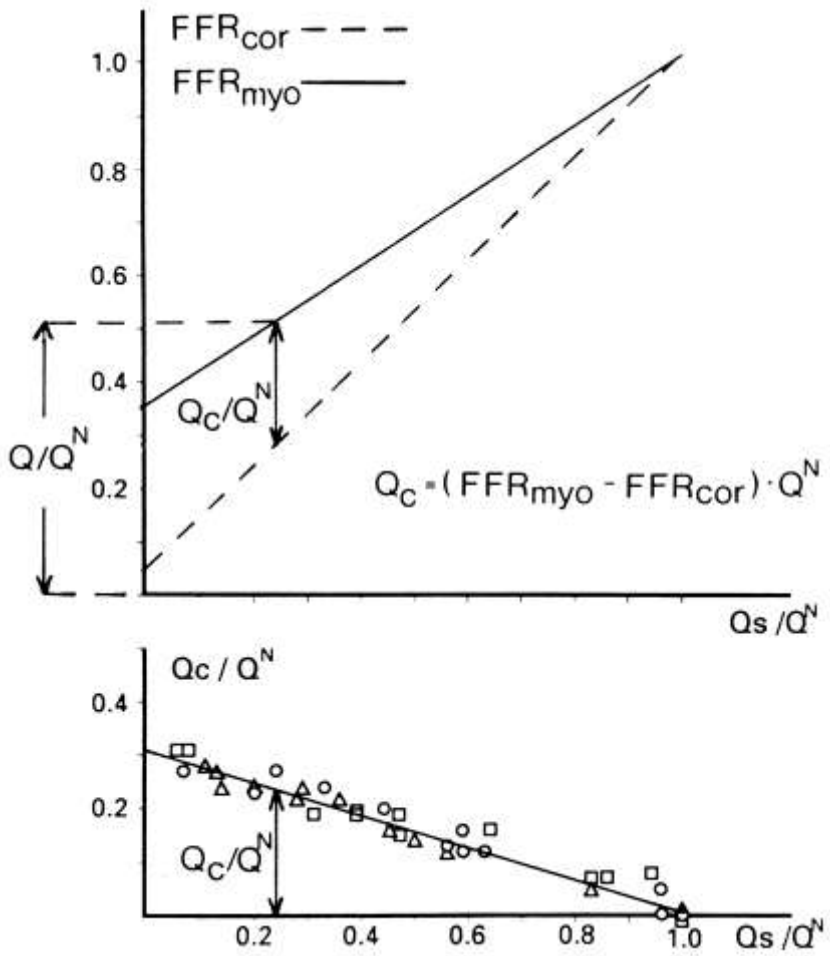
Why this high intersection With Y-axis ??

I $$\frac{P_a - P_v}{P_w - P_v} = 1 + \frac{R_c}{R} = \text{constant}$$

IIa $$\mathrm{FFR}_{cor} = \frac{P_d - P_w}{P_a - P_w} = 1 - \frac{\Delta P}{P_a - P_w}$$

IIIa $$\mathrm{FFR}_{myo} = \frac{P_d - P_v}{P_a - P_v} = 1 - \frac{\Delta P}{P_a - P_v}$$

IVa $$Q_c = (\mathrm{FFR}_{myo} - \mathrm{FFR}_{cor}) \cdot Q^N$$



Experimental basis of FFR

Horizontal axis:

