CORONARY PHYSIOLOGY IN THE CATHLAB:

STRUCTURE AND FUNCTION OF THE CORONARY CIRCULATION

Educational Training Program ESC
European Heart House
april 25th - 27th 2013

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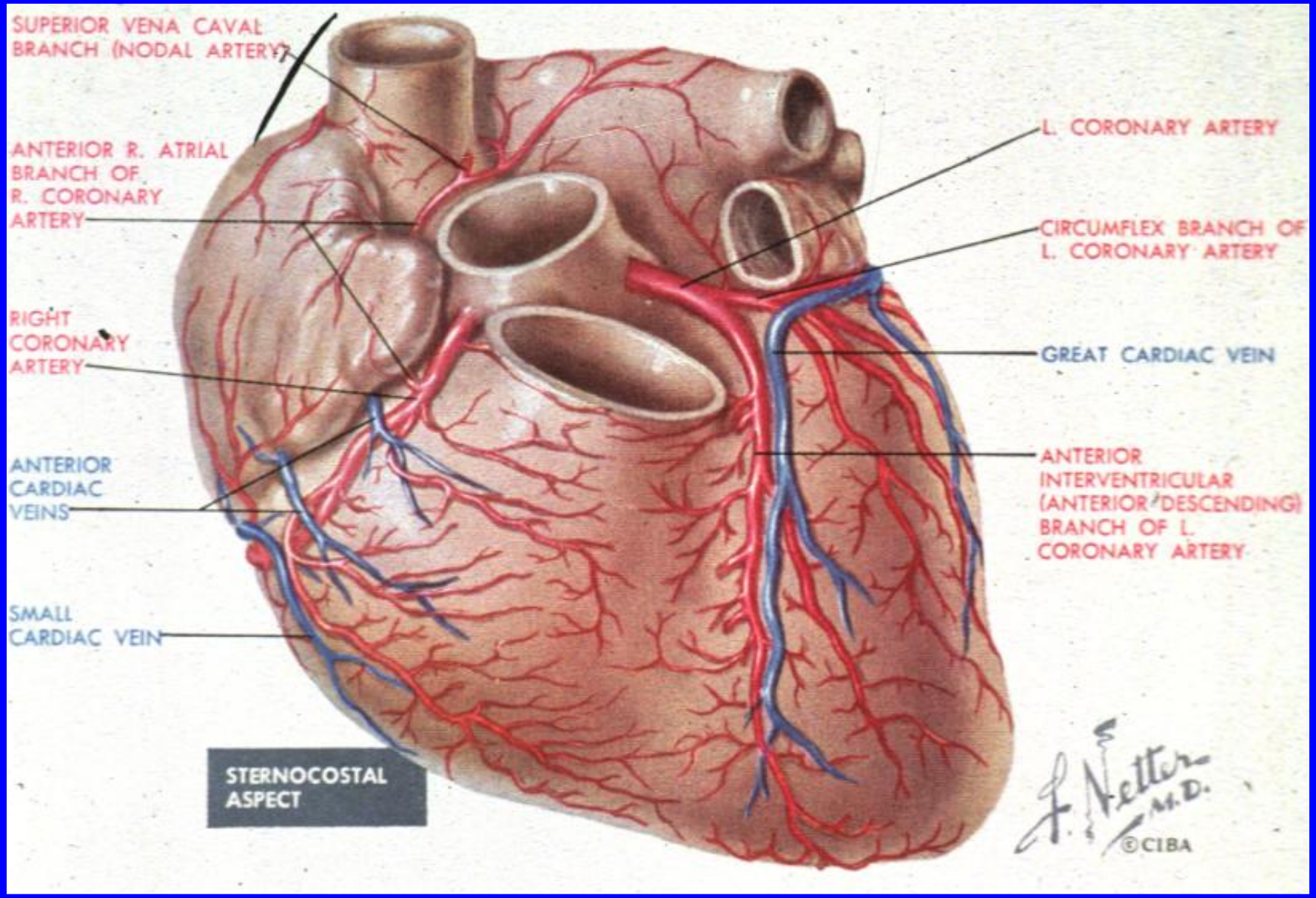
Disclosures:

Dr Pijls receives institutional research grants from St Jude Medical, and Maquet

Dr Pijls is consultant to St Jude Medical, and to Heartflow

ISSUES TO BE DISCUSSED

- structure of the coronary circulation
- relation between vessel size and perfusion area
- endothelium and development of atherosclerosis
- the 2 or 3 compartment model of the coron circulation
- collaterals
- why functional testing / FFR ?
- which lesions should be treated


SUPERIOR VENA CAVAL BRANCH (NODAL ARTERY)
ANTERIOR R. ATRIAL BRANCH OF R. CORONARY ARTERY
RIGHT CORONARY ARTERY
ANTERIOR CARDIAC VEINS
SMALL CARDIAC VEIN
L. CORONARY ARTERY
CIRCUMFLEX BRANCH OF L. CORONARY ARTERY
GREAT CARDIAC VEIN
ANTERIOR INTERVENTRICULAR (ANTERIOR DESCENDING) BRANCH OF L. CORONARY ARTERY
STERNOCOSTAL ASPECT
F. Netter M.D.
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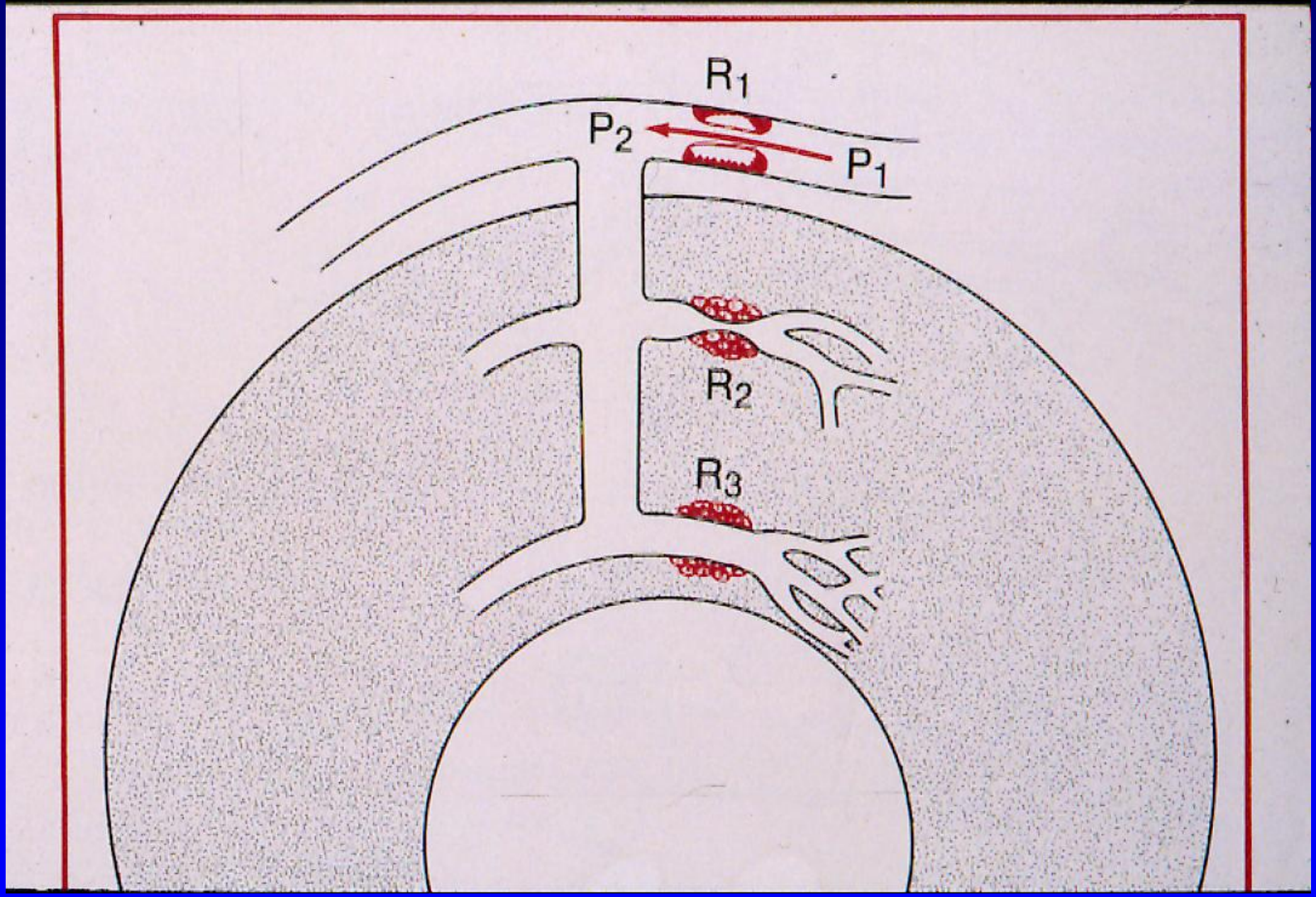
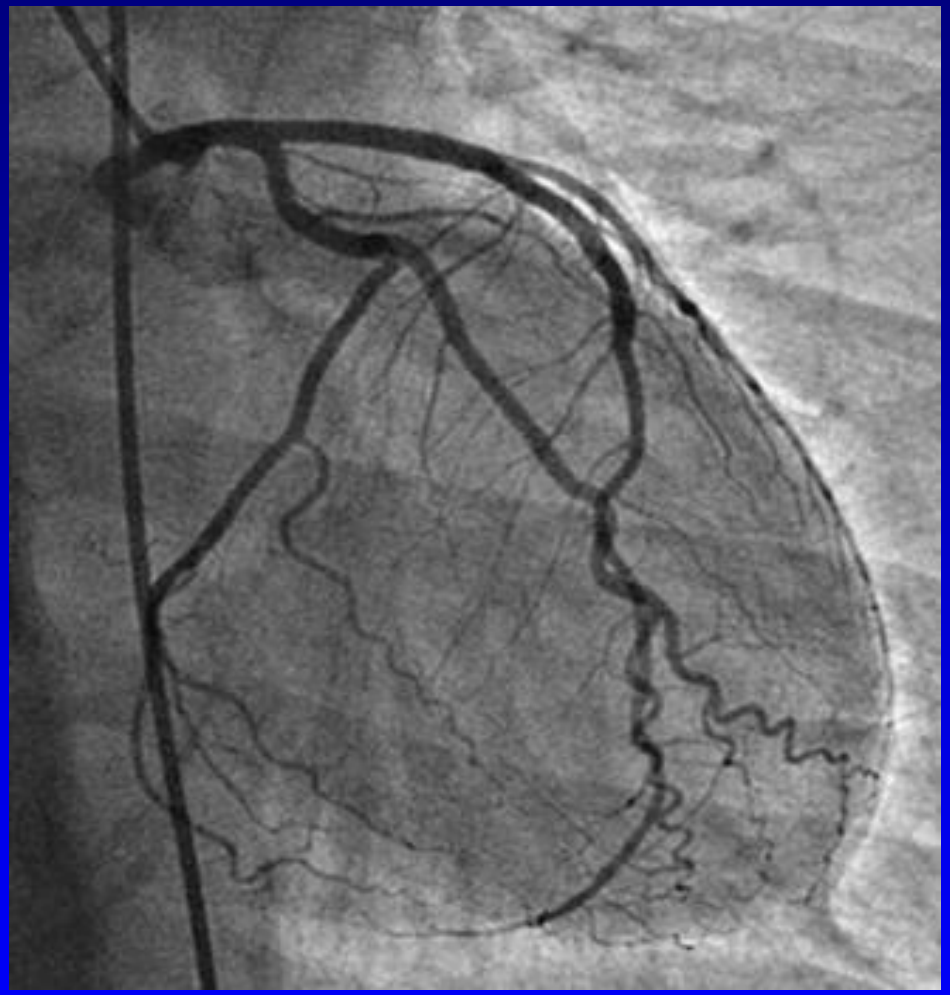
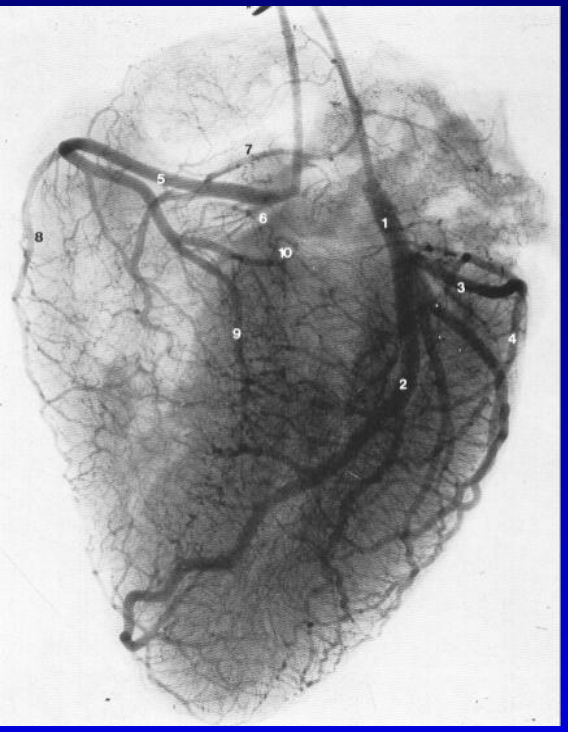


03 cc/schema Braunwald



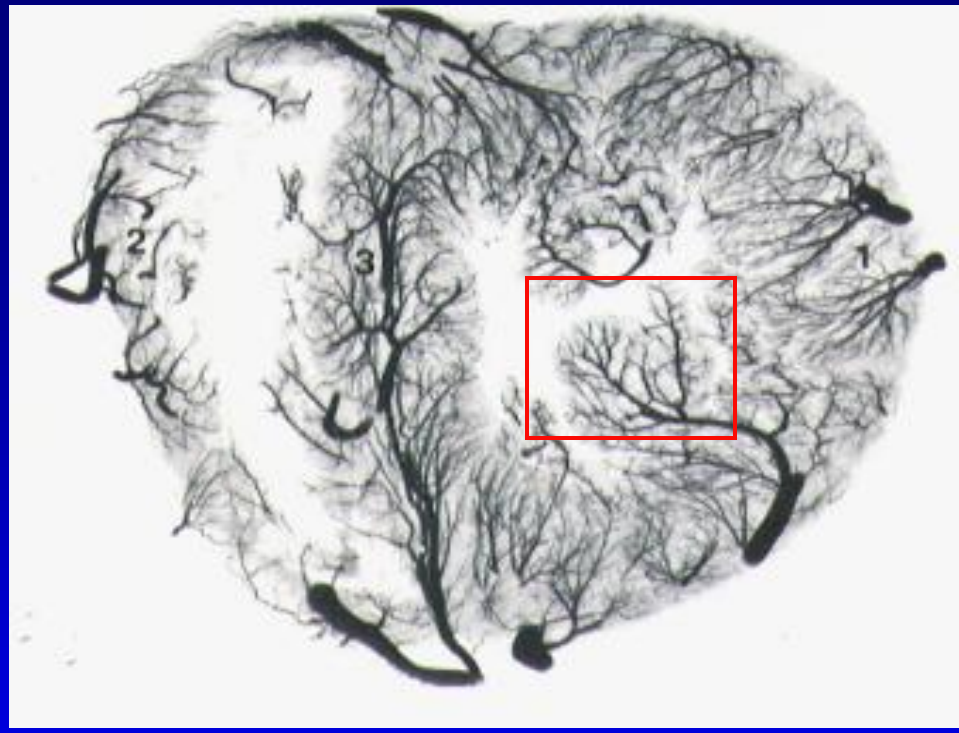
Let's have a closer look at the coronary tree…..

Fractale structure of the coronary circulation (Gould, Finet)



X 1

X 0.75

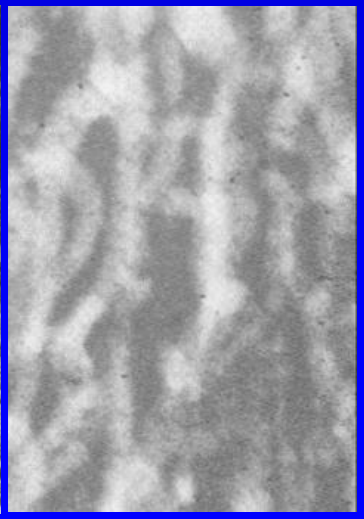


X 4.5

X 10.5

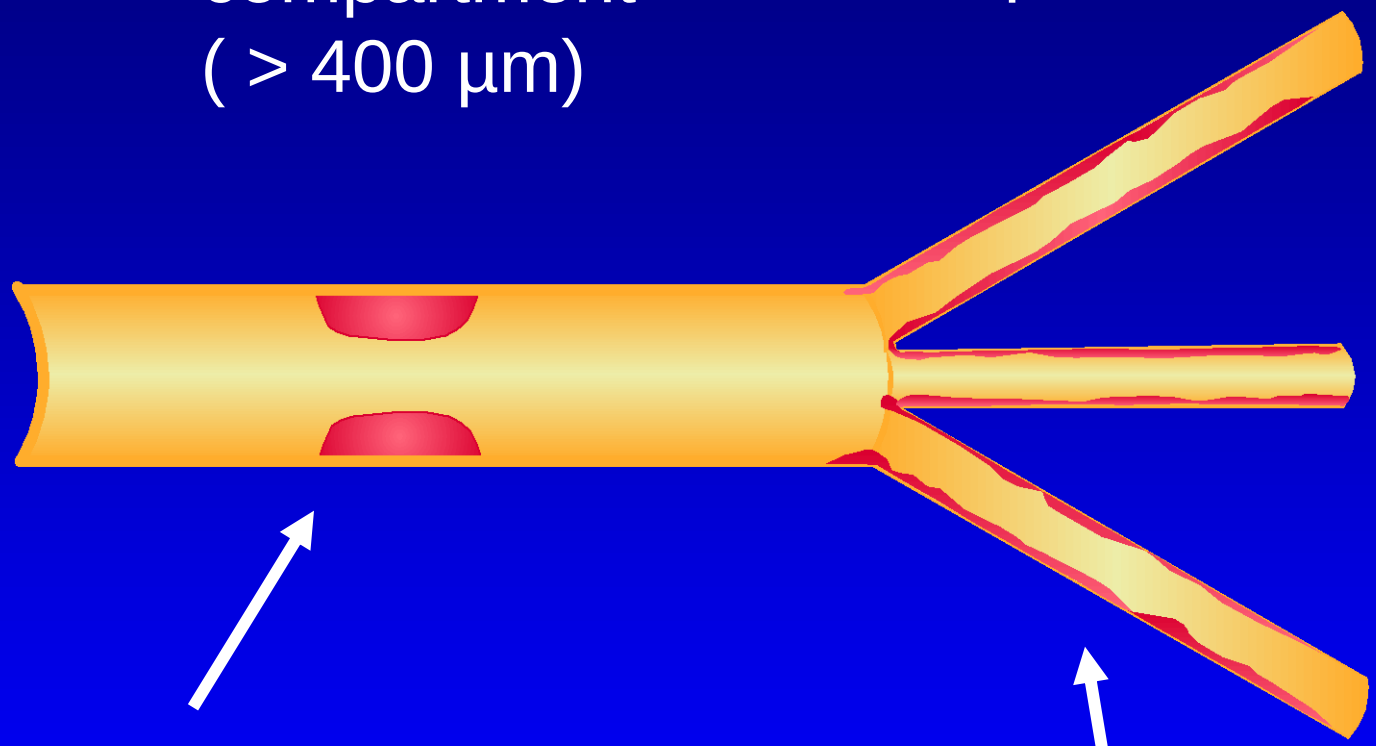
X 90

X 1100



epicardial
compartment
(> 400 µm)

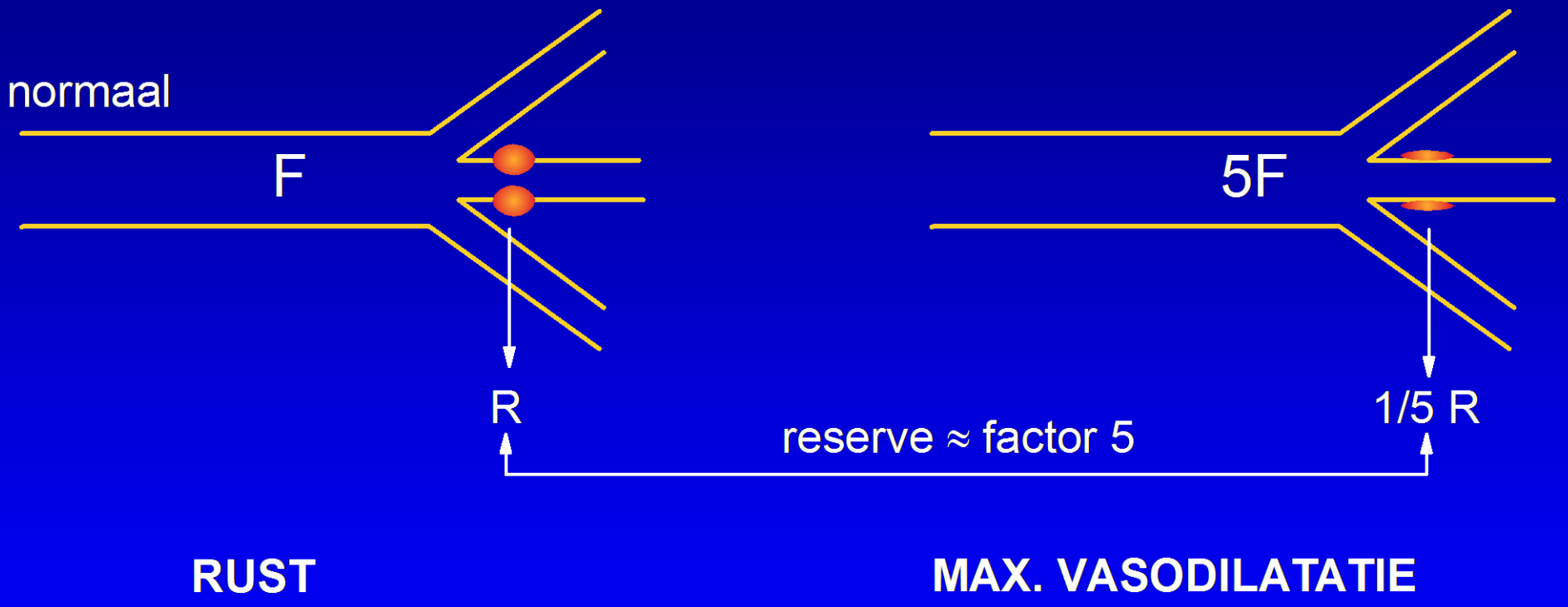
microvascular
compartment



traditionally visible by angiography
and more recently by many invasive
and non-invasive imaging methods

Black box
(until recently)