FFR_{cor} measured by true flow

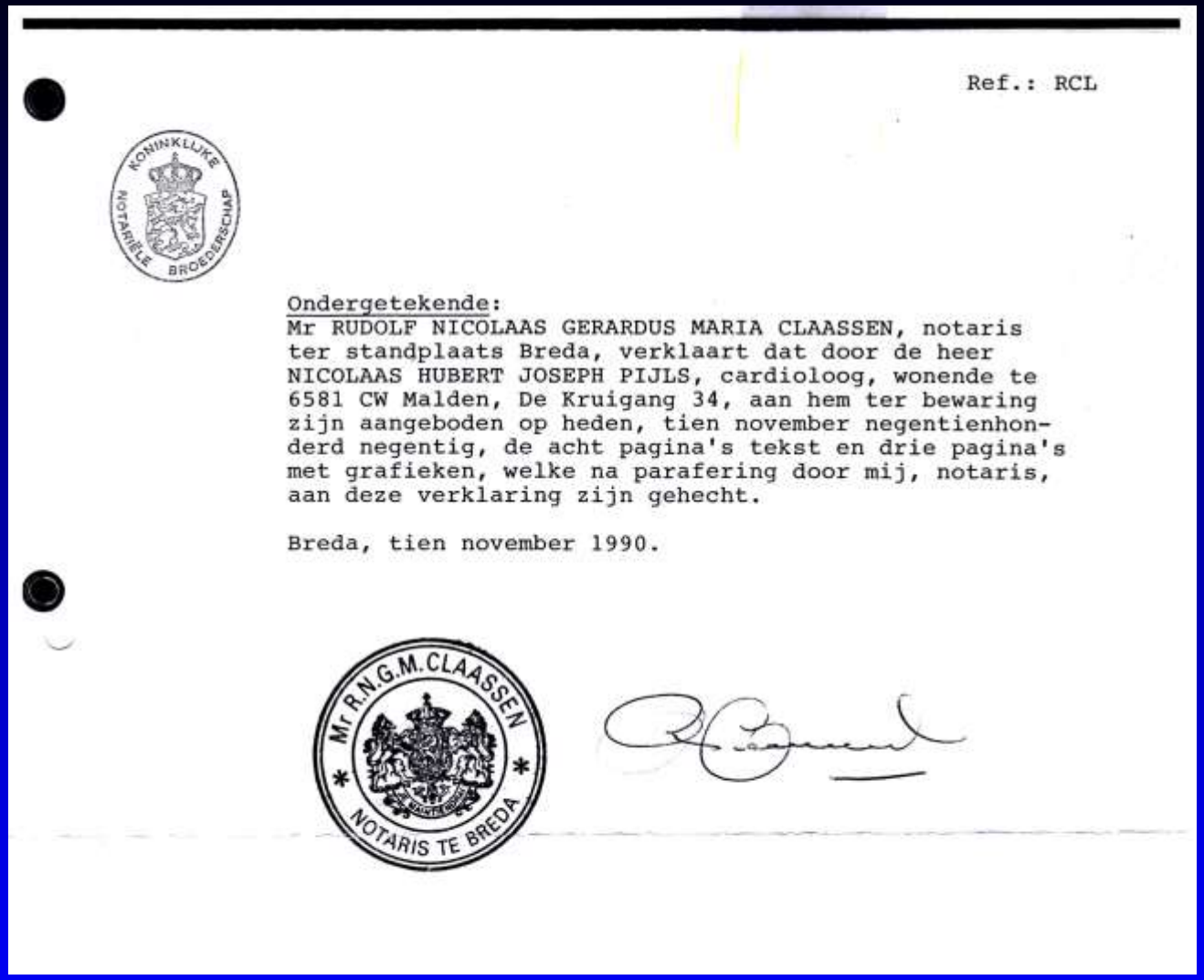
Vertical axis:

FFR_{myo} and *FFR_{coll} measured by Hyperemic pressure ratio*

The Concept of Fractional Flow Reserve (FFR) was born now ⟶

A comlete description of maximum blood flow in all parts of the coronary circulation in terms of pressure

……..although we only use a very small part of it in clinical practice today, i.e. FFR_{myo} or simply called FFR and calculated as P_d / P_a at maximum hyperemia



Ref.: RCL

KONINKLIJKE NOTARIËLE BROEDERSCHAP

Ondergetekende:
Mr RUDOLF NICOLAAS GERARDUS MARIA CLAASSEN, notaris ter standplaats Breda, verklaart dat door de heer NICOLAAS HUBERT JOSEPH PIJLS, cardioloog, wonende te 6581 CW Malden, De Kruigang 34, aan hem ter bewaring zijn aangeboden op heden, tien november negentienhonderd negentig, de acht pagina's tekst en drie pagina's met grafieken, welke na parafering door mij, notaris, aan deze verklaring zijn gehecht.

Breda, tien november 1990.