Regulation of coronary blood flow by arteriolar sphincters



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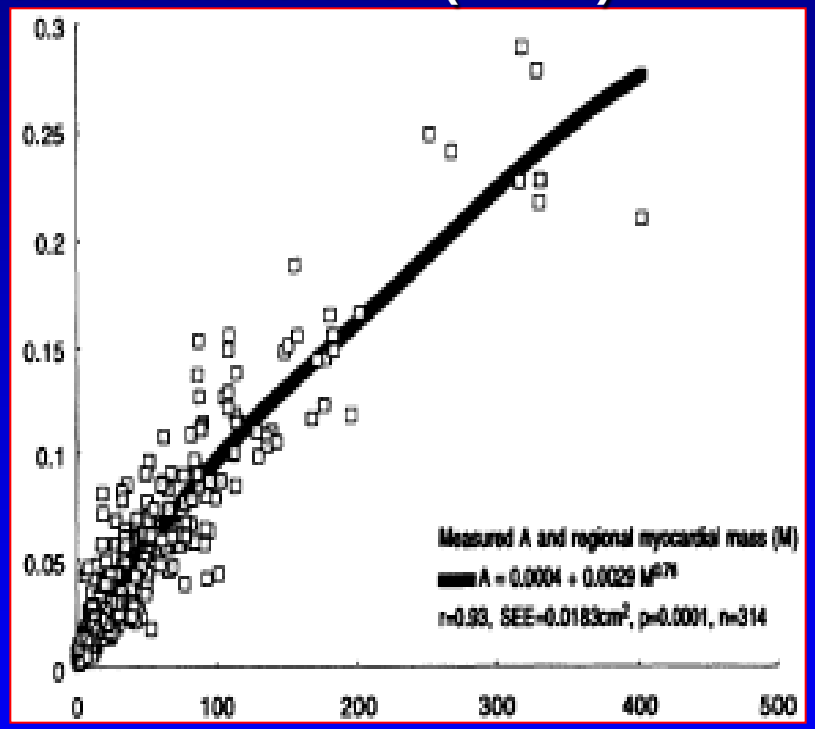
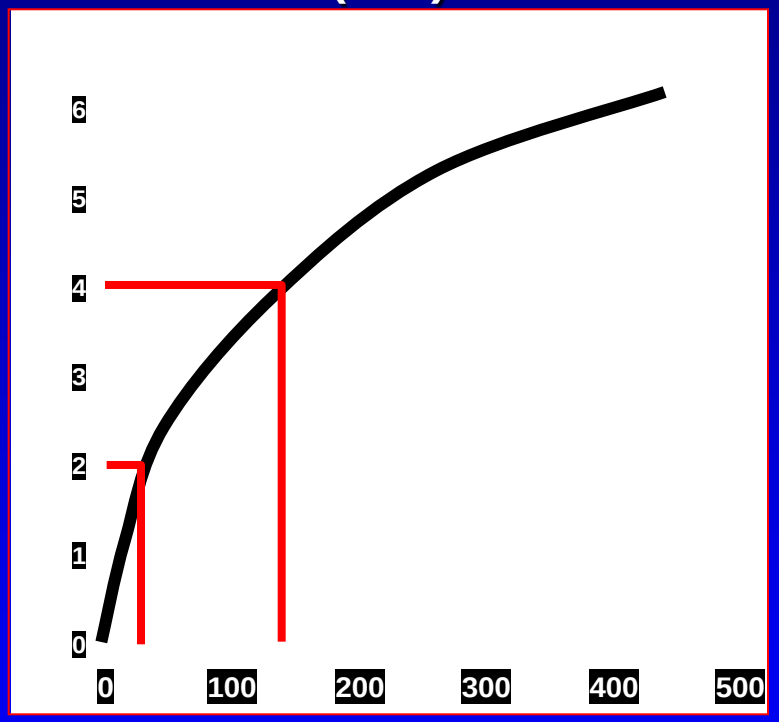
Relationship between vessel size and myocardial mass

Cross Sectional Area (~ flow)



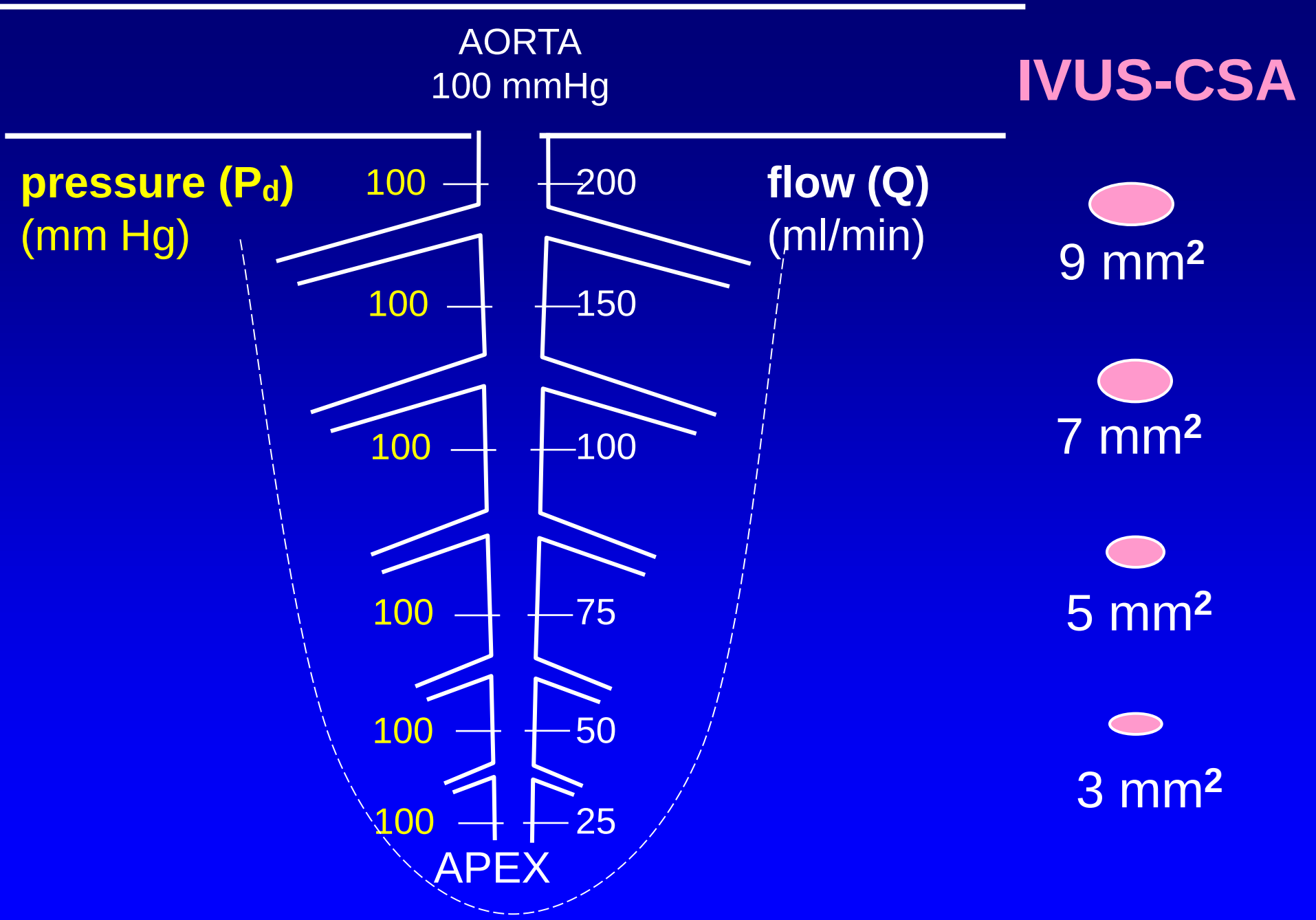
Regional Myocardial Mass

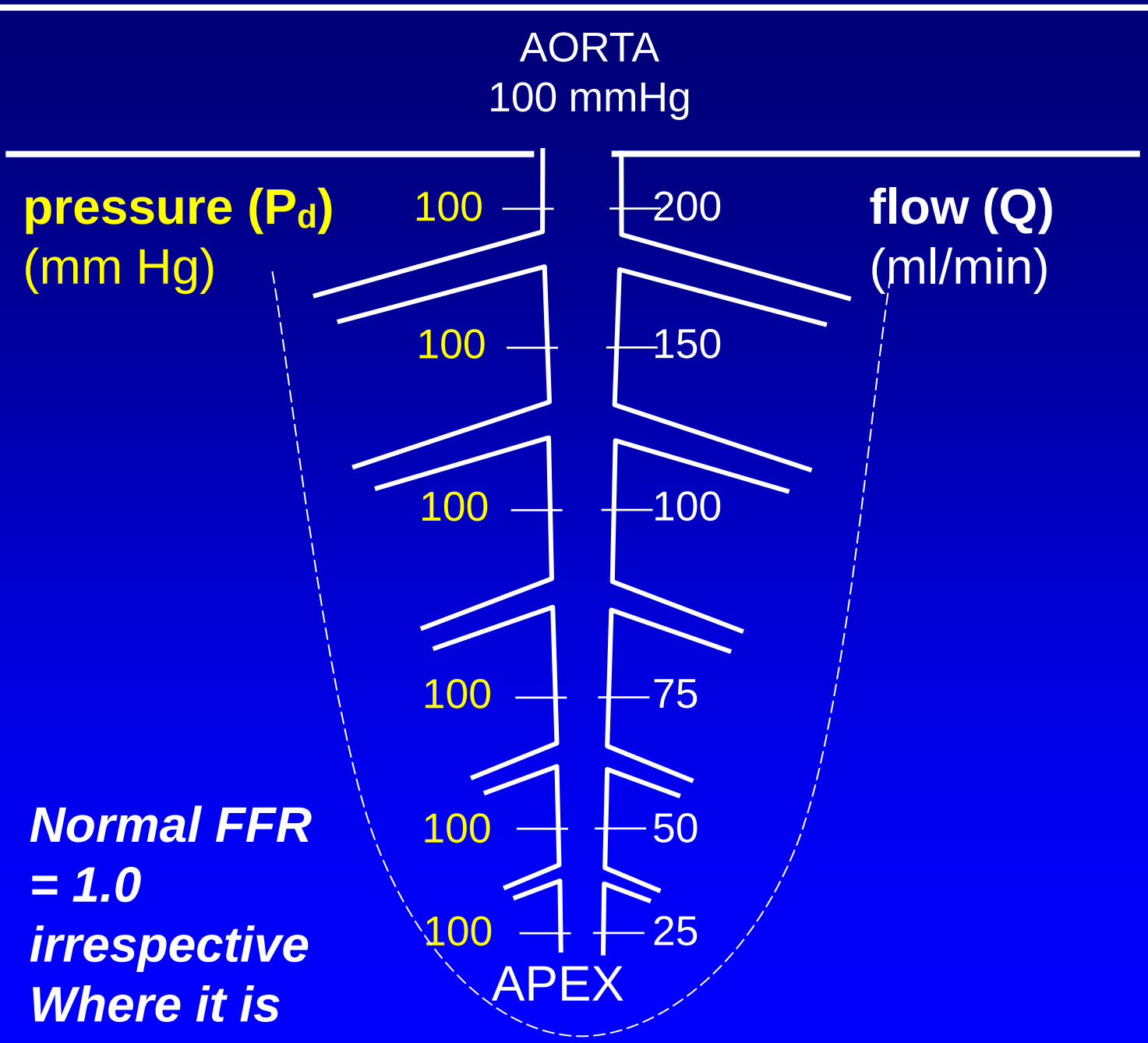
Vessel Diameter (mm)



Regional Myocardial Mass (Grams)

C. Seiler, Lance Gould, et al Circulation 1992


AORTA
100 mmHg
pressure (P_d)
(mm Hg)
flow (Q)
(ml/min)
100
200
100
150
100
100
100
75
100
50
100
25
APEX
IVUS-CSA
9 mm²
7 mm²
5 mm²
3 mm²



IVUS-CSA

9 mm²

7 mm²

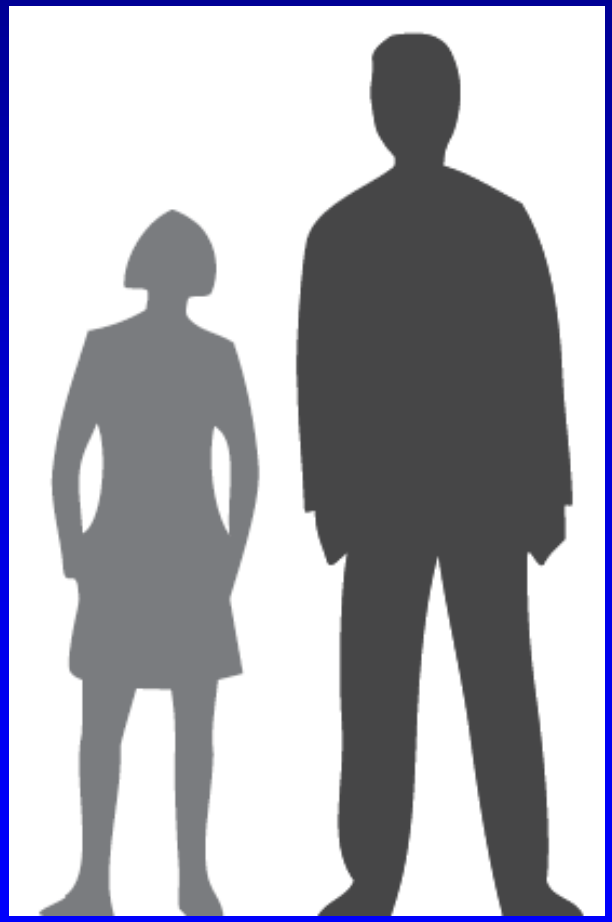
5 mm²

3 mm²

Normal FFR = 1.0 irrespective Where it is measured

SIZE of the person

FFR = 0.68 means exactly the same in both persons



CSA by IVUS = 3.3 mm^2 has a completely different meaning in both persons

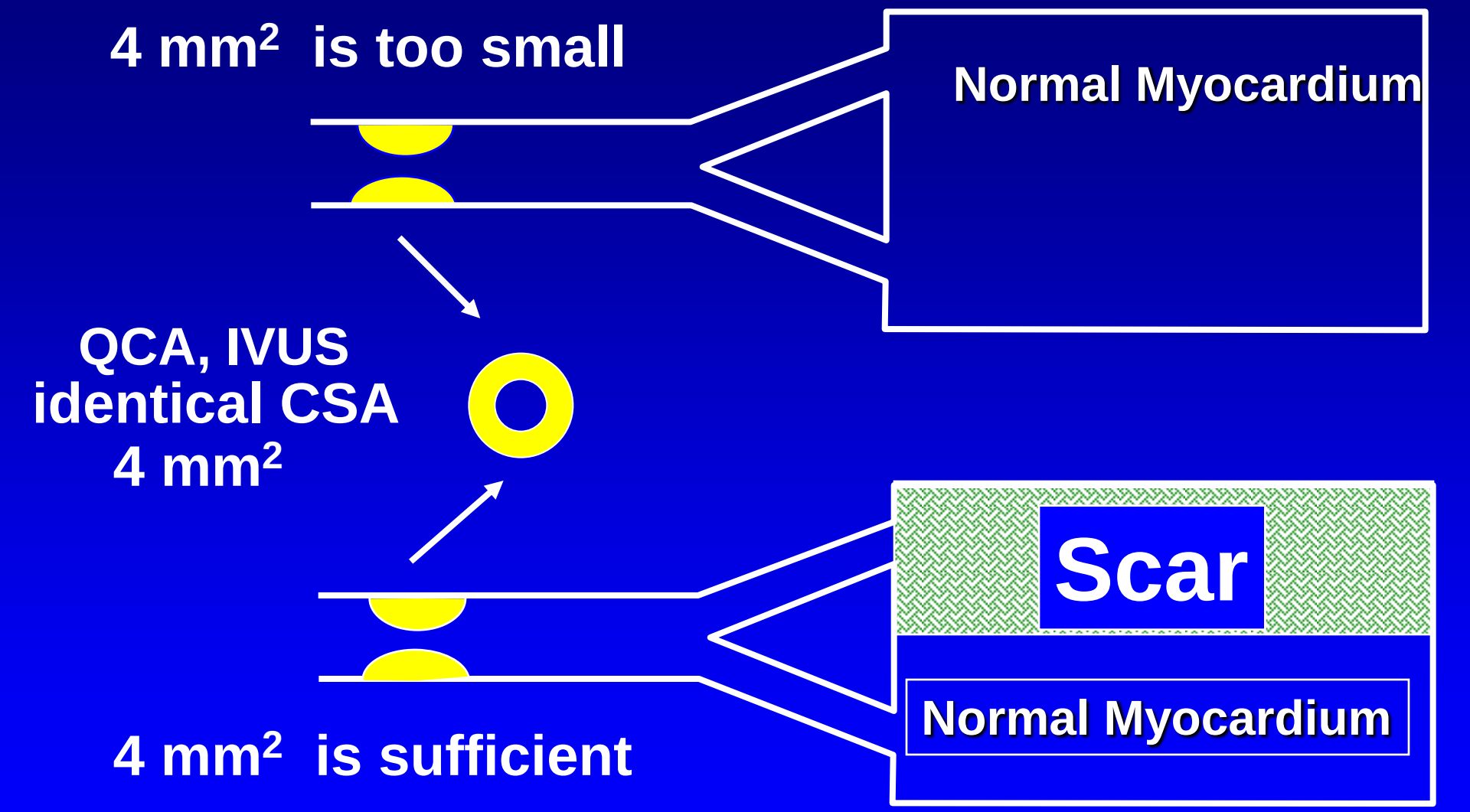
Value of ANY morphologic methodology (QCA, IVUS, OCT) to assess functional significance of a stenosis is limited by definition because there is simply no normal reference value

! We cannot understand the physiologic significance of a stenosis without taking into account the extent of the distal perfusion territory !

……*especially not under pathologic conditions, when the "physiologic match" between vessel size and perfusion area has been lost*

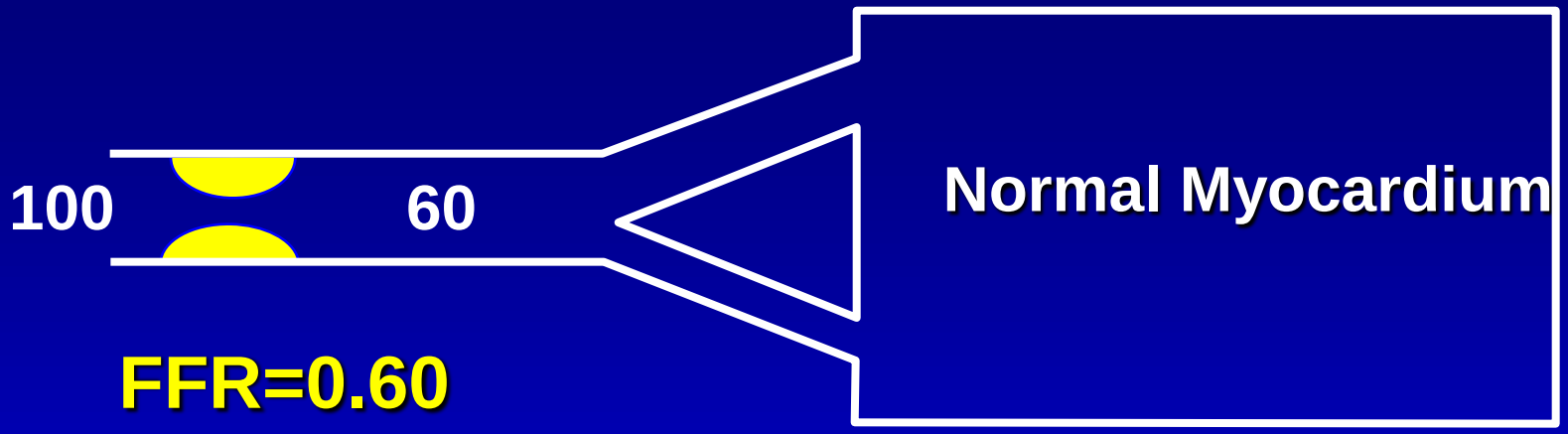
With permission of Dr Haitma Amin, Bahrain

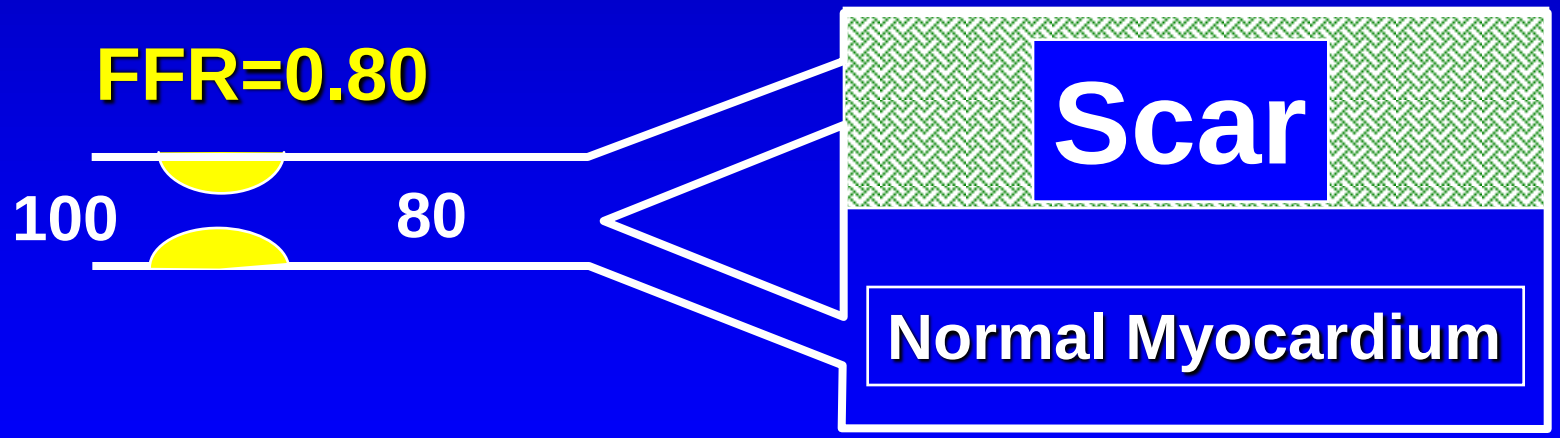
similar stenosis but different extent of perfusion area



identical CSA, but different significance of stenosis

FFR accounts for the extent of the perfusion area:

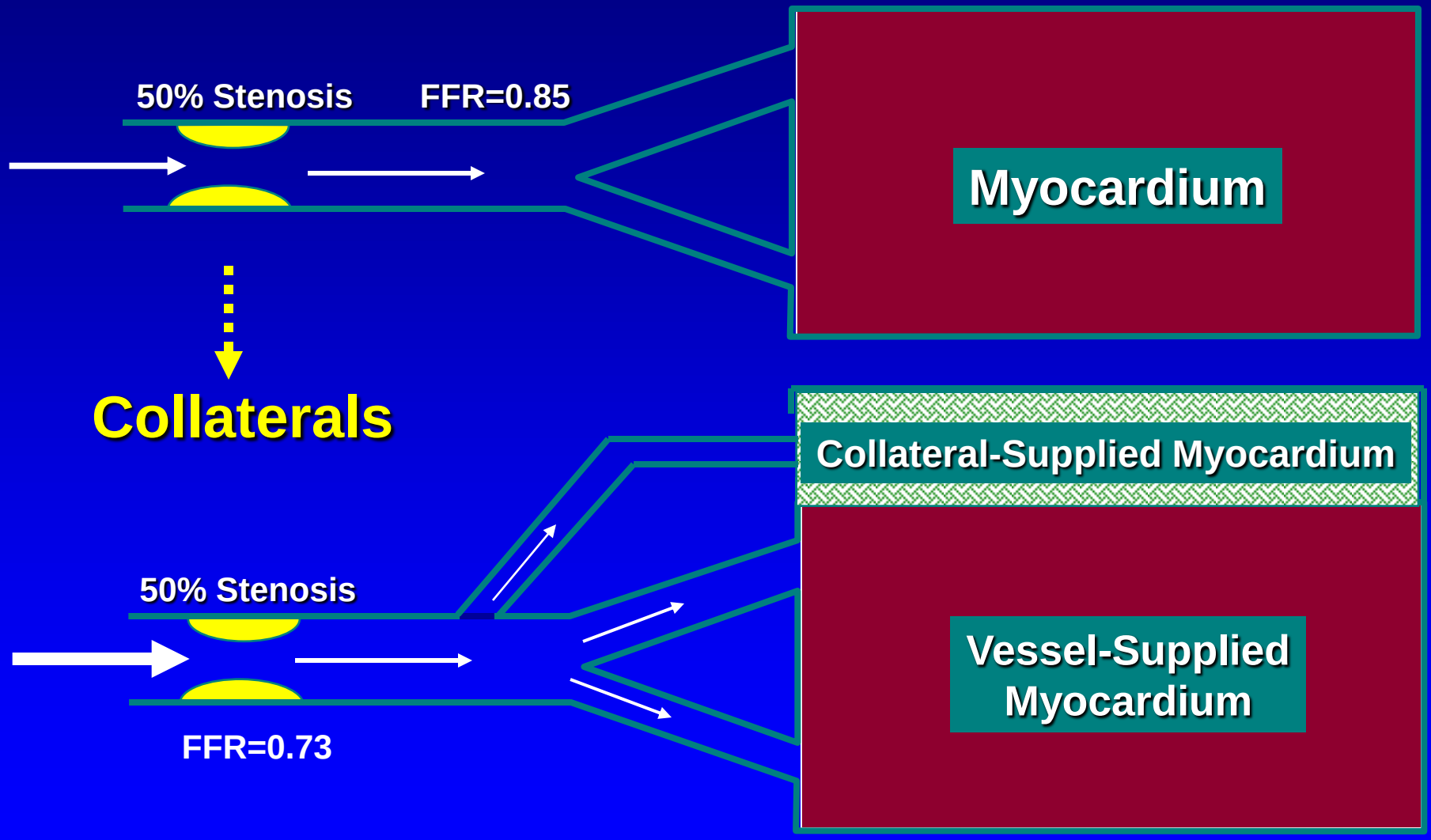




Anatomic stenosis severity by IVUS or QCA is identical but physiologic severity has decreased.

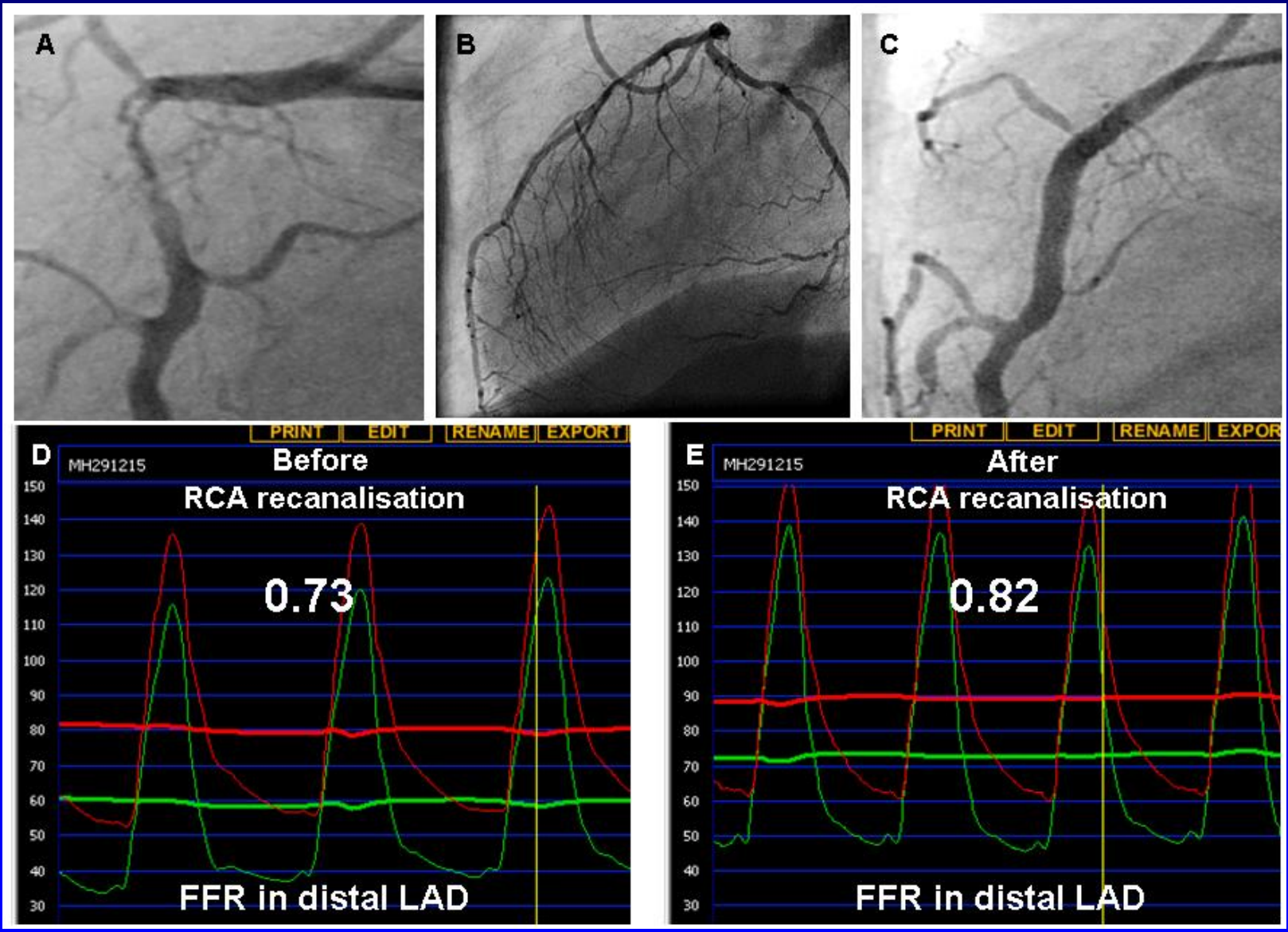
→ *FFR accounts for these changes !!!*

Disconnect between Anatomy and Physiology



…During Maximal Hyperemia

FFR in the distal LAD before and After recanalization of the RCA



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DEVELOPMENT OF ATHEROSCLEROSIS

Normal

↓

Endothelial dysfunction

↓

First stages of atherosclerosis:

↓ ***IVUS, OCT, FFR (abnormal pressure decline)***

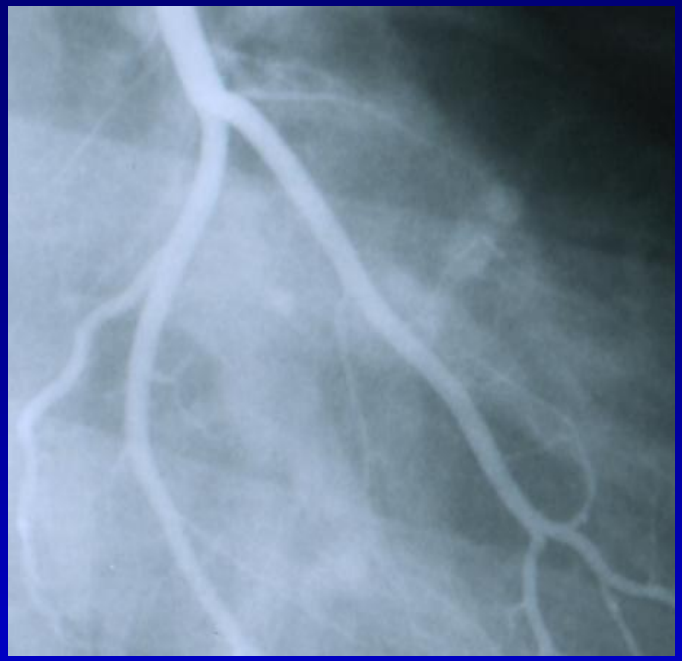
Macroscopic atherosclerotic disease:

angio,

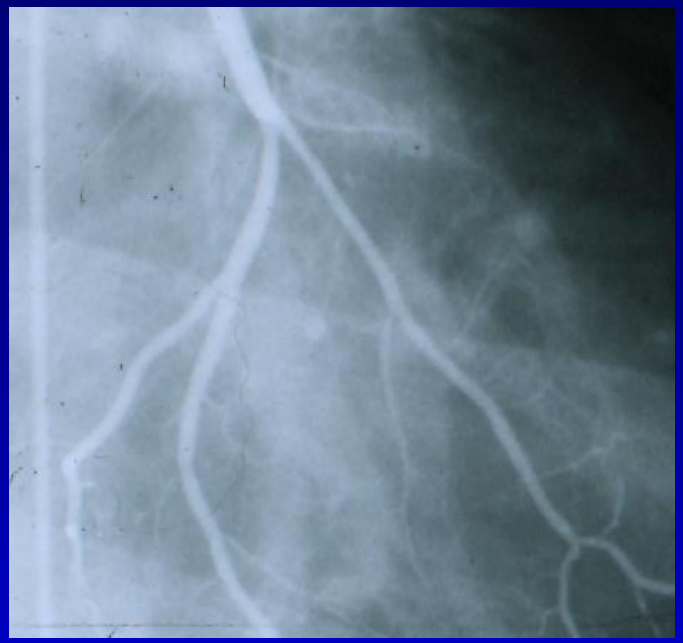
non-invasive imaging (CT, MRI)

The earliest phase of atherosclerotic coronary disease, is endothelial dysfunction.

This is unvisible by any imaging method, but can be demonstrated by functional testing.



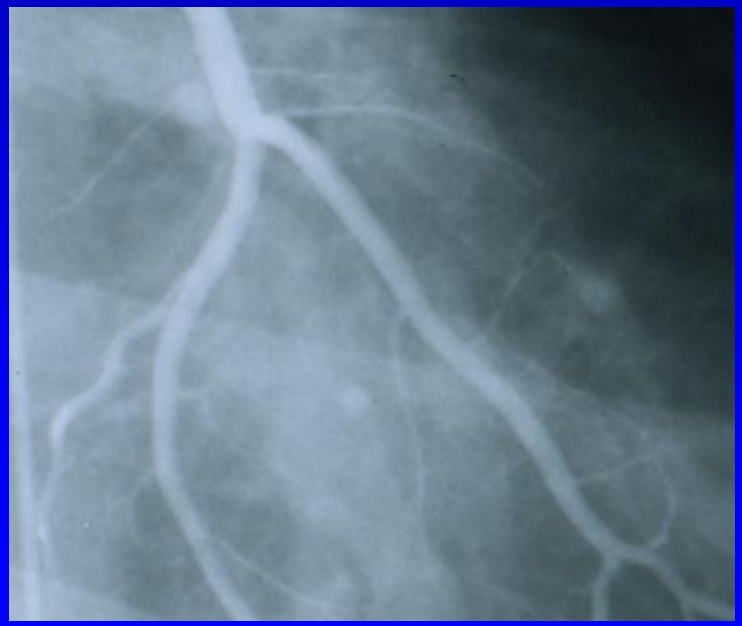
baseline



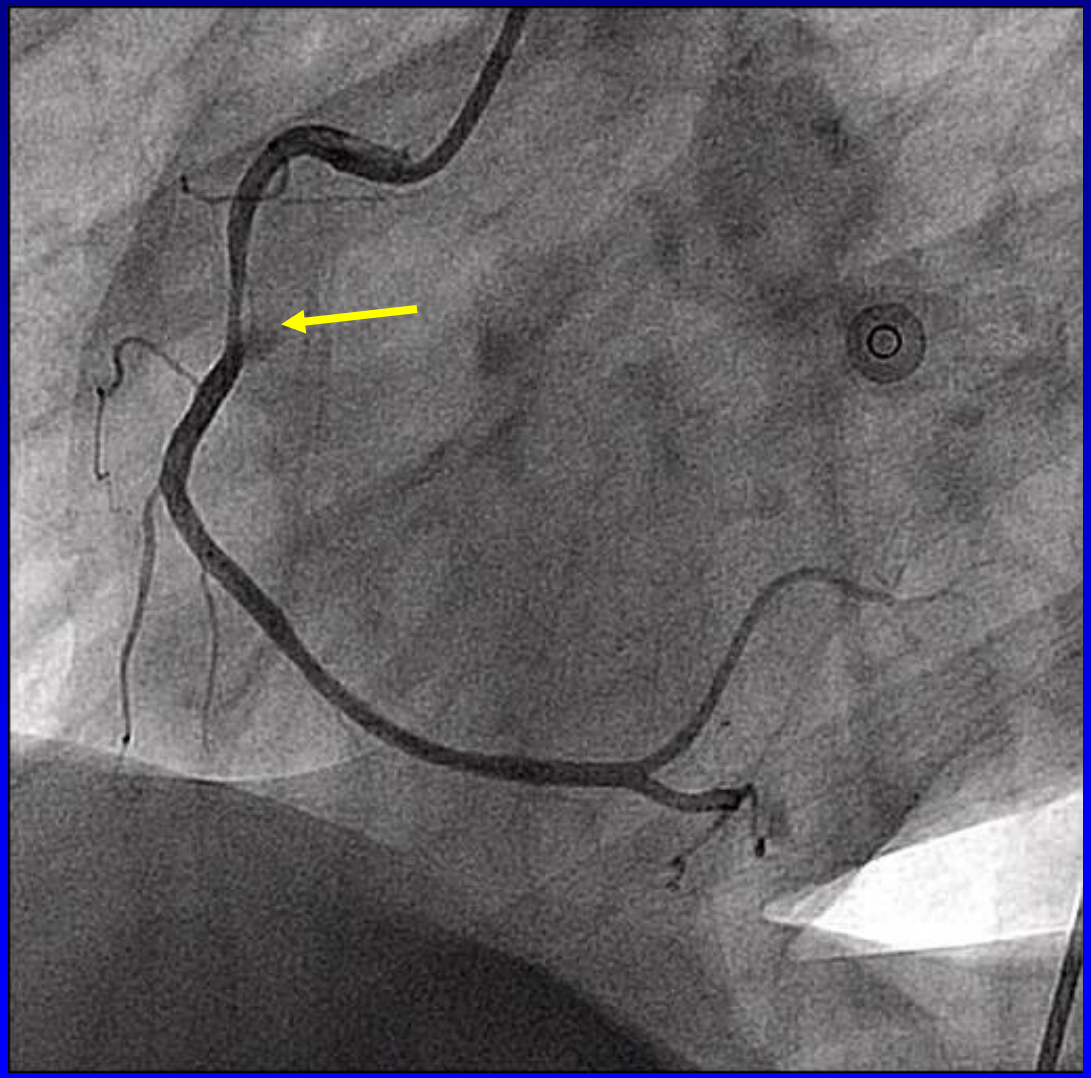
ACh

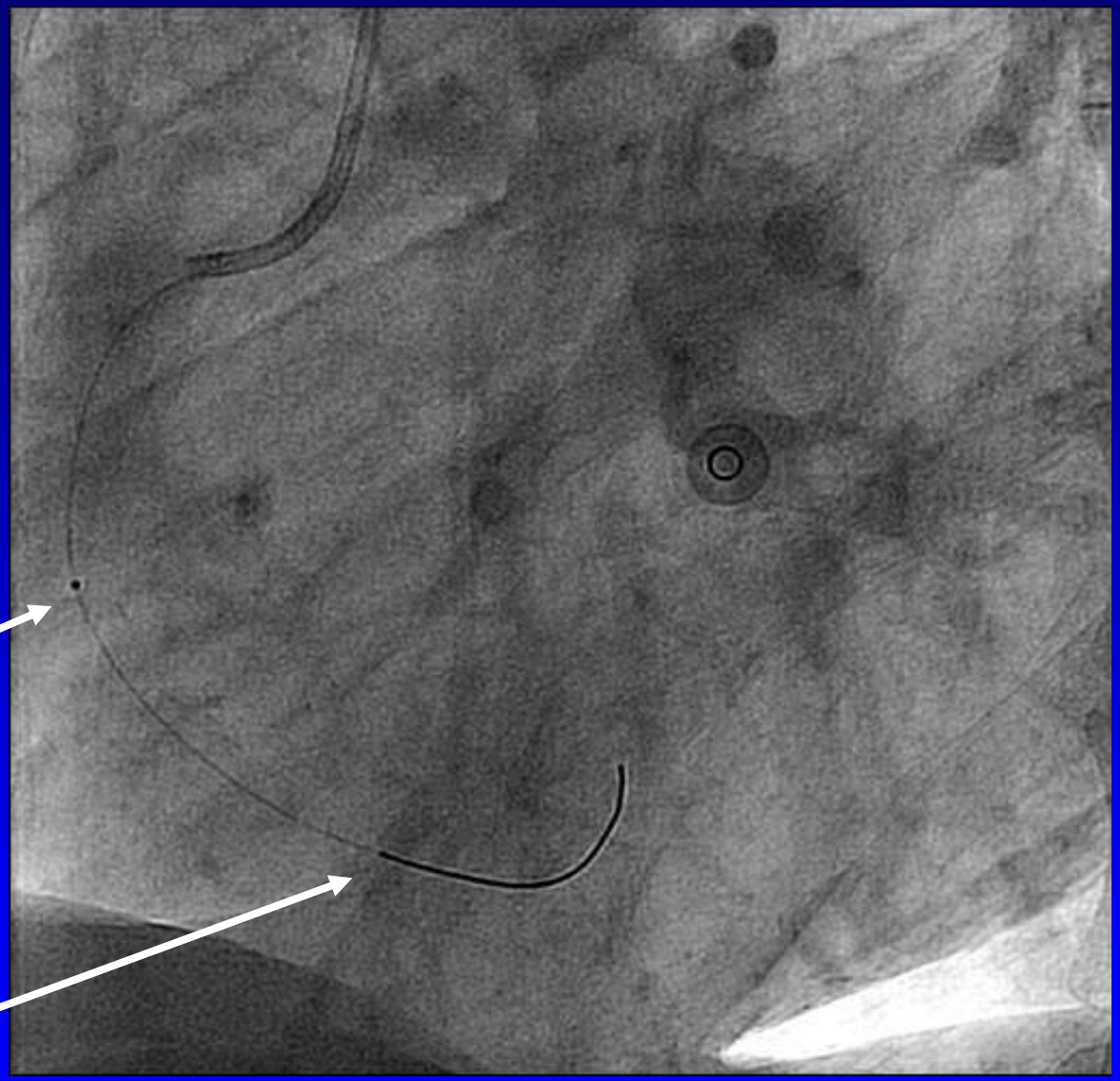
35-y-old male,
hypertension,
heavy smoker,
chest pain at exercise
and positive ET

NTG



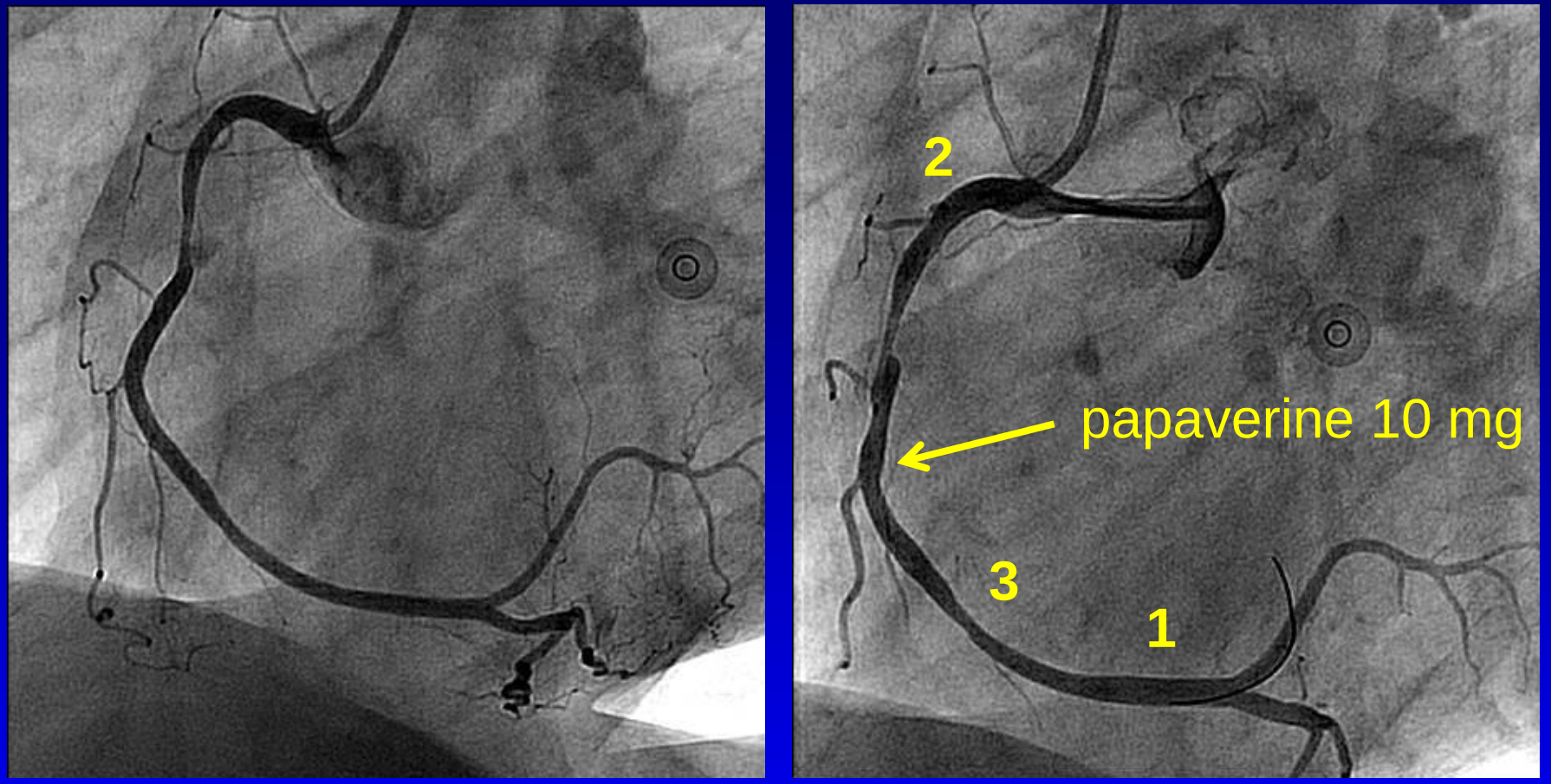
Physiologic ***and*** pathologic vasomotion in 35-year old male, heavy smoker, and chest pain at exercise