Mr R.N.G.M. CLAASSEN
NOTARIS TE BREDA

notarial deed dated november 10th 1990: ***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

first full paper in Circulation:may 1993

Circulation Vol 87, No 4 April 1993

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

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-

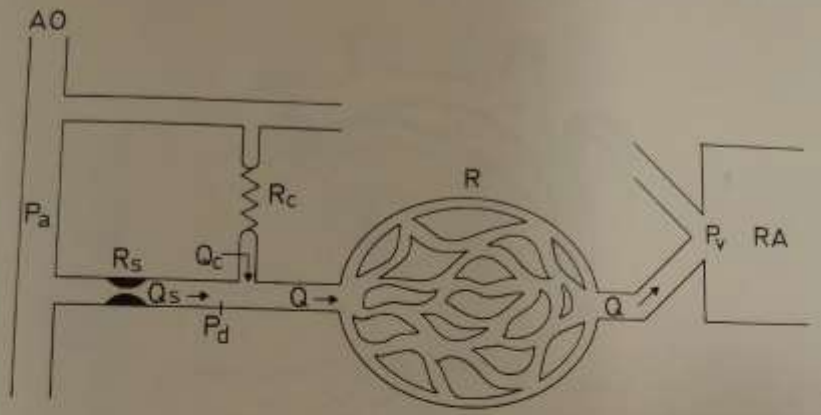


FIGURE 1. *Schematic model representing the coronary circulation. AO, aorta; P_a, arterial pressure; P_d, distal coronary pressure; P_v, venous pressure; Q, blood flow through the myocardial vascular bed; Q_c, collateral blood flow; Q_s, blood flow through the supplying epicardial coronary artery; R, 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

"Official introduction" of Fractional Flow Reserve

The first years were difficult.

- some colleagues did not believe it
  (“too simple, cannot be true”)
- others thought it was too complex
  (the complete derivation is complex indeed)
- some suffered from professional jealousie
  (and gave us a hard time at meetings)
- and some felt threatened in their business
  (“FFR leads to less interventions”)

Fortunately, along the road we got strong support from our colleagues in the Catharina Hospital in Eindhoven (NL) and the OLV Cardiovascular Center in Aalst (B)……

……from an increasing number of dedicated physiologists and cardiologists around the world……..

……and last but not least from a small company from Sweden, called RADI Medical Systems

Thomas Engstrom

Lars Tenerz

RADI Medical Systems, Uppsala, Sweden

Manufacturer of the first "pressure wire"

From the early days on, RADI always supported us in developing and validating FFR, in an extremely fair way, without trying to influence the direction of the research, without pushing for quick results…..

In that way , we could perform and continue independent and robust research, validation studies, and later large clinical prospective randomized trials

The New England Journal of Medicine

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EDITORIAL OFFICES

TELEPHONE 617/734-9800
FAX 617/739-9864

Manuscript No. 95-2627 March 13, 1996

Nico H.J. Pijls MD
Dept. of Cardiology
Catharina Hospital
P.O.Box 1350,
5602 ZA Eindhoven
THE NETHERLANDS

Dear Dr. Pijls:

Thank you for the article, "Fractional Flow Reserve For Clinical Decision Making in Intermediate Coronary Stenosis," which the Journal is pleased to accept for publication. This acceptance is made with the understanding that neither the article itself nor any part of its essential substance, tables or figures has been published or will be submitted for publication elsewhere before it appears in the Journal. News reports about the article should not appear until the date of publication. We assume that financial associations creating possible conflicts of interest for any author have been fully disclosed to the Editor or made clear in the manuscript. Please see our Information for Authors (published in each issue) for further explanation of our policy. Please notify the editor promptly if there are any questions about compliance with this policy.

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The Journal reserves the right to edit manuscripts in accordance with its established style and policy.

Any changes in the manuscript should be sent to the Journal immediately. Once the manuscript is in press, changes become increasingly difficult, and after galley corrections are made, impossible.

Galley proofs and information on reprints will be sent to you about six weeks before publication.

Sincerely yours,

Jerome P. Kassirer M.D.

Jerome P. Kassirer, M.D.
Editor-in-Chief

JPK/pml

First publication
In NEJM in 1996

Threshold value of FFR to detect significant stenosis in humans

How can you validate a new index if no Standard exists ???