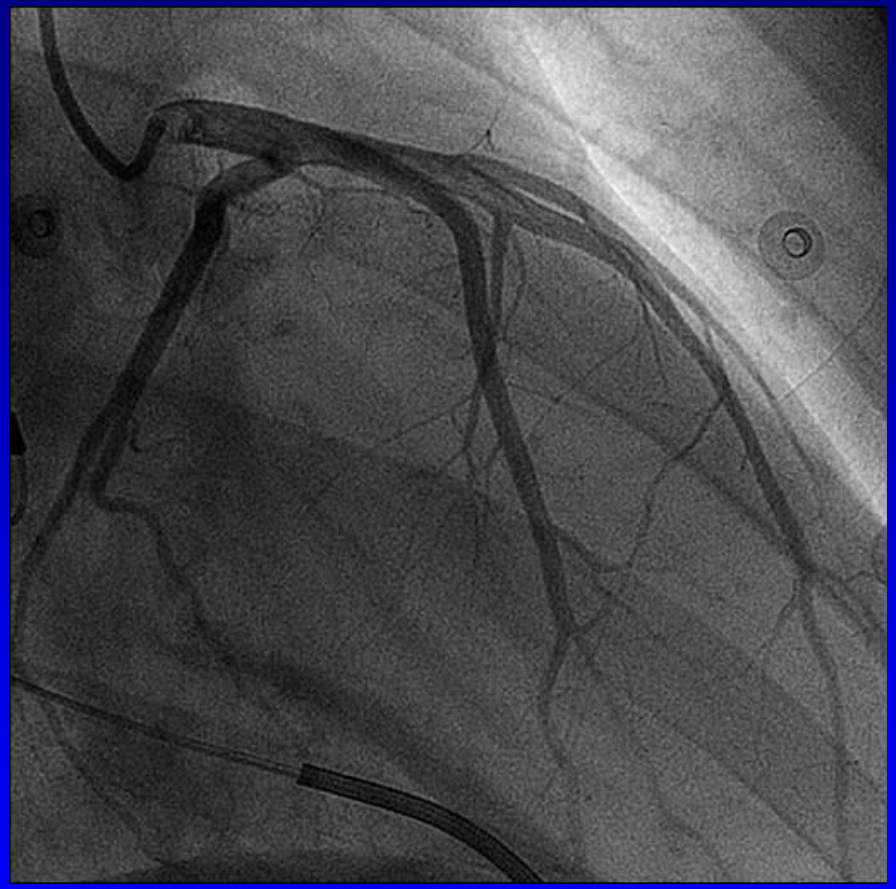
tip of infusion catheter, administration of papaverin

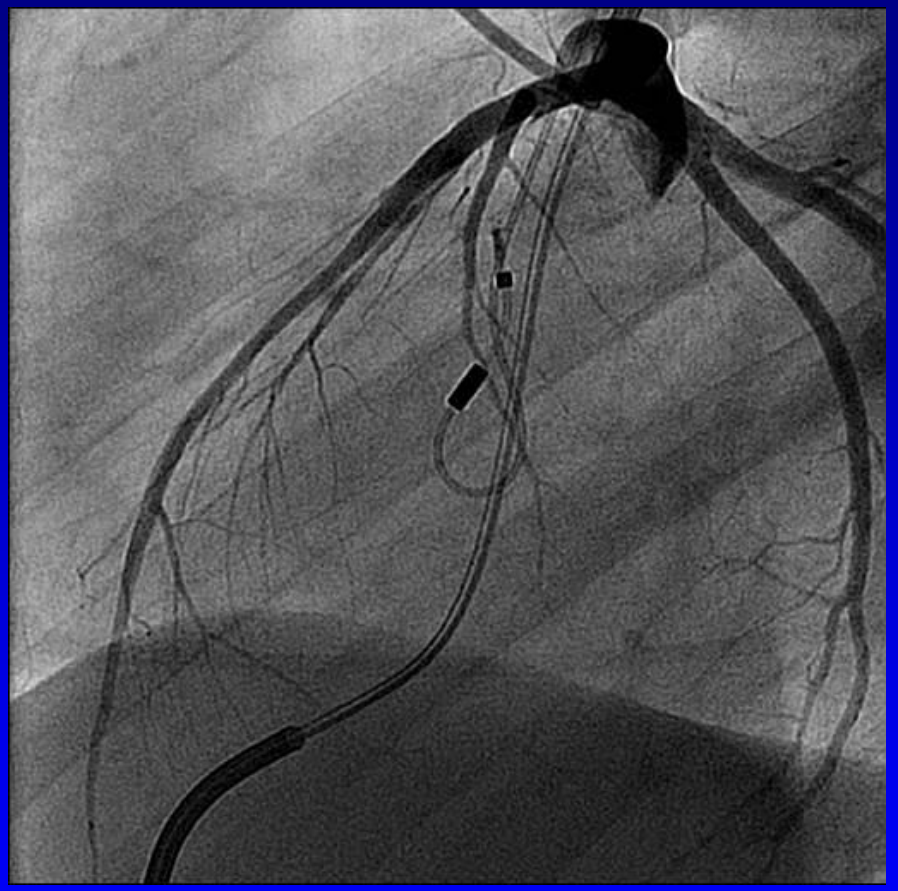
pressure guidewire



1 papaverine induced vasodilation
2 flow-induced vasodilation
3 flow-induced paradoxical vasoconstriction

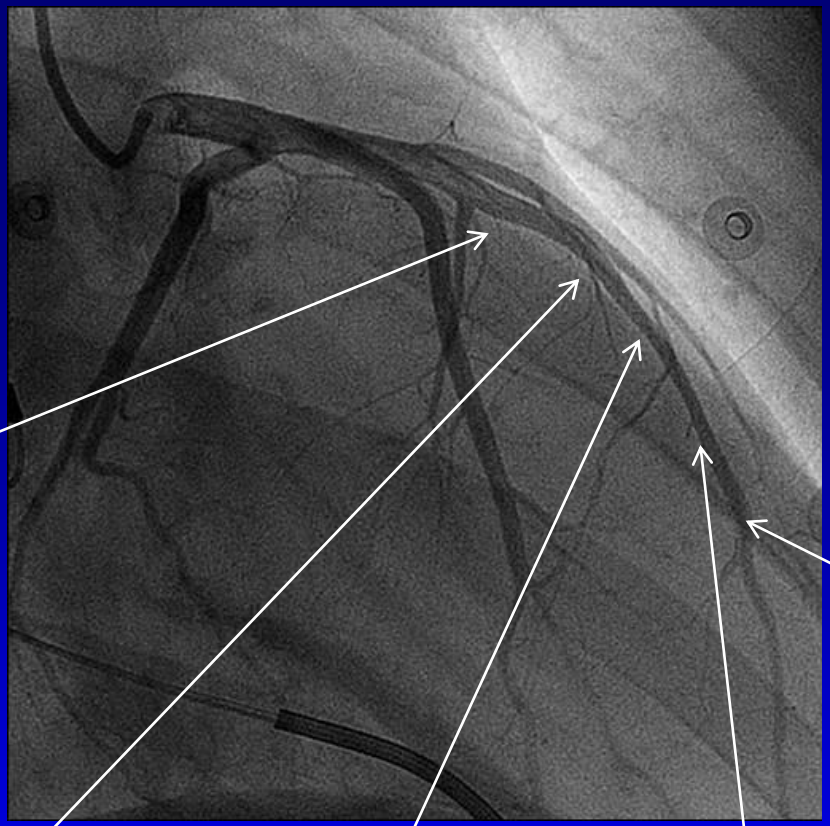
early stage of atherosclerosis

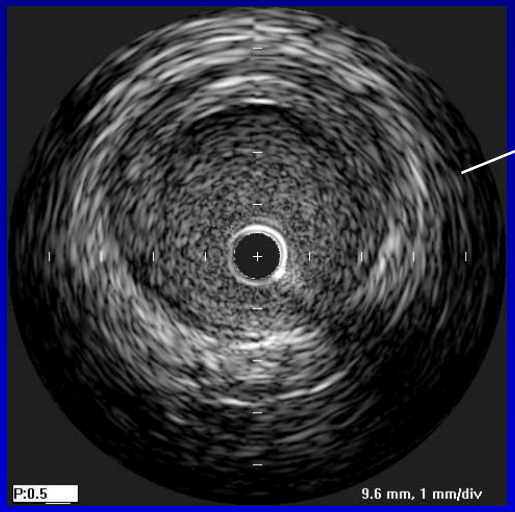




Male, 41-year-old

21-03-2006

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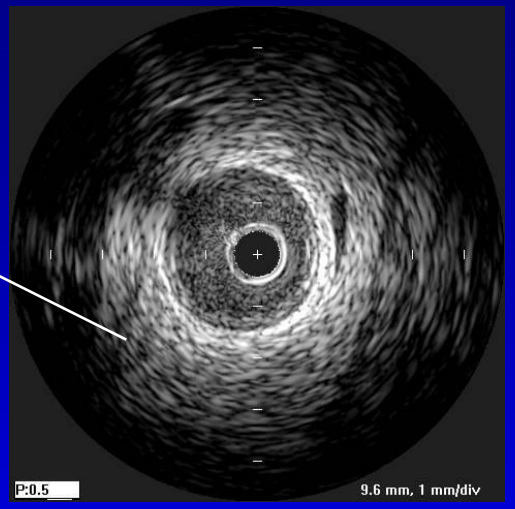
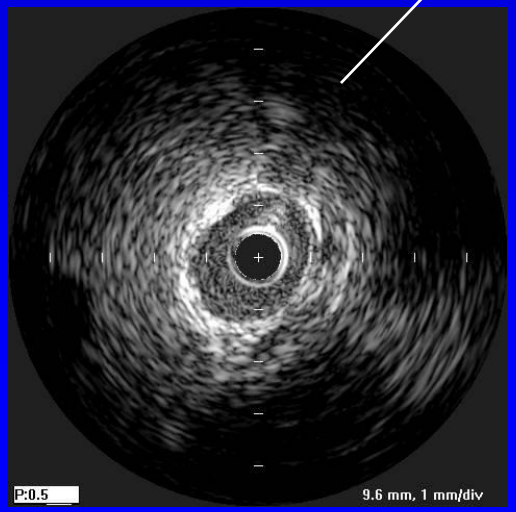
9.6 mm, 1 mm/div


P:0.5
9.6 mm, 1 mm/div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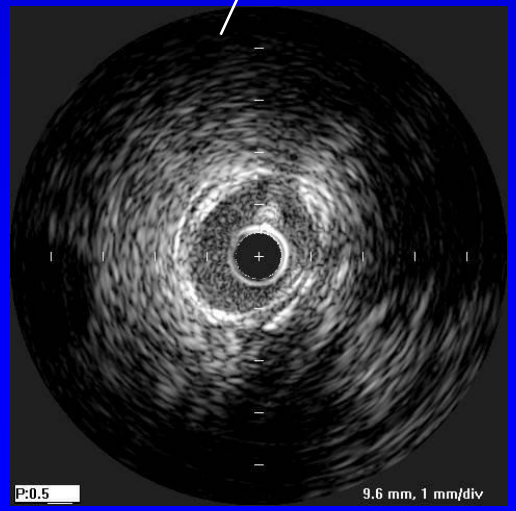
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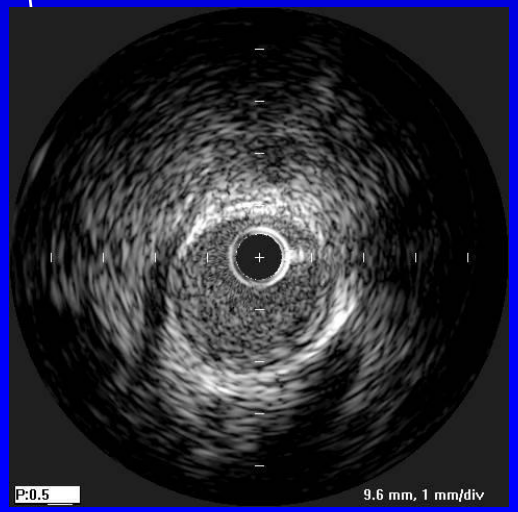
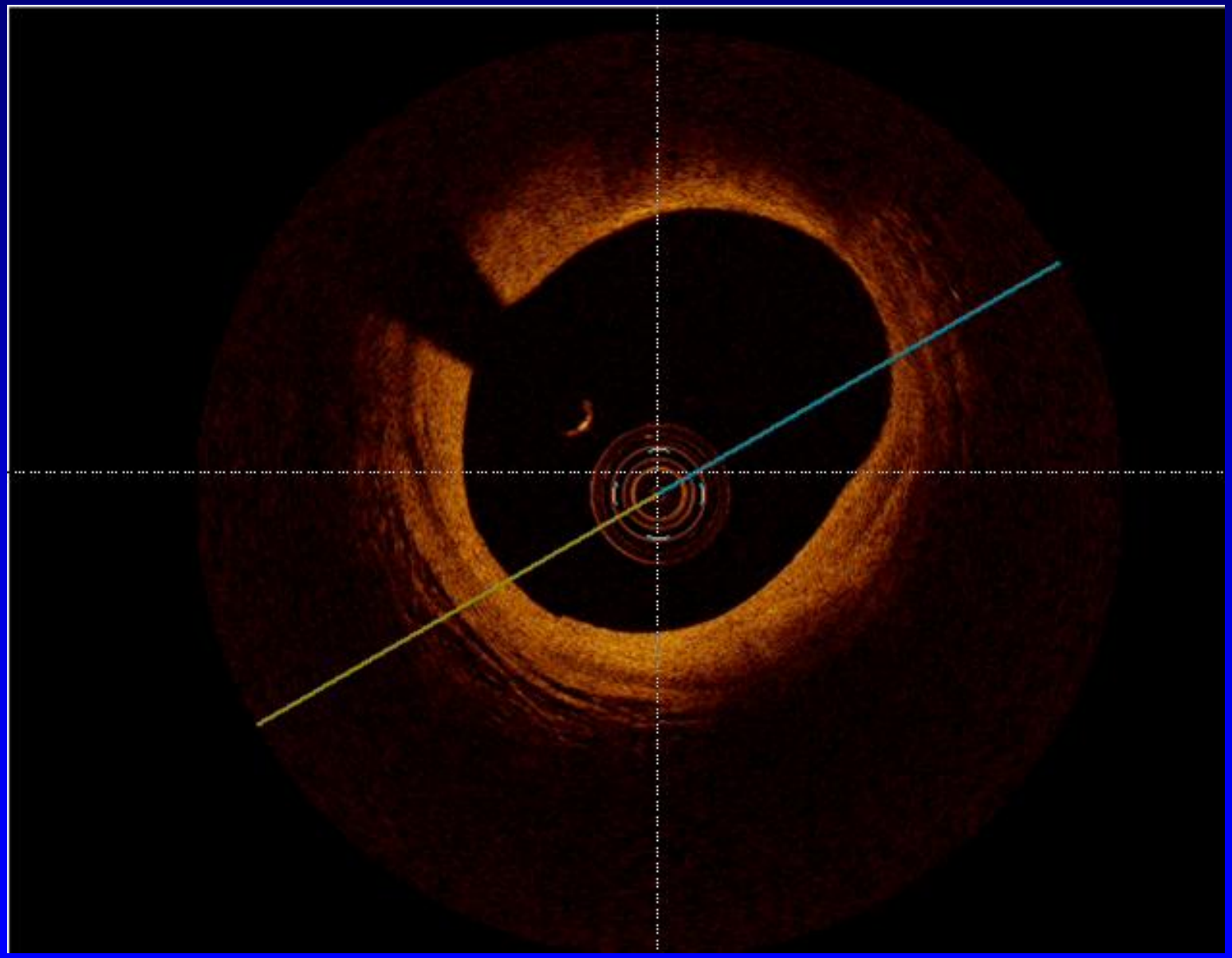
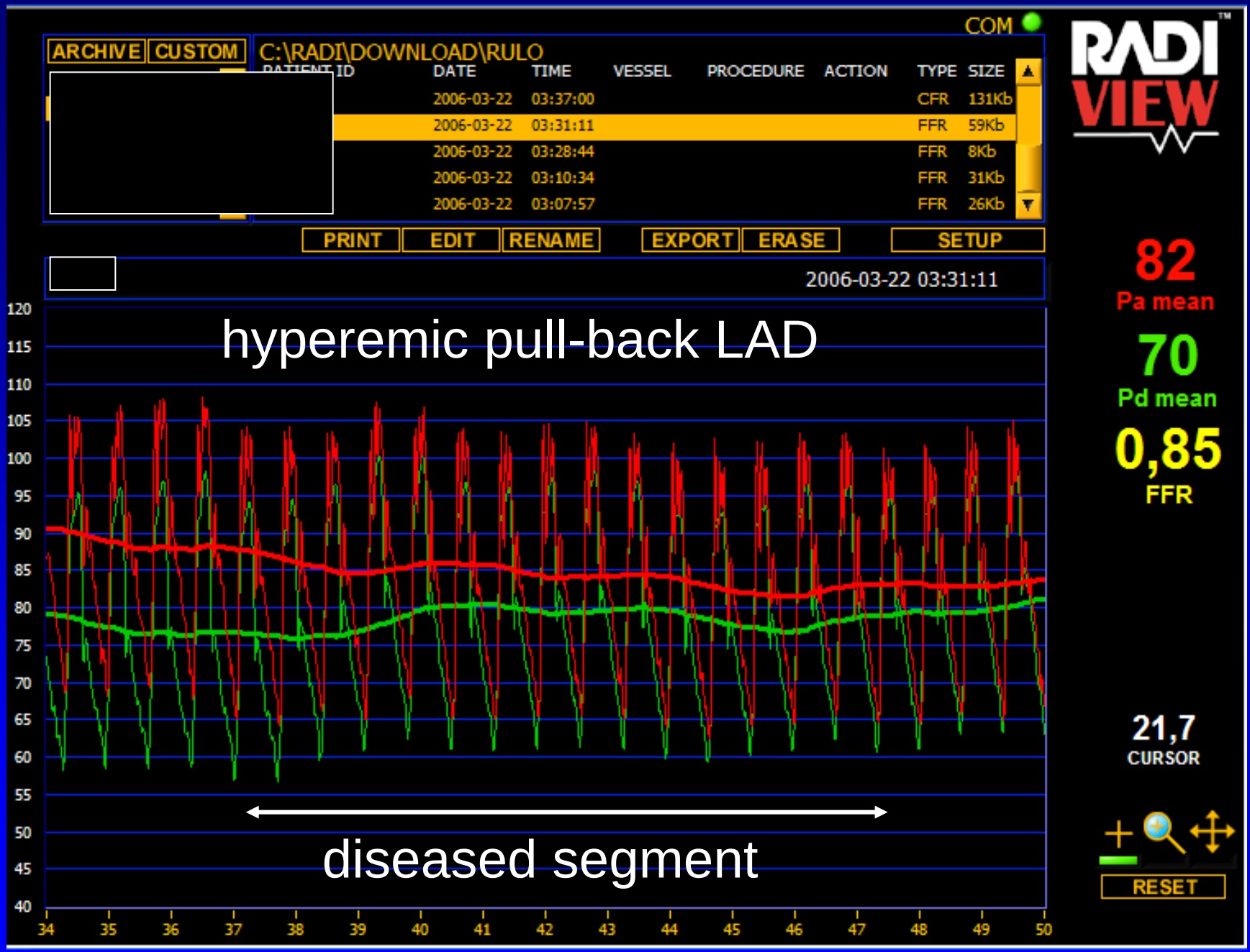

P:0.5
9.6 mm, 1 mm/div

diffuse atherosclerosis, early stage



Courtesy of Dr Pim Tonino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Pd mean
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hyperemic pull-back LAD
diseased segment
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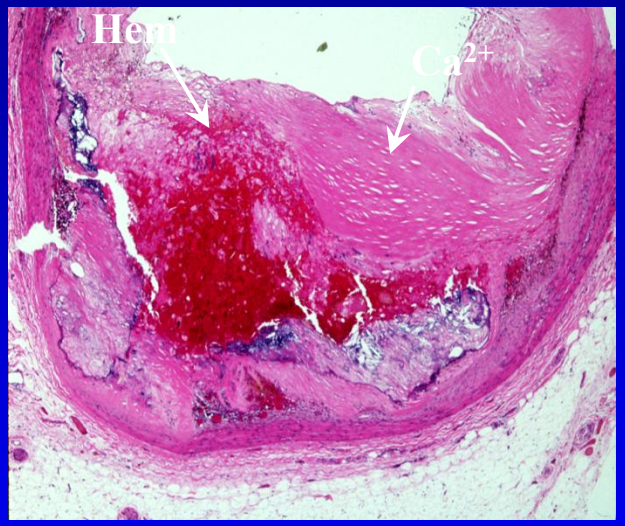
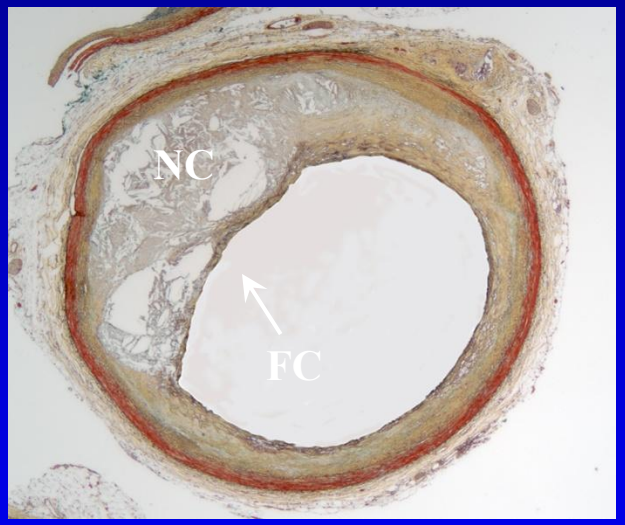
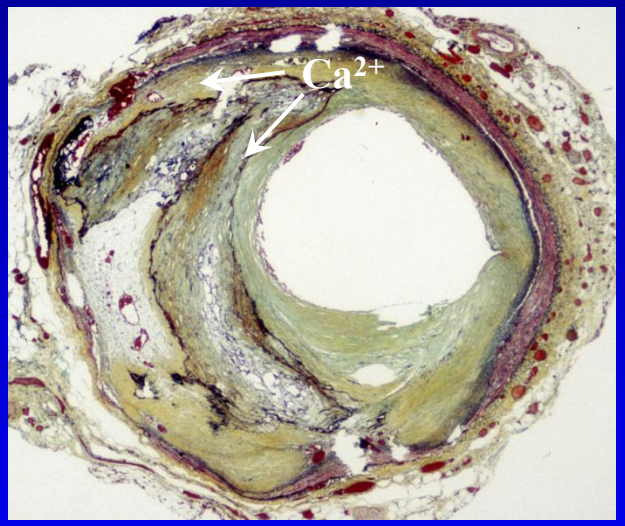
Different stages of gross coronary atherosclerosis, easily visible on angiogram and by several non-invasive methods