→ prospective multitesting Bayesian approach

Pijls et al, N Engl J Med 1996; 334:1703-1708
Oldroyd et al, Circulation 2010

Threshold value of FFR to detect significant stenosis in humans

FFR is the ***only*** functional index which has ever been validated versus a **true gold standard**.
(Prospective multi-testing Bayesian methodology)

ALL studies ever performed in a wide variety of clinical & angiographic conditions, found threshold between 0.75 and 0.80

Diagnostic accuracy 95%

Pijls et al, N Engl J Med 1996; 334:1703-1708
Oldroyd et al, Circulation 2010

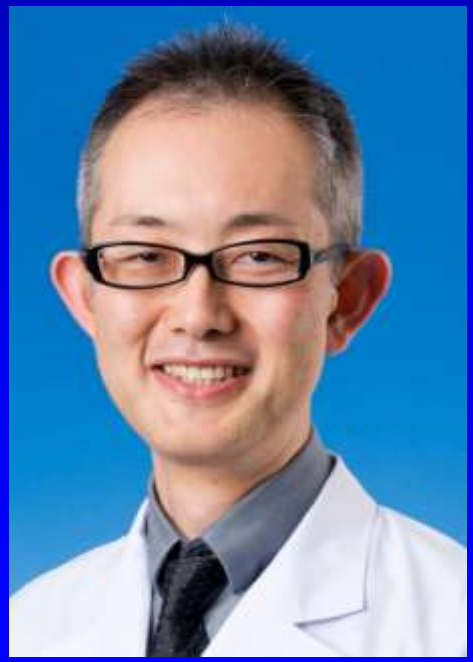
FFR in the United States (2002)

(just a few of the pioneers)

FFR in Asia

Japan and Korea
from late nineties on

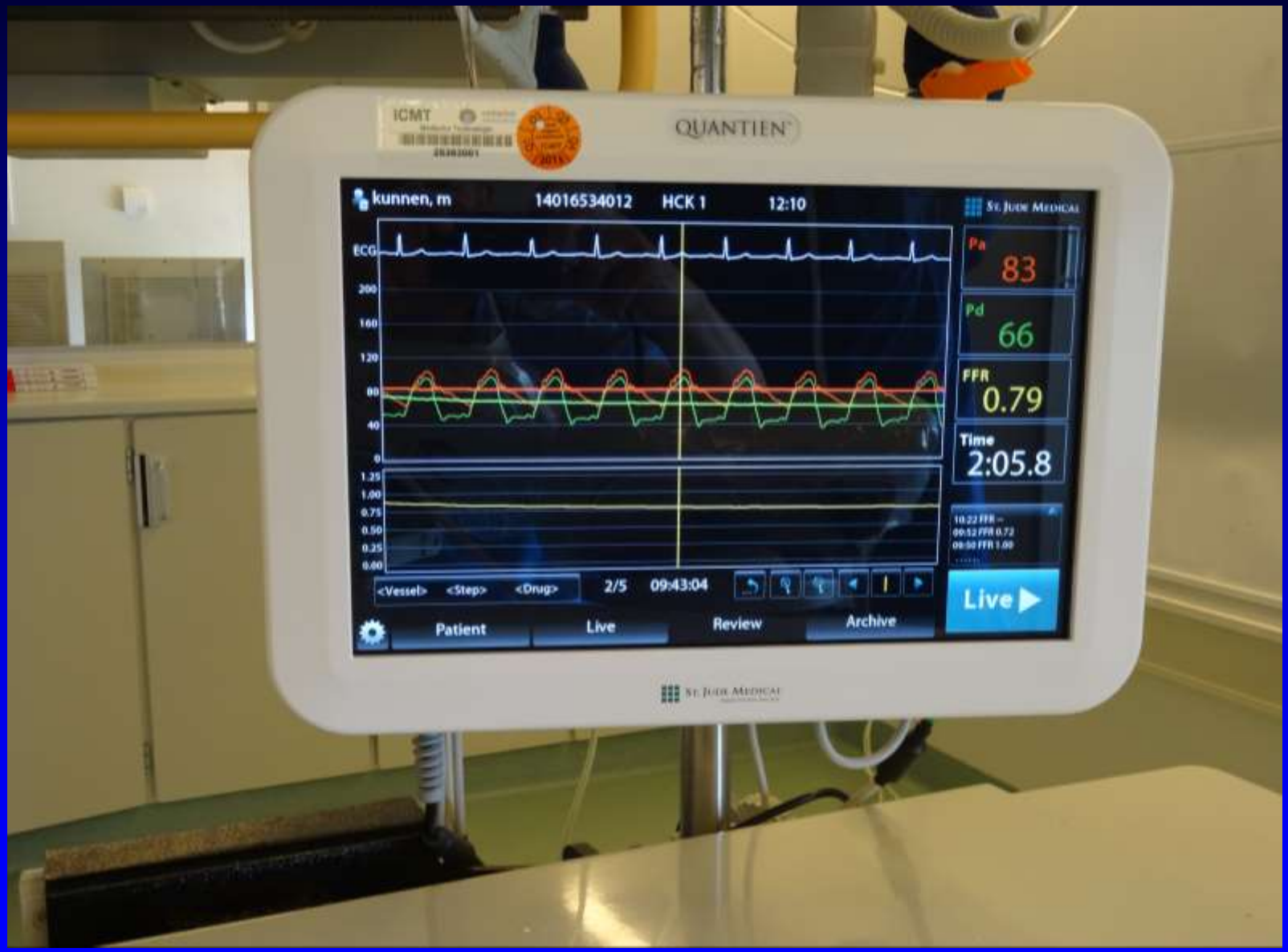
(just a few of the pioneers with whom I had the pleasure to work)



In 2008, RADI Medical Systems was taken over by a large US Company, St Jude Medical Systems, which continued to support applied coronary physiology in the cath lab in an unrestricted way and further boosted new standards in Pressure Wires and associated equipment……

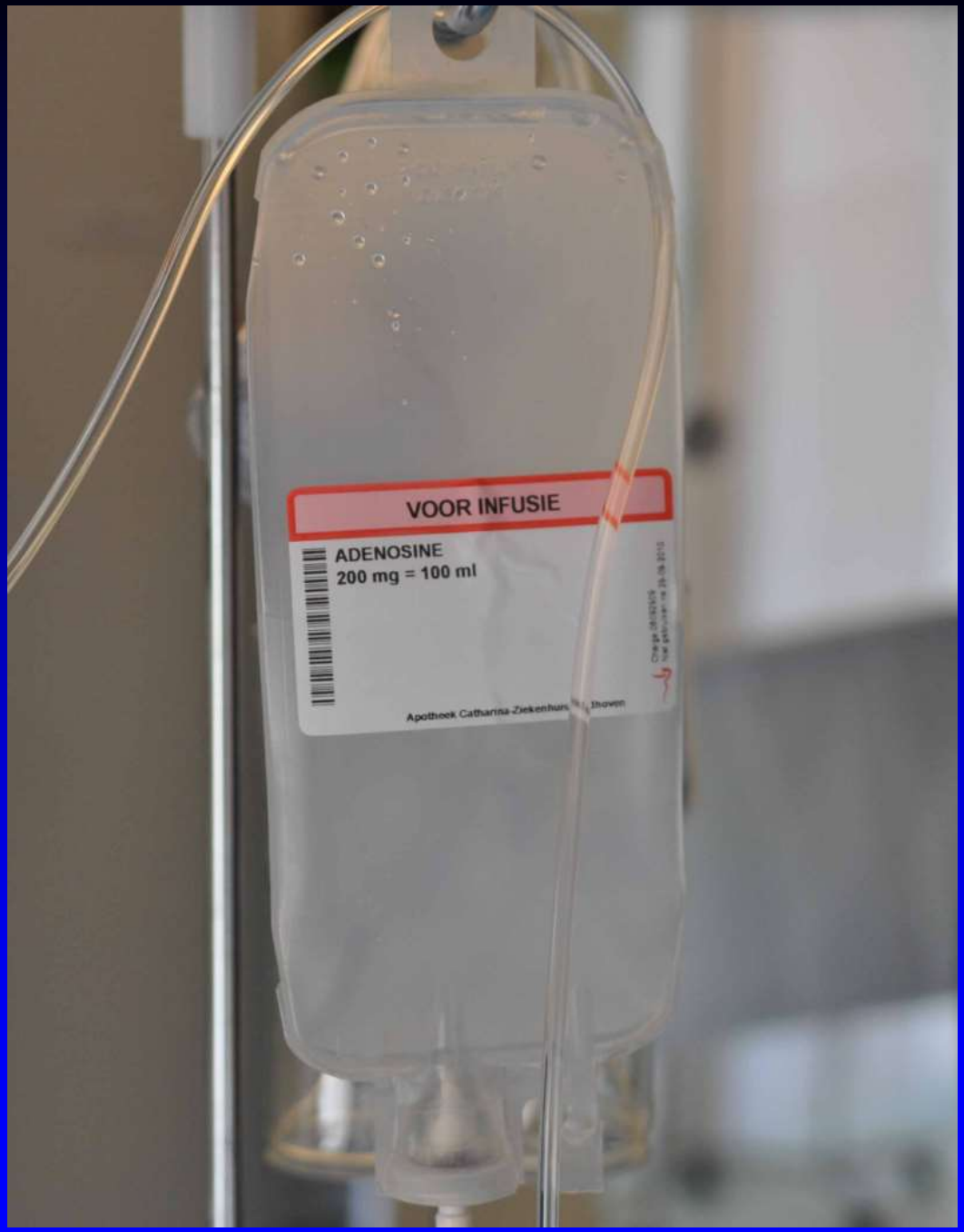
RADI → ST. JUDE MEDICAL
MORE CONTROL LESS RISK

users friendly, “quiet” interface



Logistics in the cath lab is paramount

(fixed set-up, induction of hyperemia, pullback, etc)



Adenosine for