Fibrous cap atheroma with hemorrhage

Thin fibrous cap atheroma

Fibrocalcific plaque

Virmani R, et al. Arterioscler Thromb Vasc Biol 2000;20:1262

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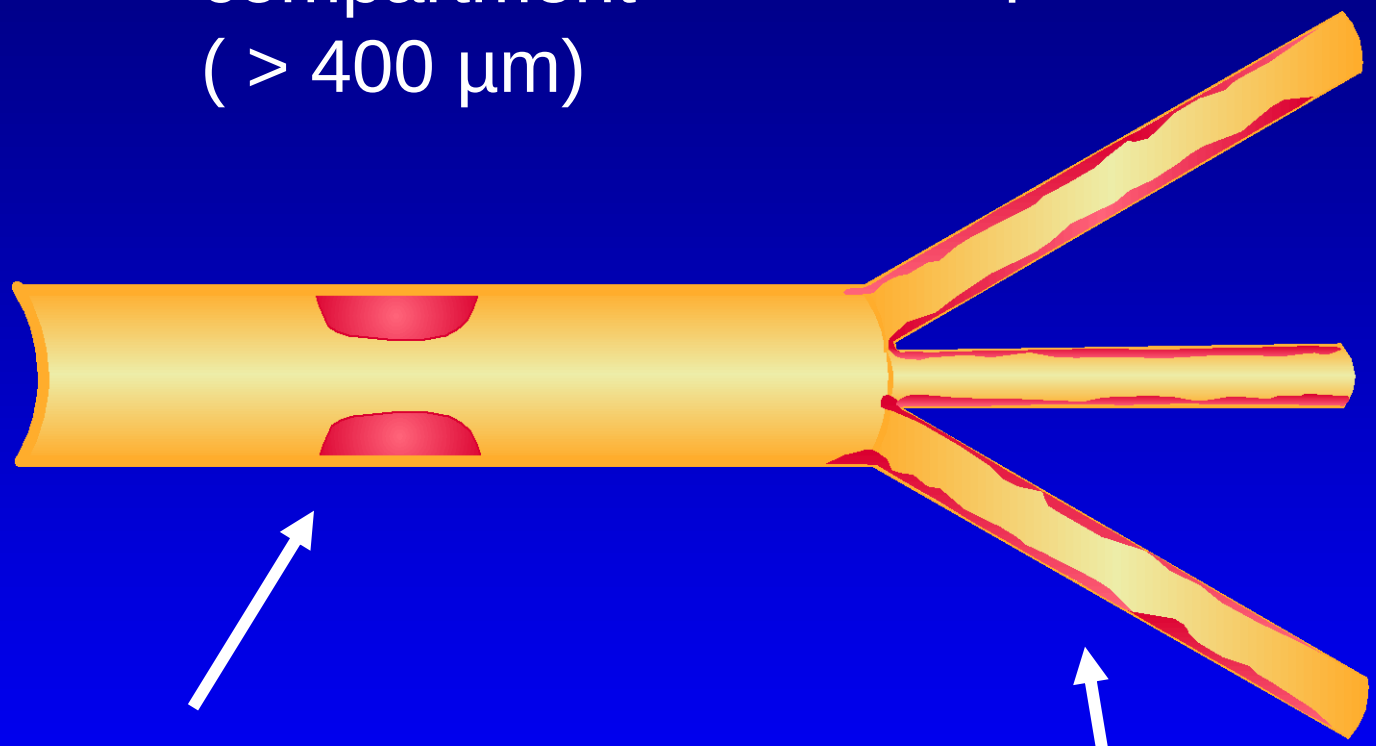
epicardial
compartment
(> 400 µm)

microvascular
compartment



traditionally visible by angiography
and more recently by many invasive
and non-invasive imaging methods

Black box
(until recently)

The coronary microcirculation:

Still a black box ??

→ **Session 3**

IMAGING OF THE EPICARDIAL COMPARTMENT

- non-invasively by CT, MRI
- invasively by angio, IVUS, OCT,and some newer techniques

FUNCTIONAL ASSESSMENT OF THE EPICARDIAL COMPARTMENT

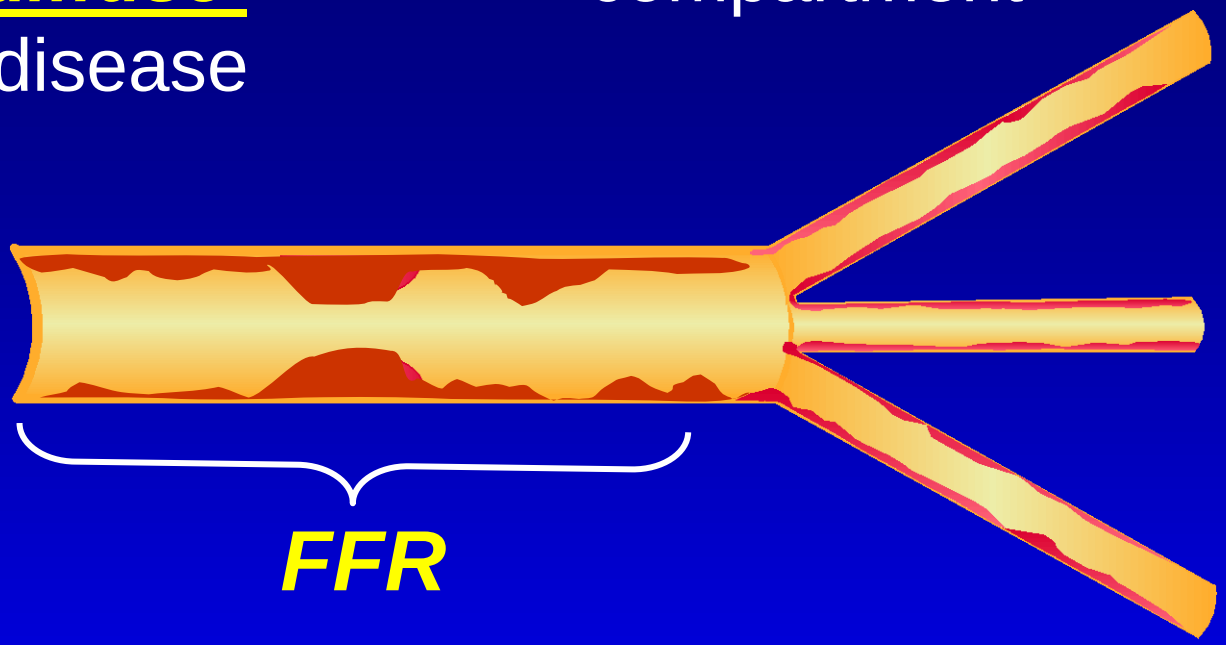
- coronary pressure & FFR

FUNCTIONAL ASSESSMENT OF THE MICROCIRCULATION:

- **IMR***(Bill Fearon,Bernard De Bruyne)*
- **absolute flow & resistance** *(Gabor Toth, Inge wijnbergen)*

The third compartment microvascular compartment

focal ***and diffuse*** epicardial disease



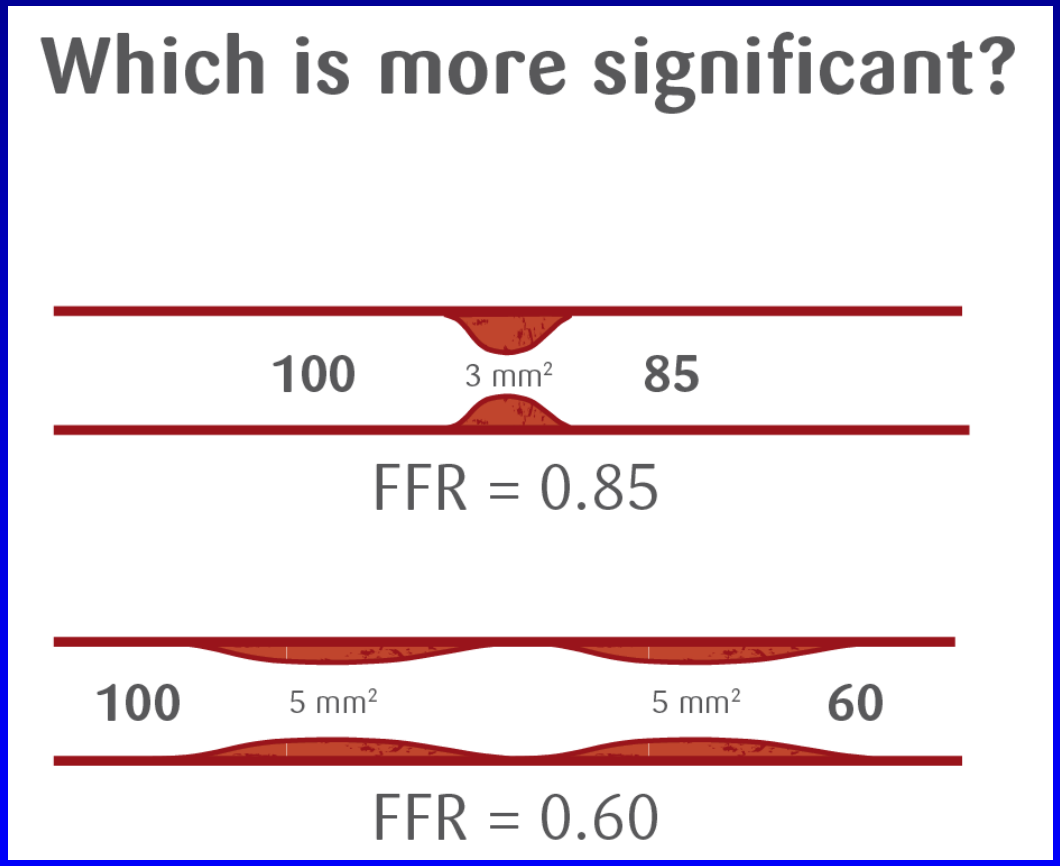
hard to distinguish by traditional methods, but easily assessed and quantified by FFR (hyperemic pullback recording)

The 3rd compartment:

Diffuse epicardial coronary disease, whether or not with super-imposed focal disease

(Nils Witt, tomorrow)

How to assess the functional significance of diffuse disease, whether or not with super-imposed focal lesions?



CCTA,Angiography, IVUS, or OCT

→ ***Impossible by anatomic methods***

The 3rd compartment:

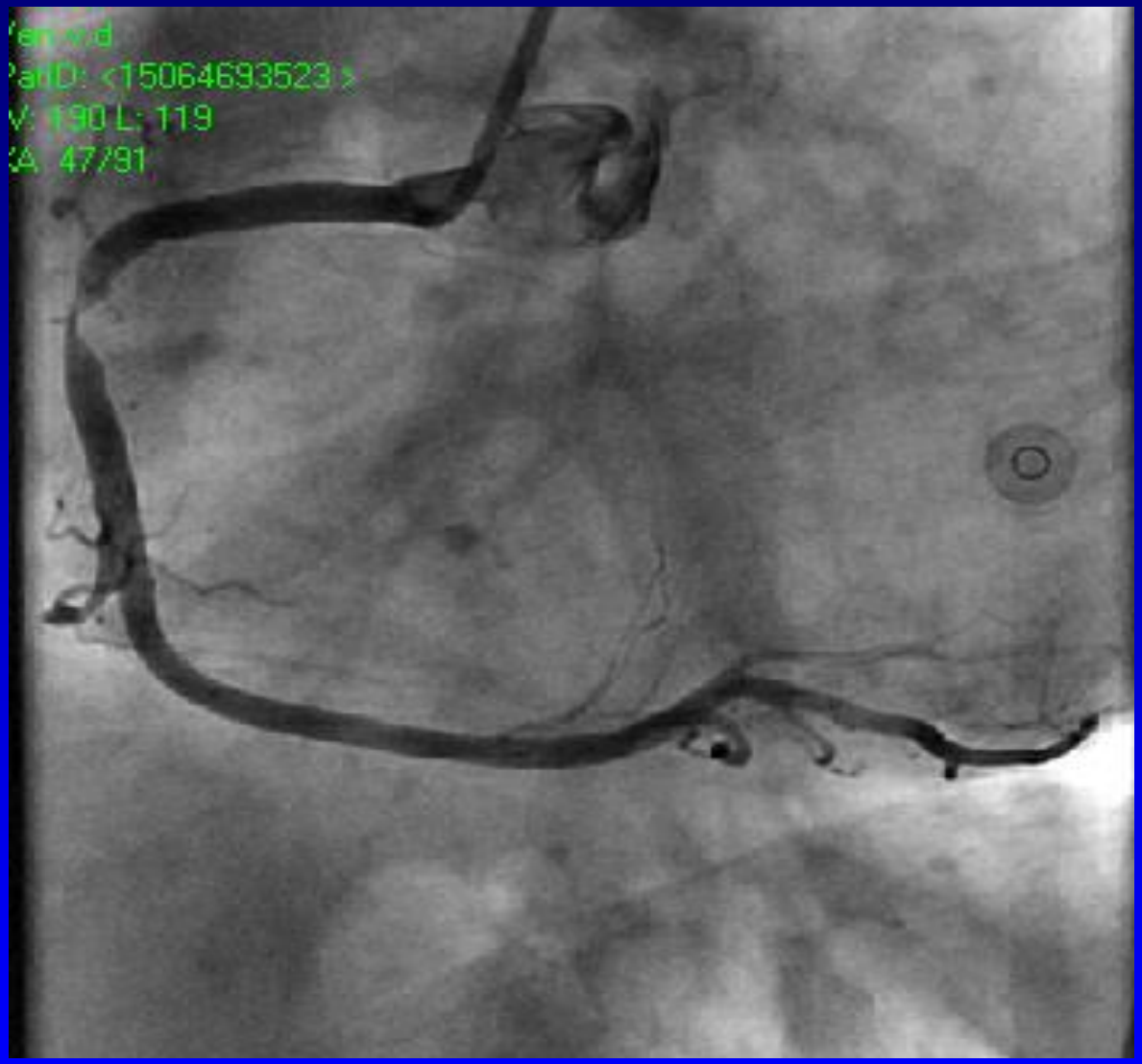
Diffuse epicardial coronary disease
(Nils Witt)

→ **easily evaluable by FFR**
(pressure pull-back recording)

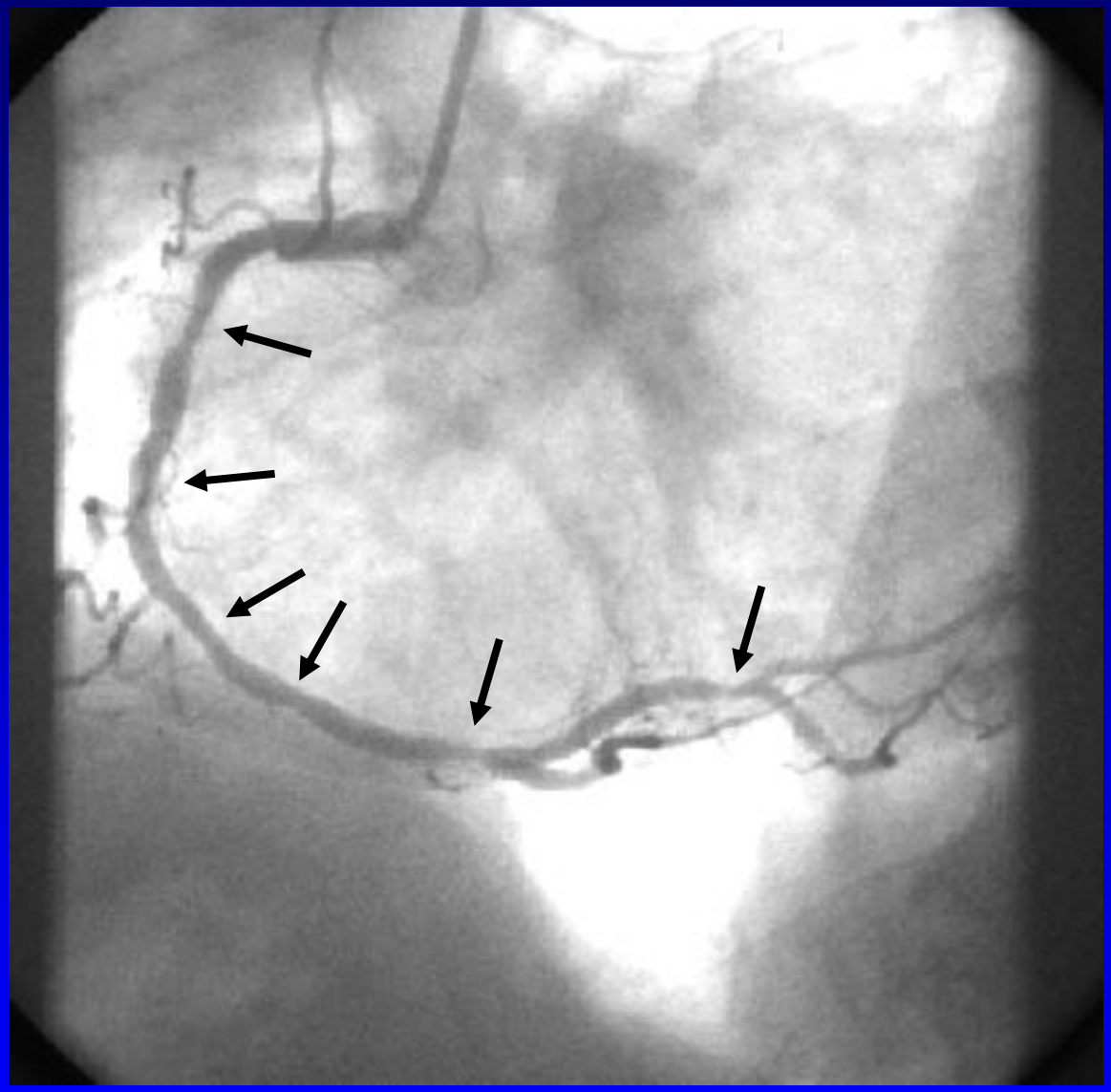
↓

important consequence for treatment
(interventional or medical)

Male 58-y-old



Typical chest pain; positive MIBI-Spect inferior wall



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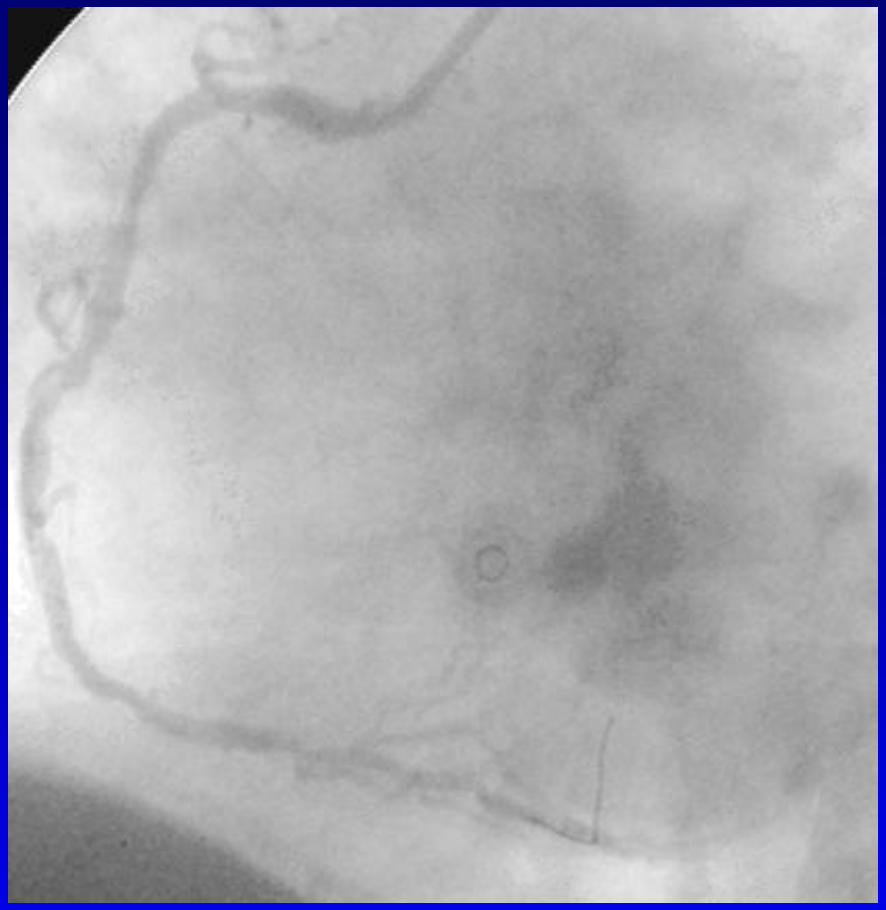
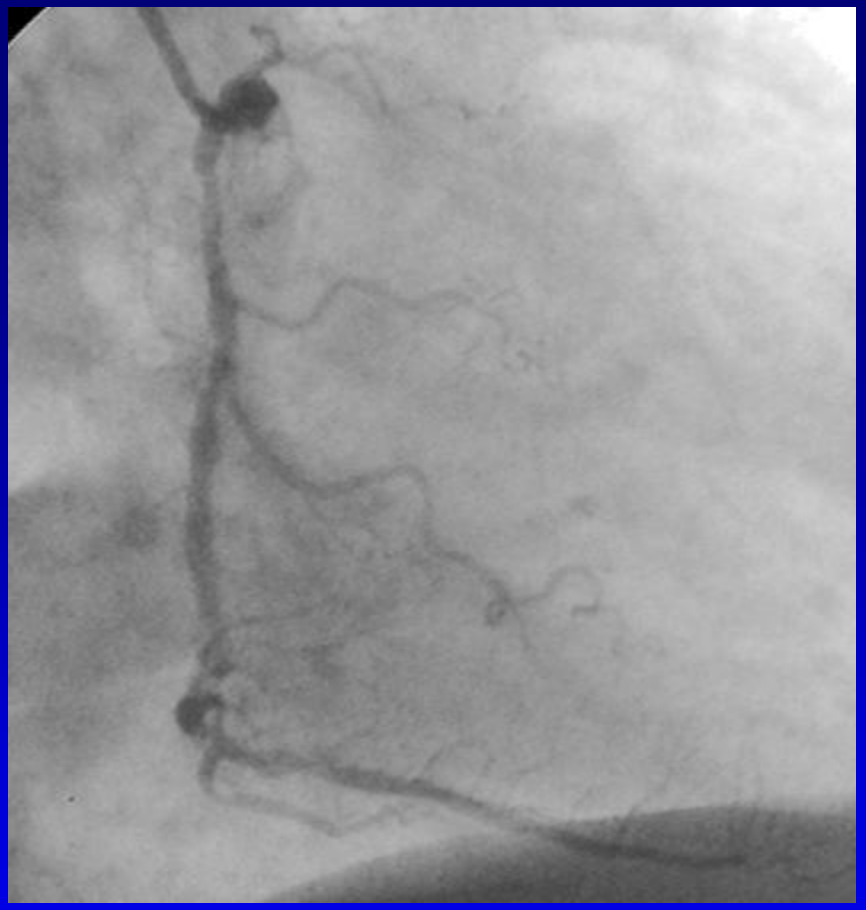
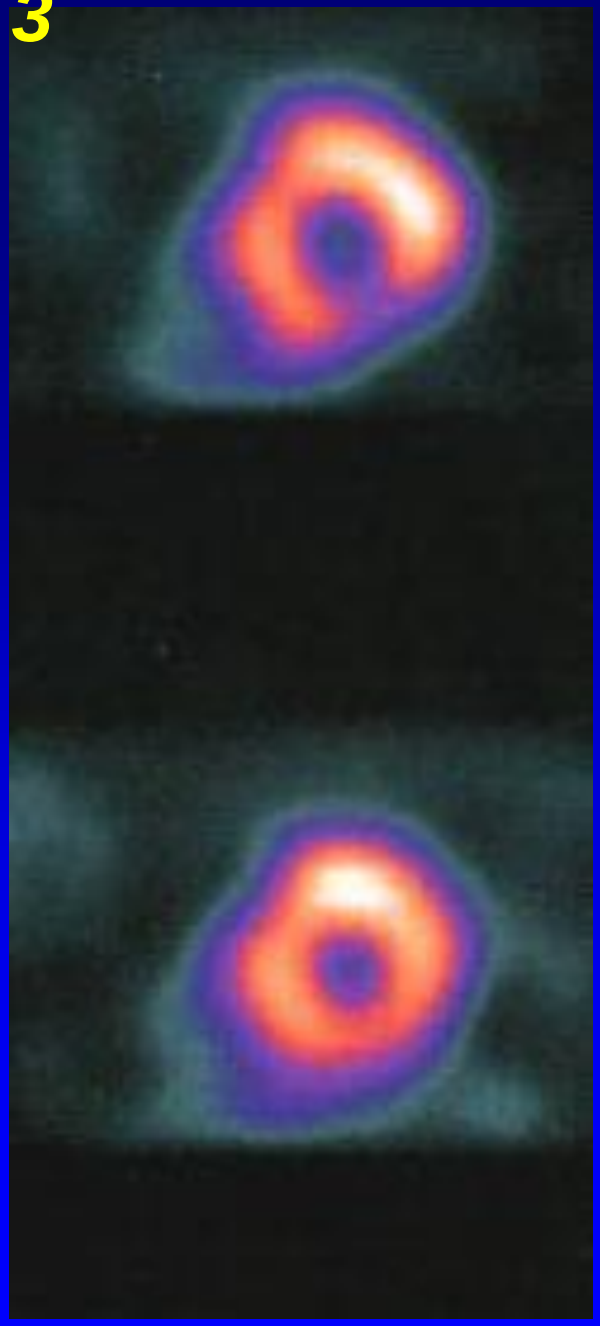
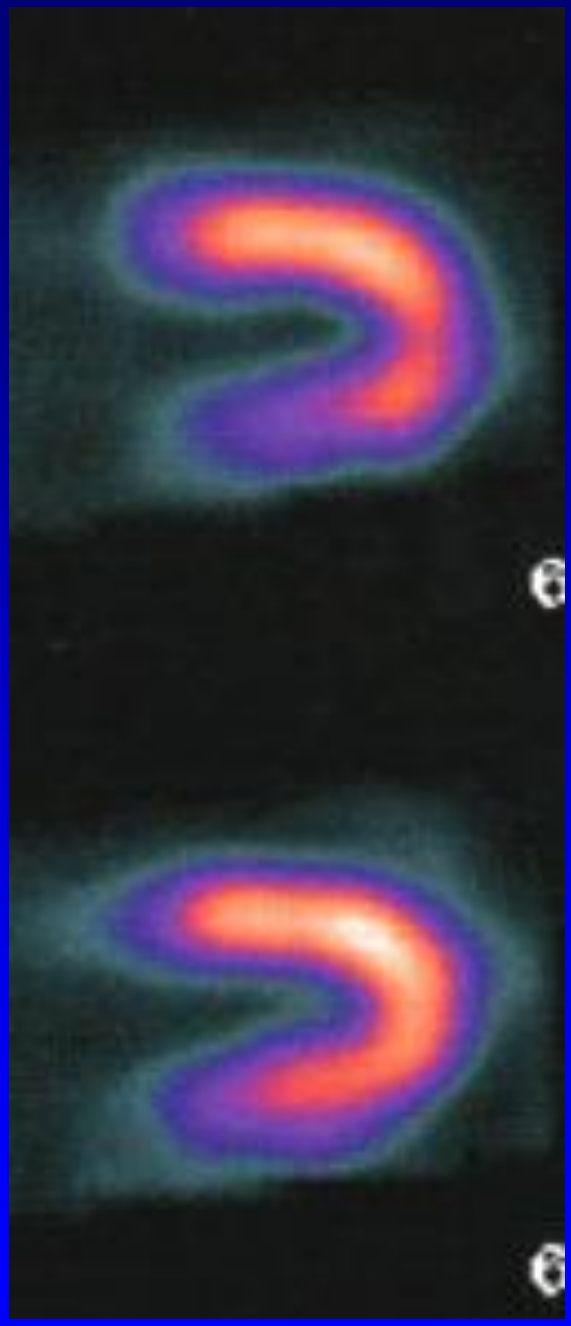