i.v. infusion

(standard bag
200 mg = 100 ml)

price: Euro 2,=
per bag

prepared by
hospital pharmacy

manifacturing
protocol available
at carias@cze.nl

adenosine

Infusion pump

Quantien

- *no preparation in the lab*
- *no difficult calculations*
- *always the same dilution*
- *no risk of dosage error*
- *no loss of time*

HYPEREMIA MANDATORY ?

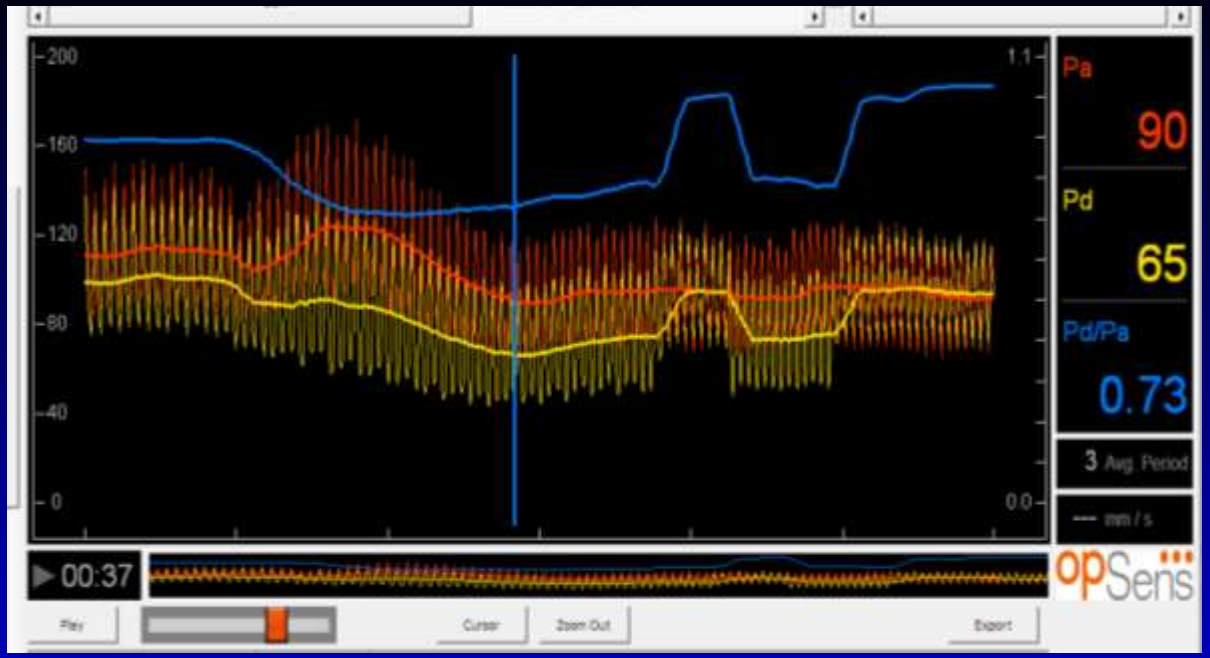
- Next presentation by Dr Fearon
- Lectures by Dr Escaned and Dr Pijls
  Tomorrow afternoon 2.25-2.41 p.m.