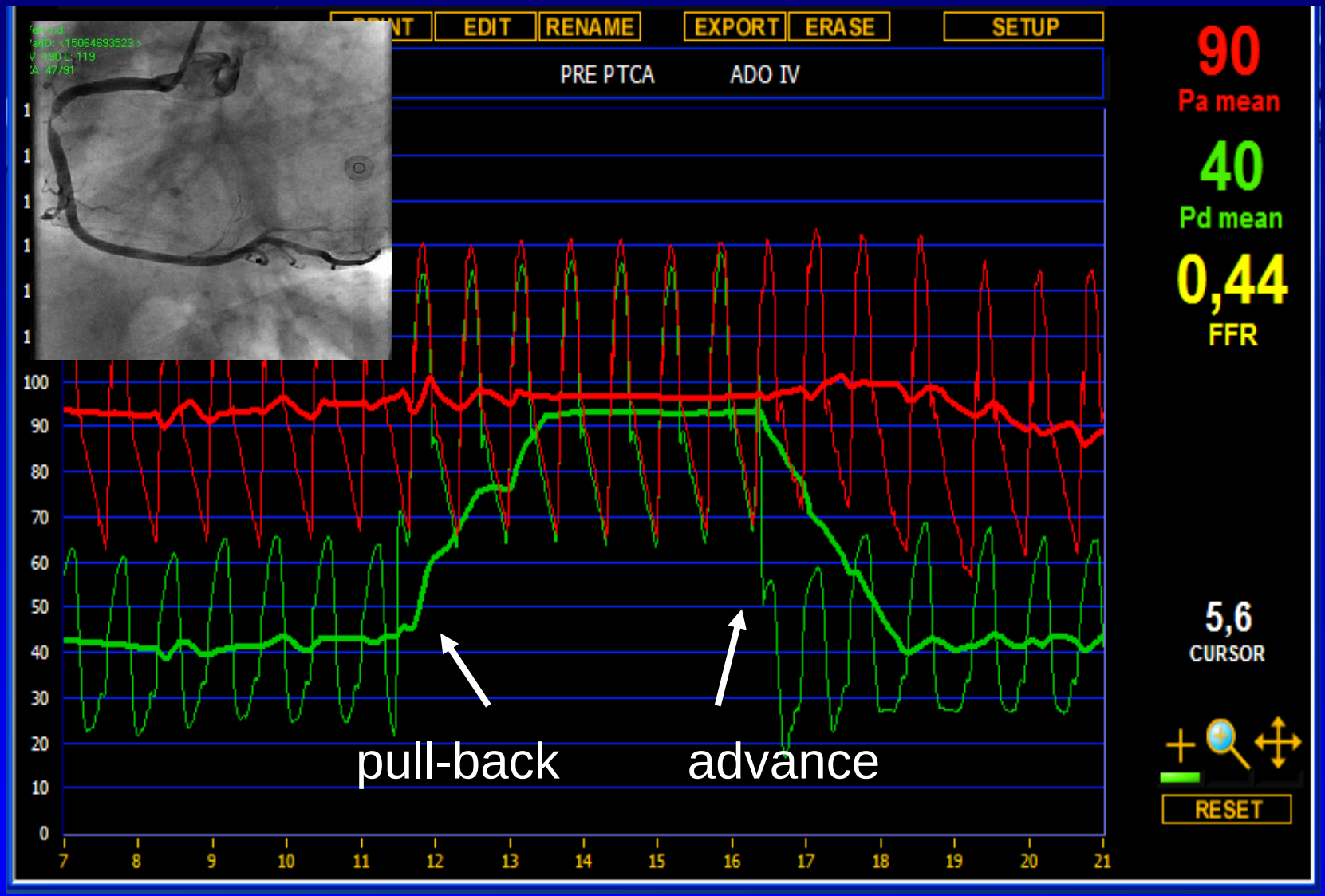


Typical chest pain; positive MIBI-Spect inferior wall

CASE # 3






EDIT
RENAME
EXPORT
ERASE
SETUP
PRE PTCA
ADO IV
90
Pa mean
40
Pd mean
0,44
FFR
5,6
CURSOR
RESET
pull-back
advance
100
90
80
70
60
50
40
30
20
10
0
7
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10
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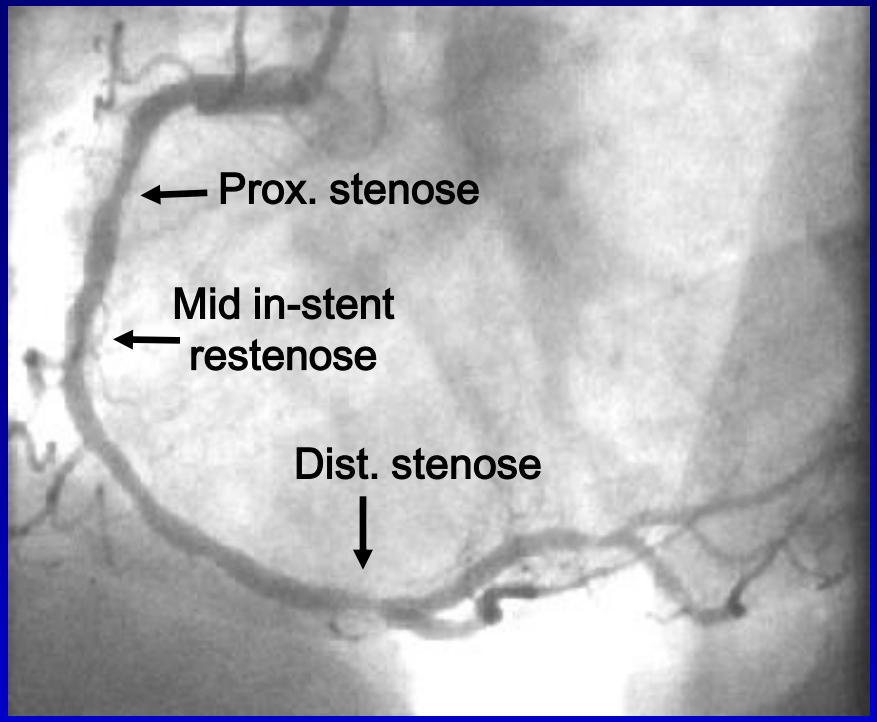
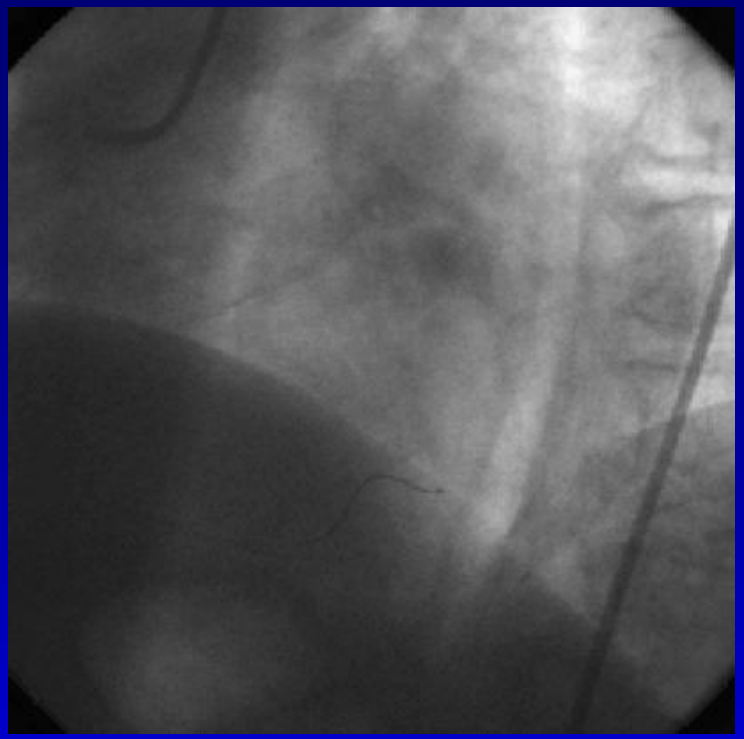
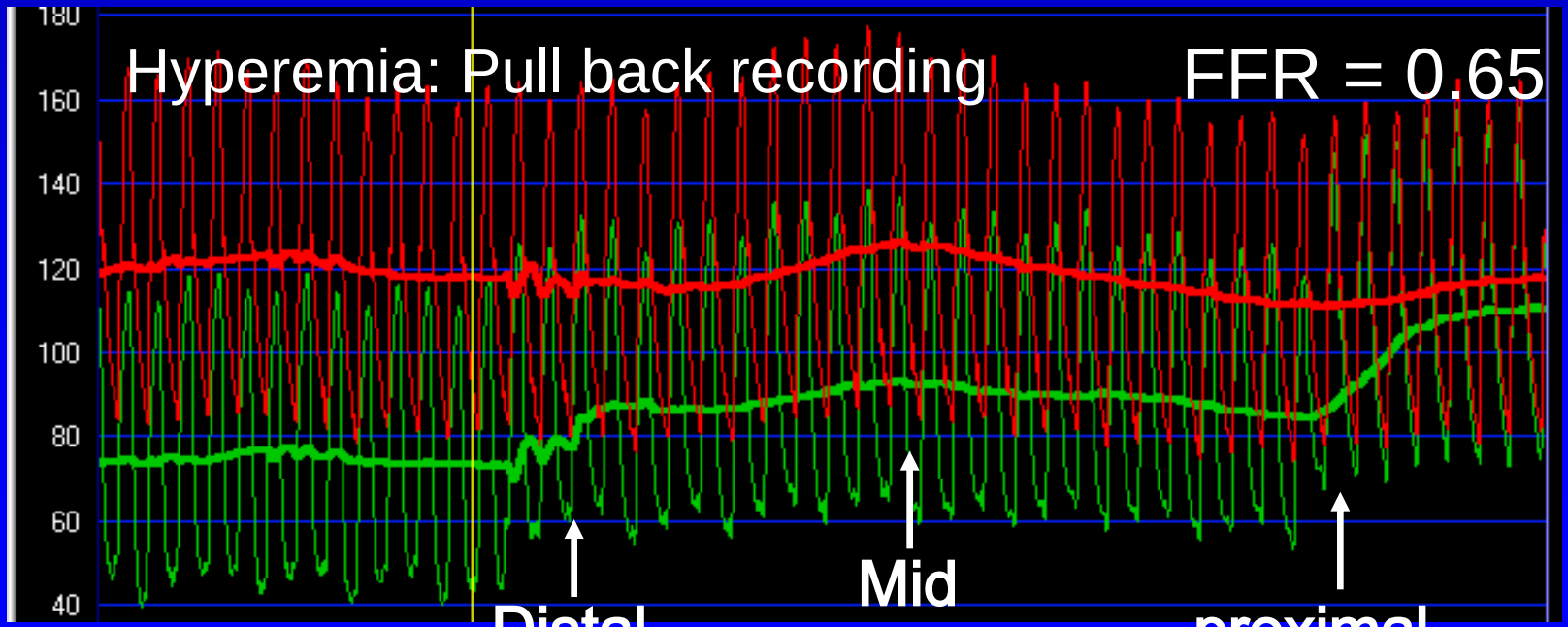
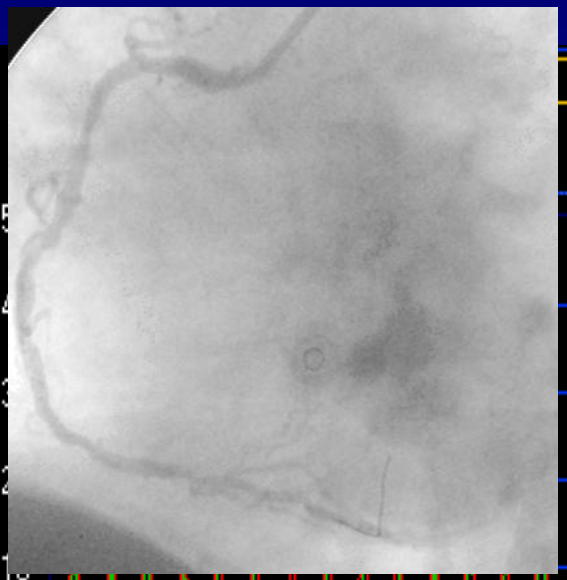

Prox. stenose
Mid in-stent restenose
Dist. stenose




Hyperemia: Pull back recording
FFR = 0.65
180
160
140
120
100
80
60
40
Distal
Mid
proximal



EDIT RENAME EXPORT ERASE SETUP

2004-06-14 15:55:19

109
Pa mean

84
Pd mean

0,77
FFR

7,9
Cursor

RESET

Hyperemic pull-back recordingalong the RCA

FFR: The Pressure Pull-back Curve

Pressure pull-back curve at maximum hyperemia:

- place sensor in distal coronary artery
- induce sustained maximum hyperemia by i.v. adenosine, or i.c. papaverine
- pull back the sensor slowly under fluoroscopy
- the individual contribution of every segment and spot to the extent of disease can be studied in this way

Coronary pressure is unique in this respect and such detailed spatial information cannot be obtained by any other invasive or non-invasive method

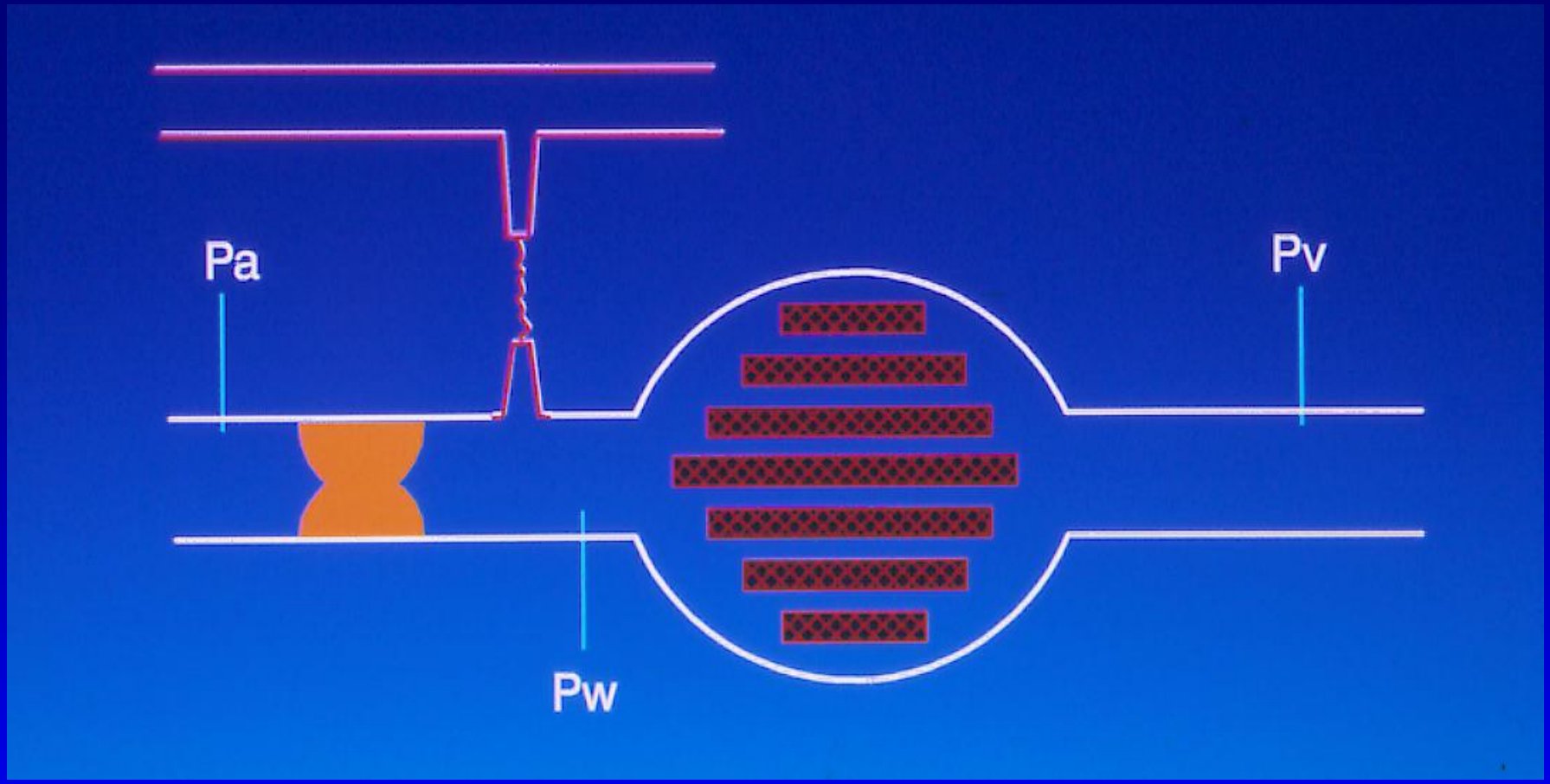
ISSUES TO BE DISCUSSED

- structure of the coronary circulation
- relation between vessel size and perfusion area
- endothelium and development of atherosclerosis
- the 2 or 3 compartment model of the coron circulation
- ***collaterals***
- why functional testing / FFR ?
- which lesions should be treated

$$Q_{myo} = Q_{cor.artery} + Q_{collateral}$$

Quantitave assessment of the contribution of ***coronary arterial*** and ***collateral flow*** to total ***myocardial flow*** is possible by coronary pressure measurements, but not trivial

Pijls & De Bruyne:
Circulation 1993
Coronary Pressure, sec edition, Kluwer 2000



Fractional collateral flow (also called CFI*p*) =

$$FFR_{coll} = \frac{Pw - Pv}{Pa - Pv}$$

Venous pressure not negligible anymore !

ISSUES TO BE DISCUSSED

- structure of the coronary circulation
- relation between vessel size and perfusion area
- endothelium and development of atherosclerosis
- the 2 or 3 compartment model of the coron circulation
- collaterals
- ***which lesions should be treated ?***
- ***why functional testing / FFR ?***

} **next 2 days**

In patients with coronary artery disease, the most important factor with respect to *both*

- ***functional class (symptoms)***
- ***and prognosis (outcome)***

Is the *presence and extent of inducible ischemia*

→ **knowledge if and which lesion(s) is / are responsible for inducible ischemia, is paramount for adequate treatment in the cath.lab**

→ ***FRACTIONAL FLOW RESERVE***

IN SUMMARY:

- There is complex interrelation between the structure and function of the coronary circulation, not only under physiologic circumstances in healthy persons *(vessel size/perfusion area relation, endothelium, regulation of coronary blood flow*), but also under pathologic circumstances *(atherosclerosis, plaques, stenosis, vulnerabilty, and ischemia).*

- Understanding this relation is paramount to treat our patients in the cathlab in the best possible way.

- Hopefully, this course will contribute both to that *understanding* and to its translation into *practical skills*

EINDE

EVIDENCE-BASED MEDICINE:

- ***PCI of "ischemic" lesions (associated with reversible ischemia) makes sense and improves symptoms and sometimes also outcome***

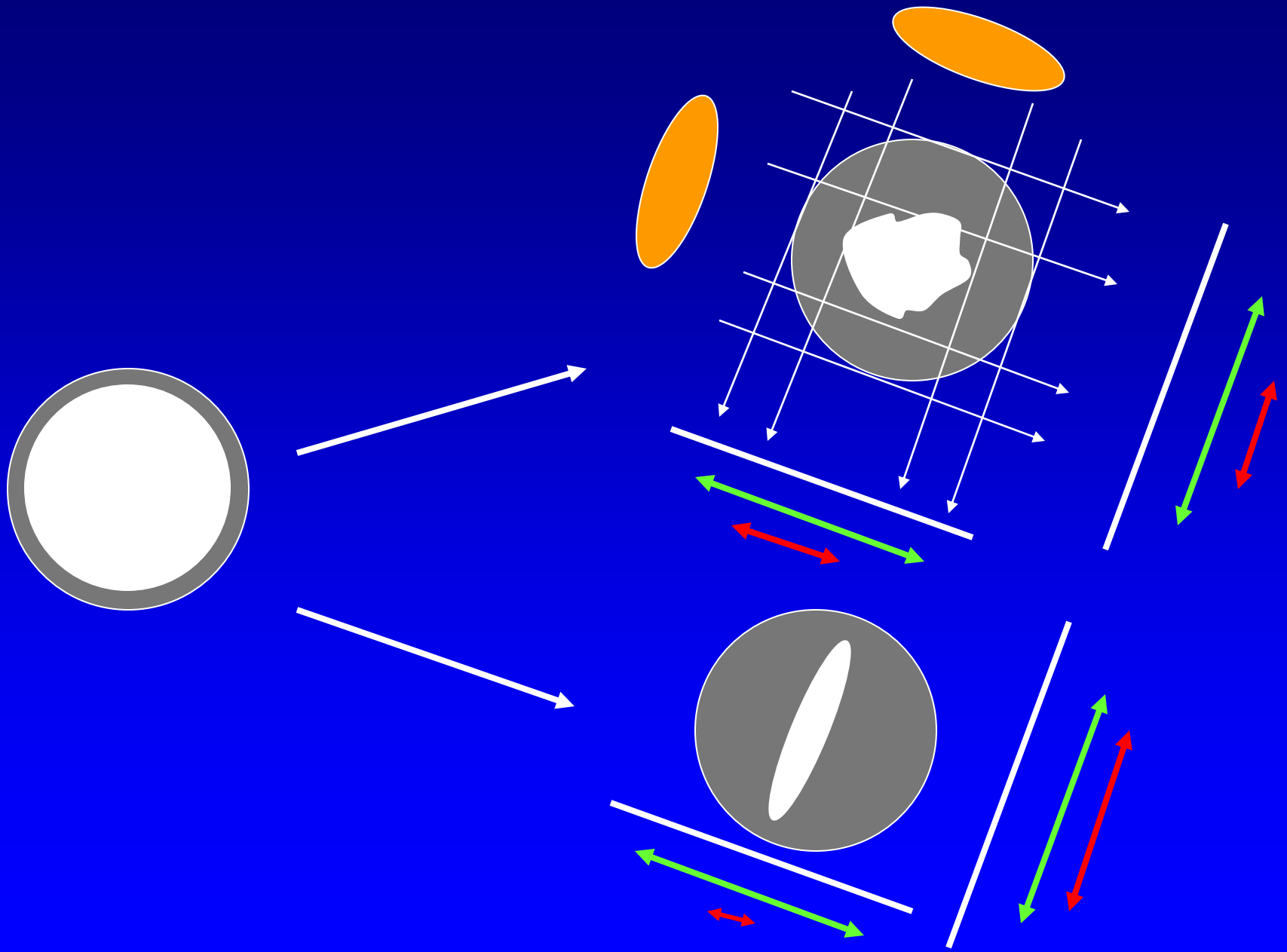
- ***PCI of non-ischemic lesions has no benefit, is no evidence-based medicine, is potentially harmful, and unnecessary expensive***

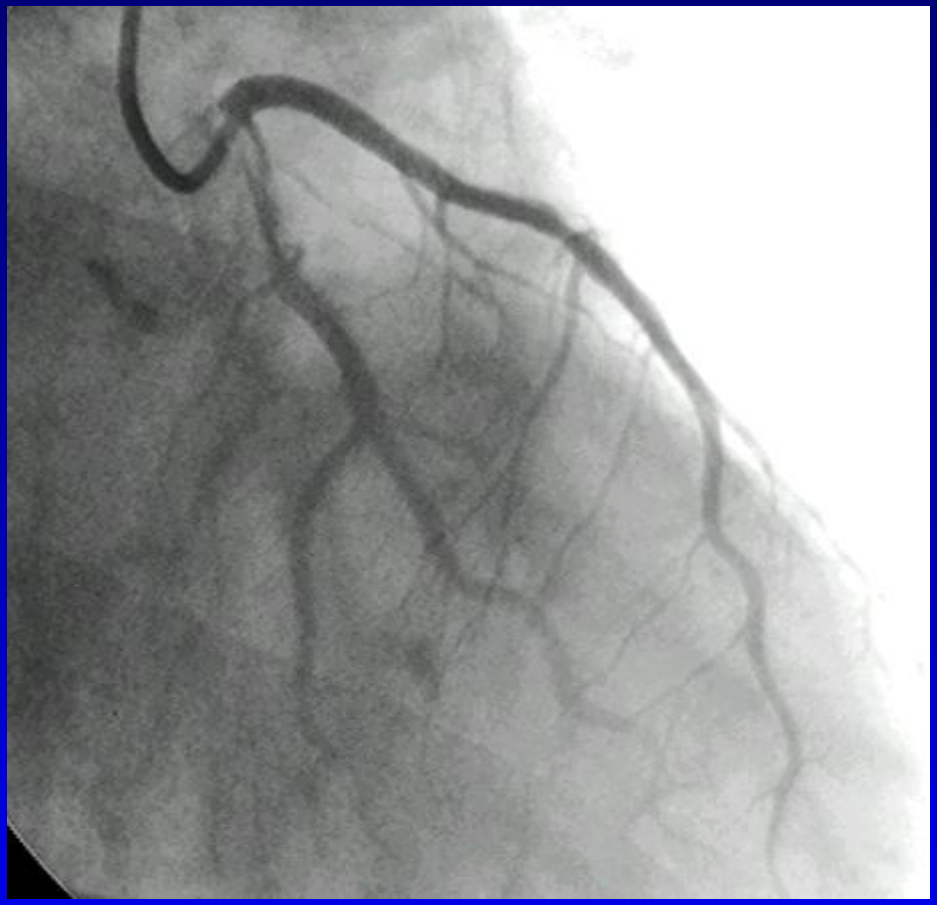
→ **knowledge if and which lesion(s) is / are responsible for inducible ischemia, is paramount for adequate treatment in the cath.lab**

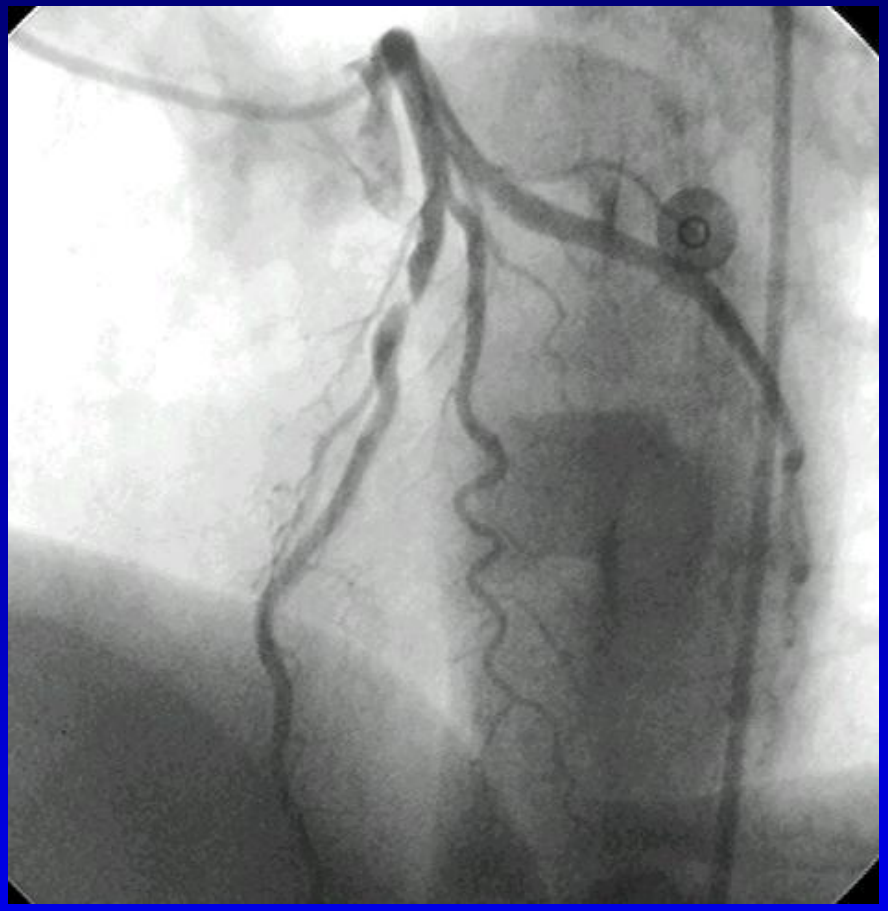
→ ***FRACTIONAL FLOW RESERVE***

THE CORONARY ANGIOGRAM IS ONLY A CRUDE TOOL TO PREDICT IF A STENOSIS CAUSES ISCHEMIA:

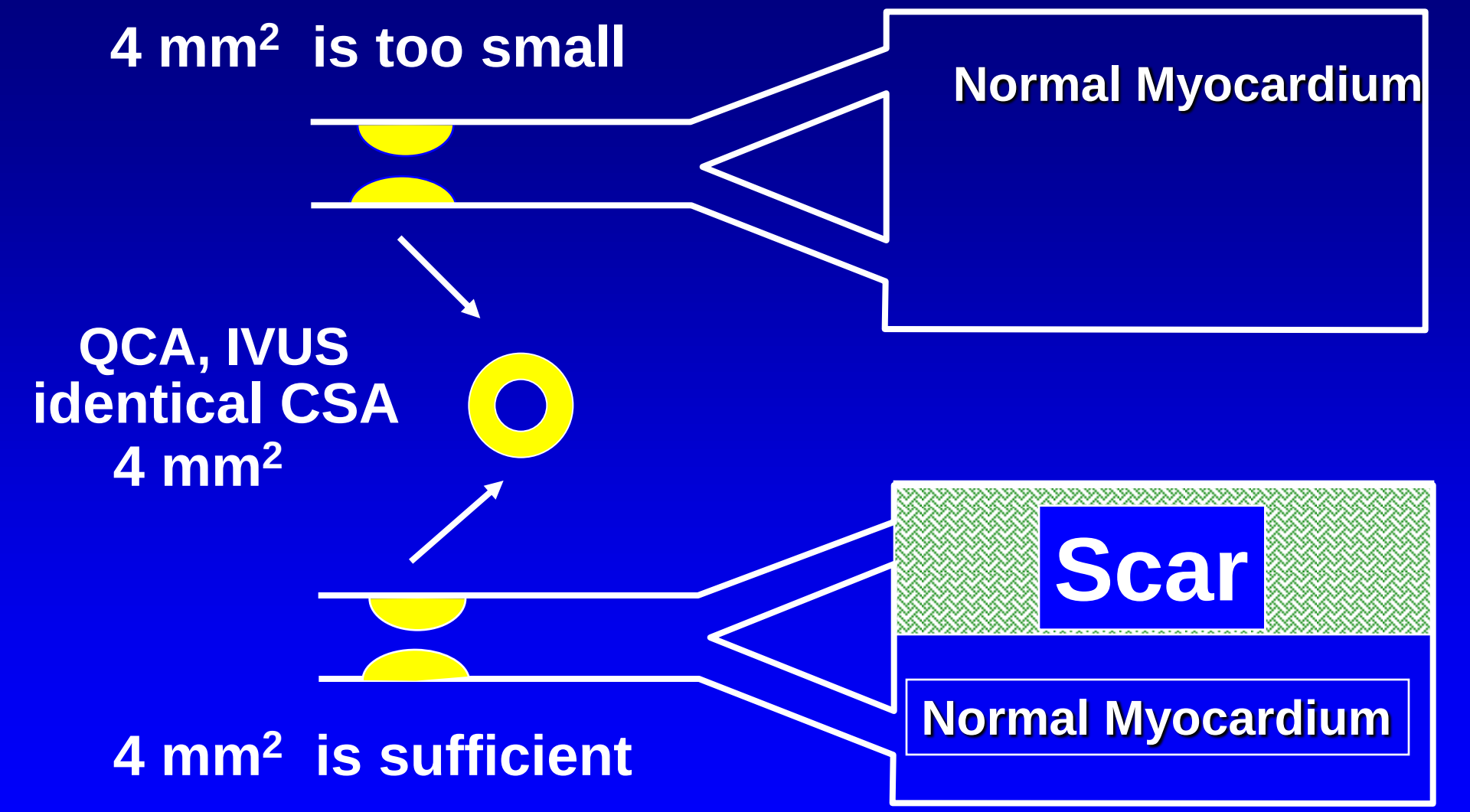
- shortcomings of imaging itself
- discrepancy between structure and function *(especially under pathologic conditions)*
- very hard to predict functional severity of disease from structural abnormalities
- complex influence of pathologic structure on blood flow



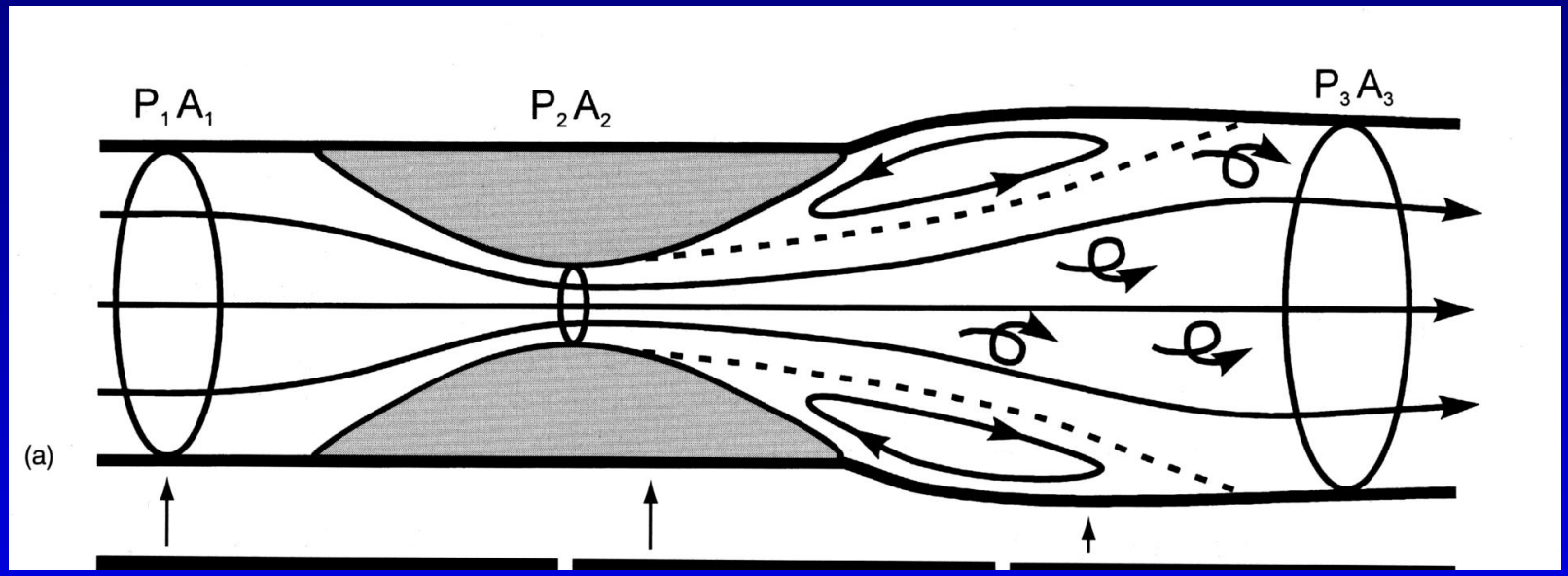


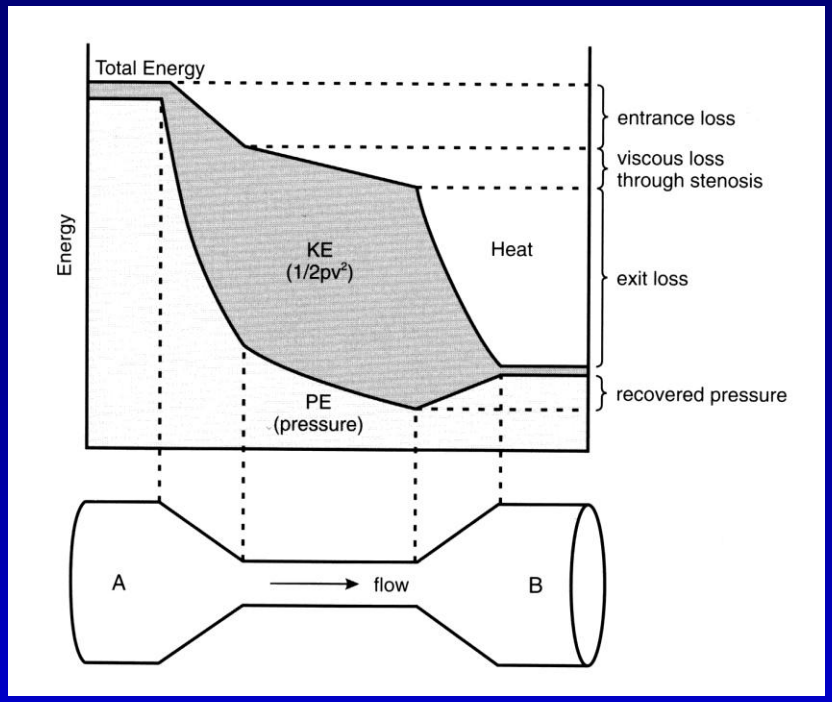


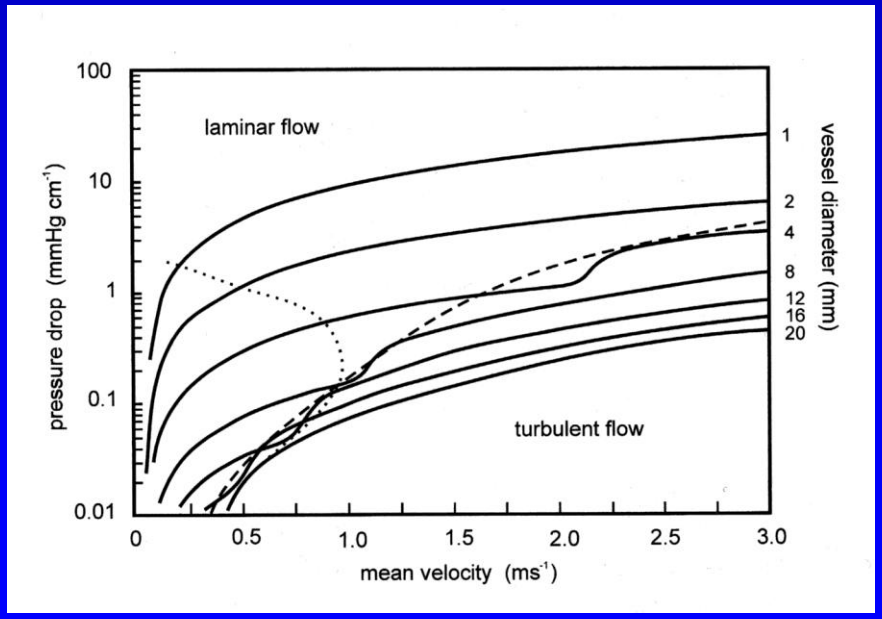
similar stenosis but different extent of perfusion area

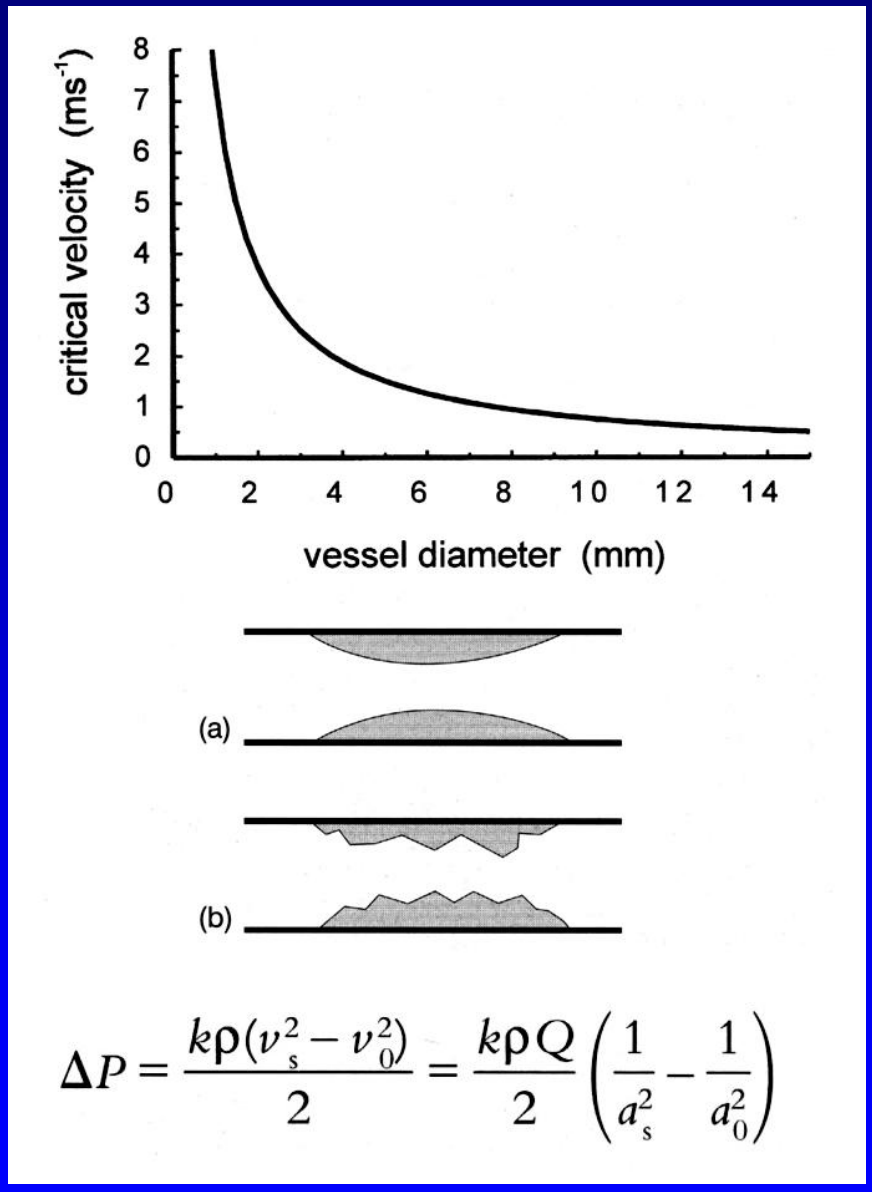


identical CSA, but different significance of stenosis


P1 A1
P2 A2
P3 A3
(a)







$$\Delta P = \frac{k\rho(v_s^2 - v_0^2)}{2} = \frac{k\rho Q}{2}\left(\frac{1}{a_s^2} - \frac{1}{a_0^2}\right)$$