Presently, several new players have entered the market with fiberoptic presssure wires…….

- ***ACIST:*** ***micro-catheter Navvus***
  caveat: overestimation of gradients

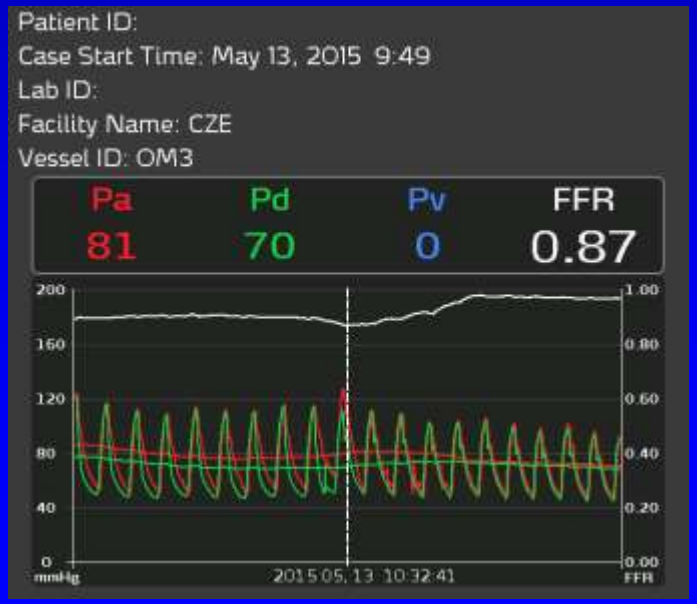
- ***OPSENS: fiberoptic pressure wire (Optowire)***
  (available in Japan and Europe, in USA Q1-2016)

- ***Boston Scientific: Q1-2016***



OPSENS fiberoptic Pressure wire OPTOWIRE-2

Acist micro-catheter



FFR has been validated in almost all clinical and Angiographic conditions:

- multivessel disease
- left main and ostial stenosis
- diffuse disease
- bifurcation lesions
- tandem lesions
- unstable angina
- previous myocardial infarction
- etc….

- ….*but not to be used in acute STEMI*

FINALLY:……..

……The windtunnel for every technique is clinical outcome !!

→ **FAME, DEFER, and many other studies**

(tomorrow at 3.40 pm)

FAME 1 and FAME 2 Studies, supported by RADI and St Jude Medical, showed that:

FFR –guided PCI:

- **improves outcome**
- **improves quality of live**
- **is cost-saving**
- **reduces radiation and contrast exposure**
- **does not prolong time of procedure**

→ **makes PCI to a better and safer treatment**

Tonino et al, NEJM 2009; Pijls et al, JACC 2010
De Bruyne et al, NEJM 2012

"the third stage of truth: being accepted as self-evident"

GUIDELINES ESC SEPTEMBER 2010-2014

FFR UPGRADED TO LEVEL I A INDICATION

10 – Procedural aspects of PCI

Table 28: Specific PCI devices and pharmacotherapy		
	Class	**Level**
FFR-guided PCI is recommended for detection of ischemia-related lesion(s) when objective evidence of vessel-related ischamia is not available	**I**	**A**
DES* are recommended for reduction of restenosis/reocclusion, if no contraindication to extended DAPT	**I**	**A**
Distal embolic protection is recommended during PCI of SVG disease to avoid distal embolisation of debris and prevent MI	**I**	**B**
Rotablation is recommended for preparation of heavily calcified or severely fibrotic lesions that cannot be crossed by a balloon or adequately dilated before planned stenting	**I**	**C**

ESC-EACTS Guidlines for Myocardial Revascularisation, August 30, 2010