Even in the geometrically most “ideal” stenosis, it is impossible to predict the functional severity and influence on blood flow from hydraulic theory

In summary: EVIDENCE-BASED MEDICINE:

- **knowledge if and which lesion(s) is / are responsible for inducible ischemia, is paramount for adequate treatment in the cath.lab**

- ***The angiogram (and IVUS!) have fundamental Shortcomings to indicate ischemia correctly***

- ***Rationale of Fractional Flow Reserve***

Whatever the stenosis might look like..., whatever the pressure/flow relations across the stenosis might be....,

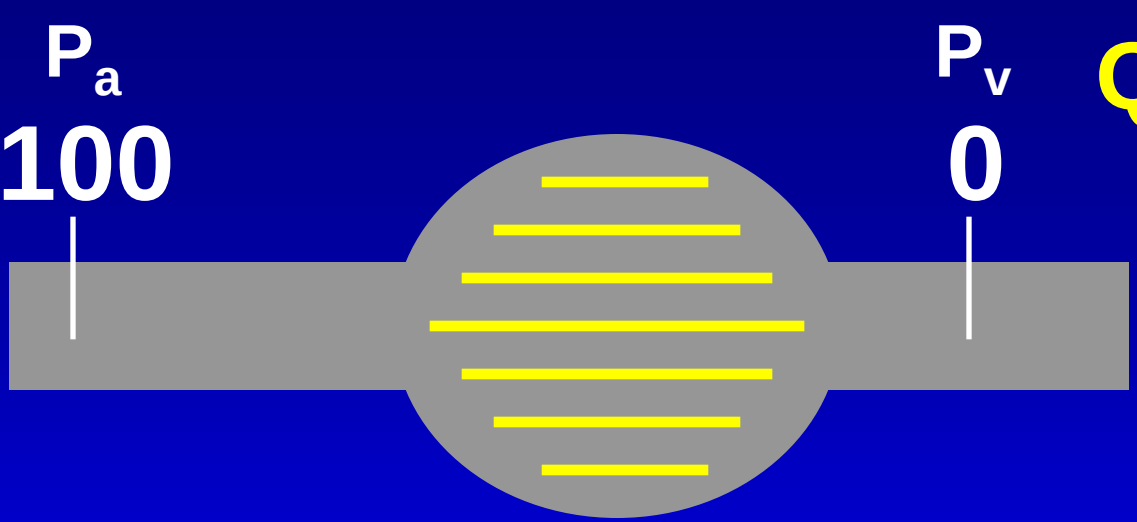
To understand the meaning of the stenosis for the patient, the MOST important number to know is the resulting distal perfusion pressure at hyperemia, as a fraction of normal perfusion pressure (= aortic pressure)

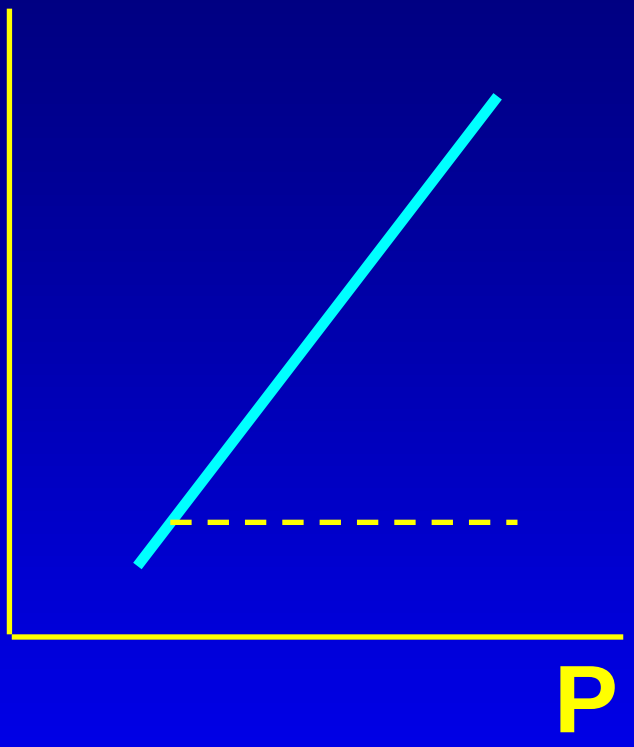
This ratio determines completely the physiologic significance of the stenosis and its consequences for the patient !!

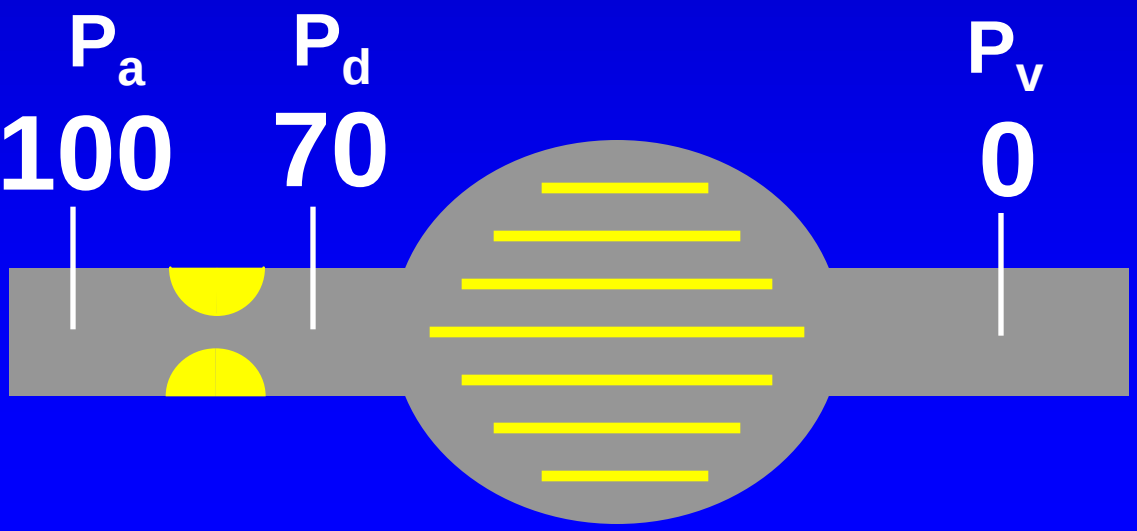
It is called FFR

einde

During Maximal Vasodilatation







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

$$= 0.70$$

ISSUES TO BE DISCUSSED

- structure of the coronary circulation
- relation between vessel size and perfusion area
- endothelium and development of atherosclerosis
- the 2 or 3 compartment model of the coron circulation
- collaterals
- why functional testing / FFR ?
- **which lesions should be treated**

  ⟶ **those causing ischemia**
- ***ischemia & vulnerability: paradox or antithesis ?***

  (Bernard De Bruyne, later today)

ISSUES TO BE DISCUSSED

- structure of the coronary circulation
- relation between vessel size and perfusion area
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- why functional testing / FFR ?
- ***which lesions should be treated***

  ⟶ ***those causing ischemia***
- ischemia & vulnerability: paradox or antithesis ?

Paradox or anthithesis ?

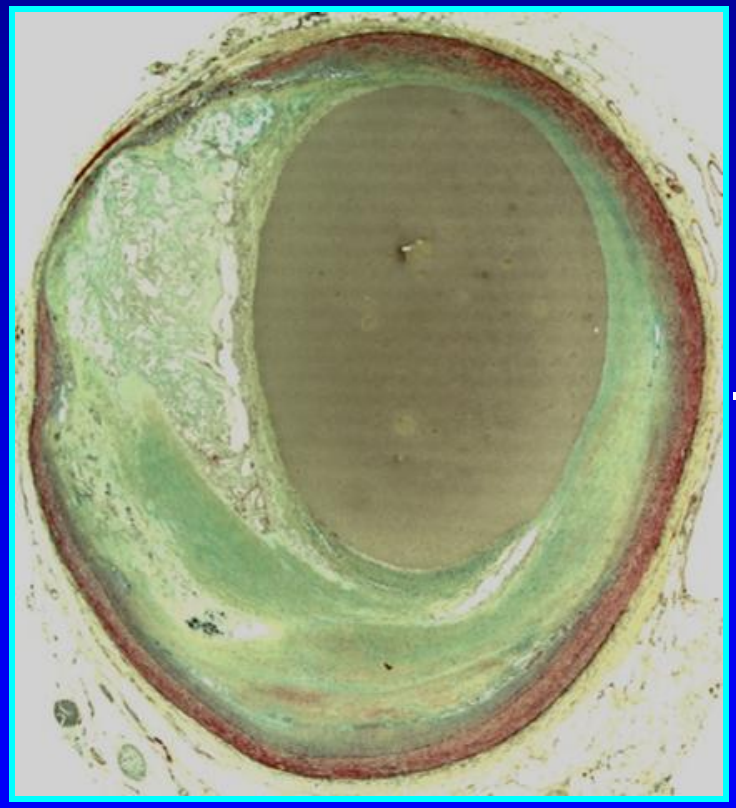
Excellent outcome of medical treatment in non-ischemic stenosis
(DEFER study, many non-invasive studies)

versus

concept of vulnerable plaque

today ? tomorrow

TCFA



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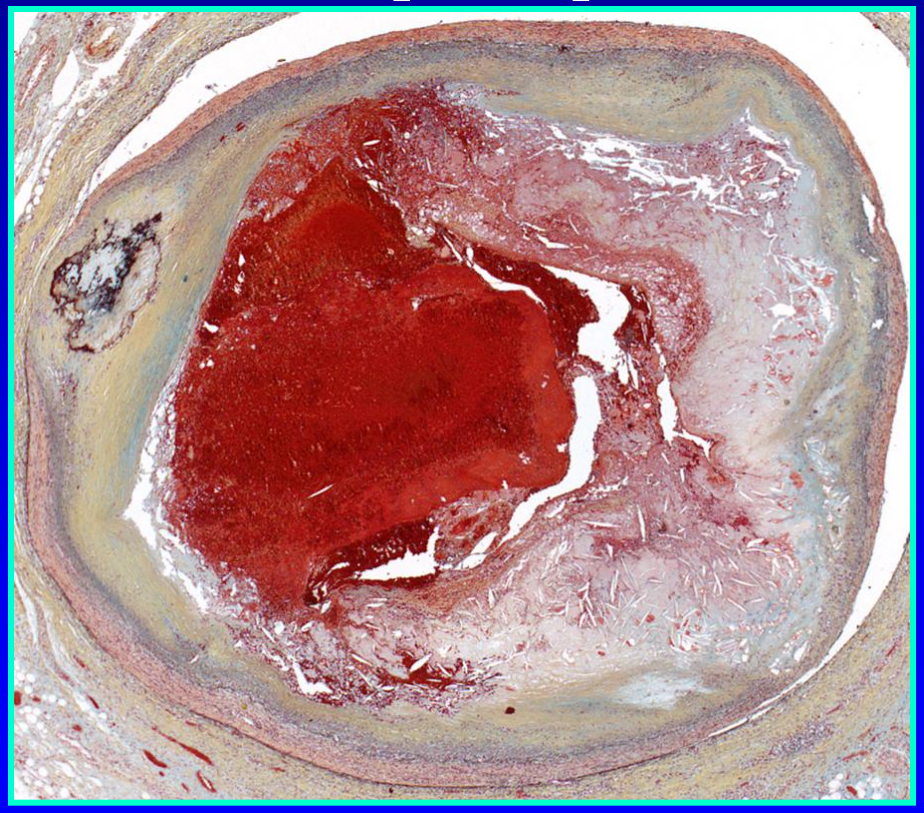
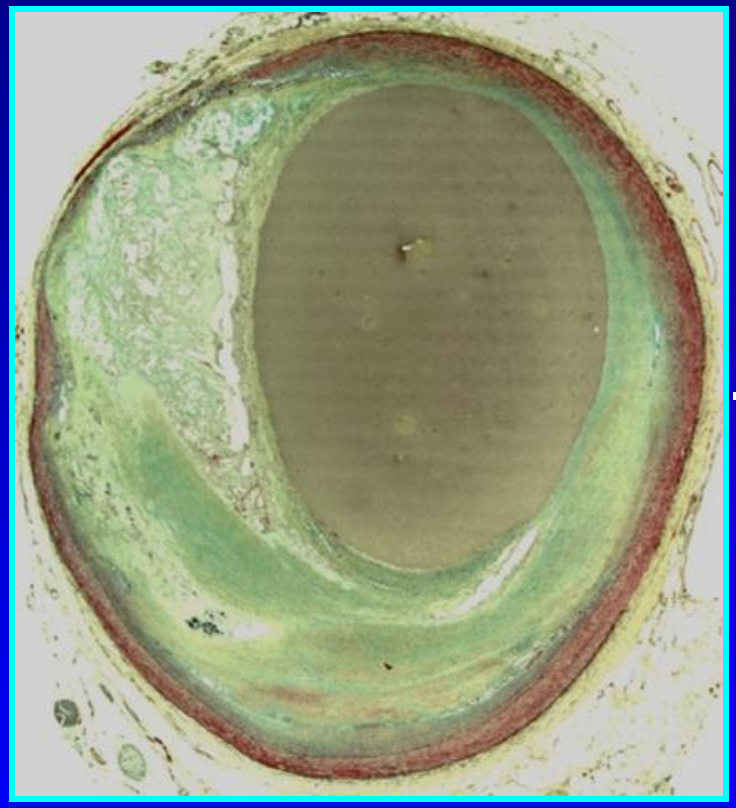
Plaque Rupture



Renu virmani, ETP course 2005

today ? tomorrow

TCFA



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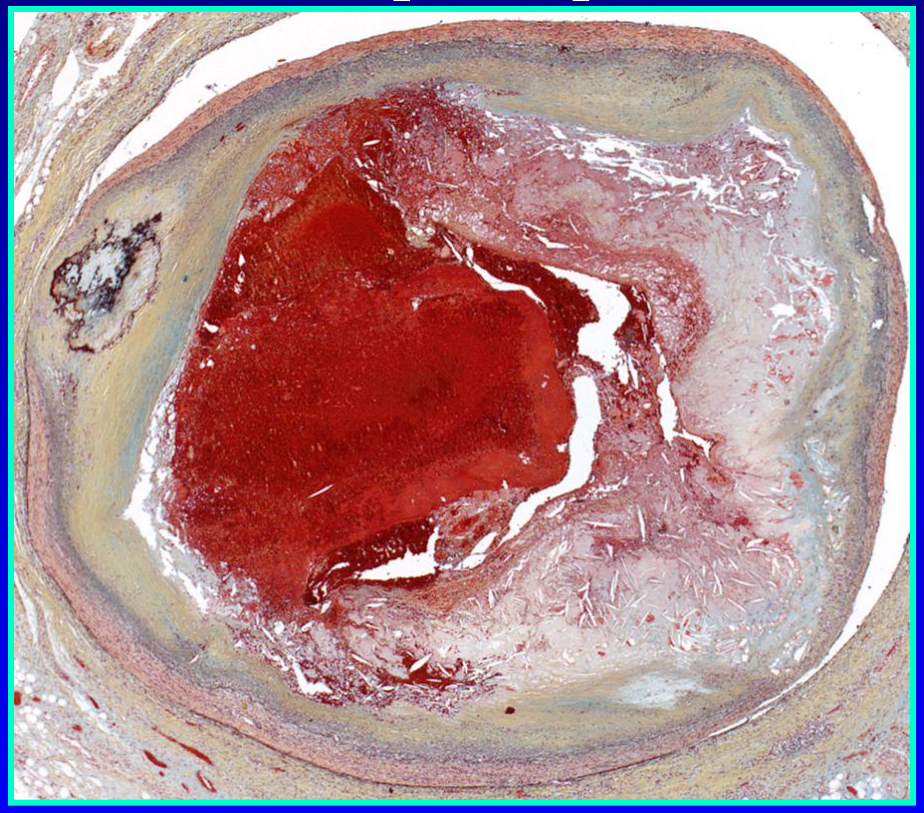
Plaque Rupture



Let's look a little bit more critical to such "plaques"….
What are the facts ?? What is the fiction ??

(Vulnerable) Plaque: Facts and Fiction

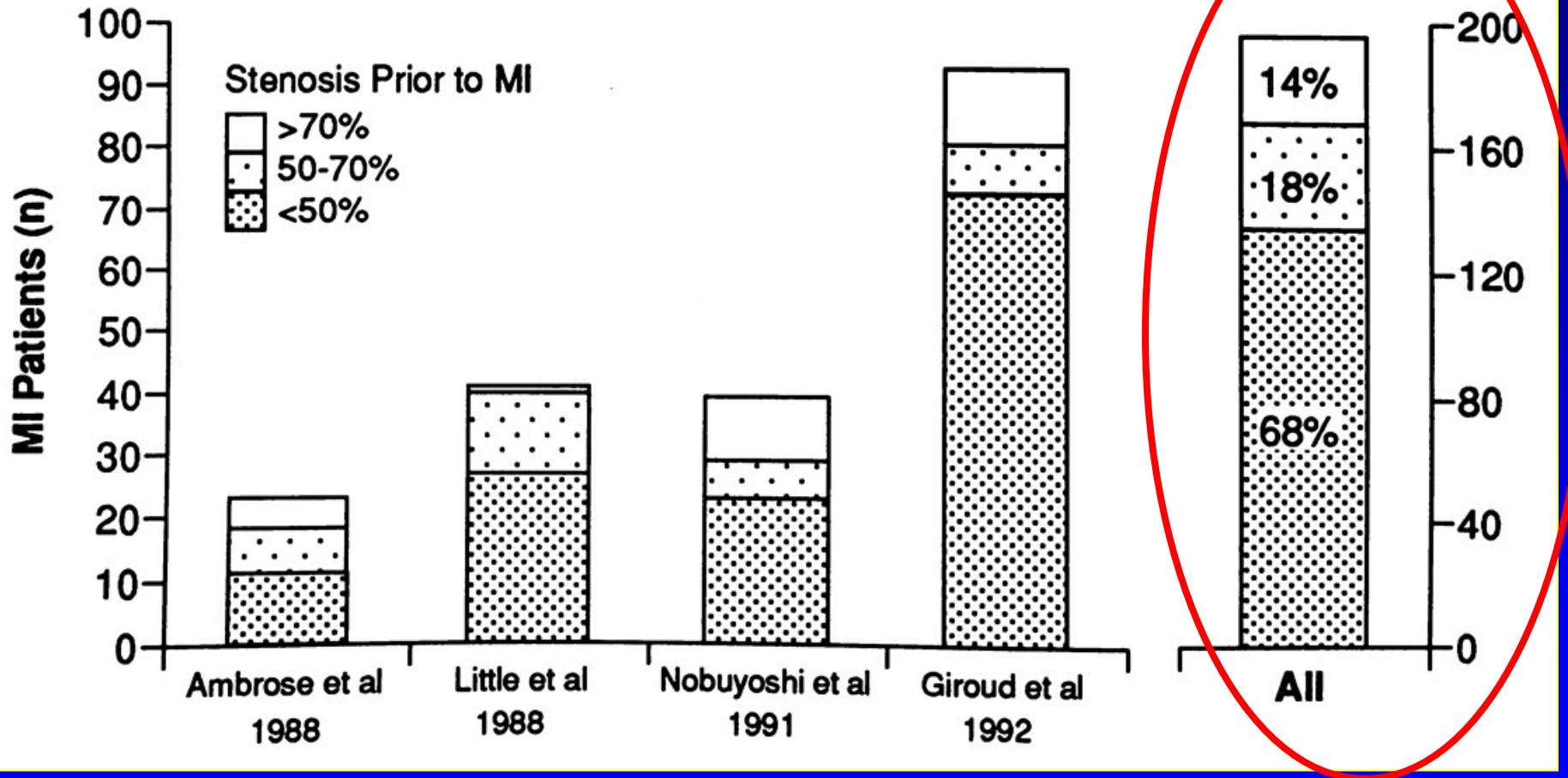
FACTS:

- plaques are very common
- majority of plaques has an excellent prognosis with medical treatment
- only few plaques are vulnerable
- strongest indicator with respect to prognosis is *associated ischemia*

FICTION:

- every plaque is vulnerable
- every vulnerable plaque leads to ACS
- most ACS occurs in mild plaques
- vulnerabilty can be assessed by imaging

Underlying Stenosis Severity of Abrupt Total Occlusions



Falk, Shah and Fuster, Circulation 1995

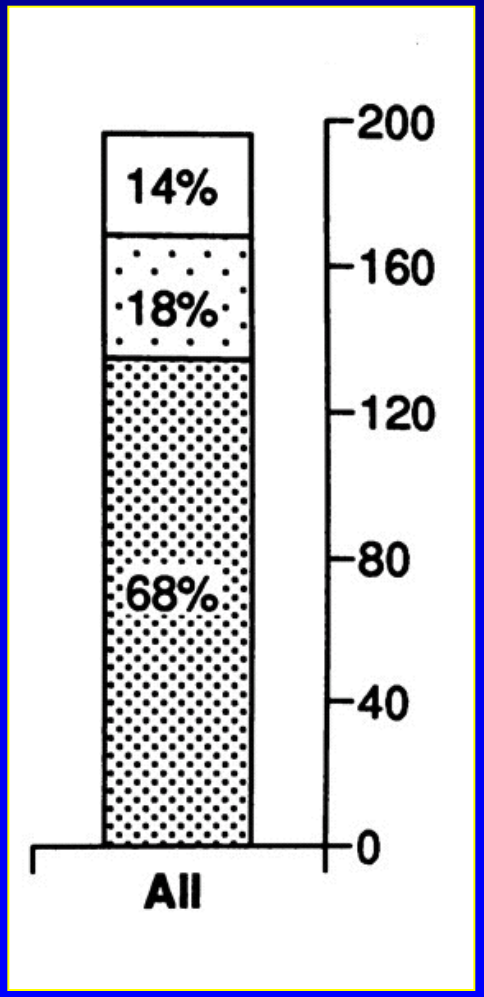
"Acute Coronary Syndromes most often occur at the site of mild stenoses"

Do Myocardial Infarctions Evolve from Mild Stenoses ?

Serial Angiographic (Retrospective) Studies in Patients with MI and a Prior Coronary Angiogram

No QCA, No IVUS but unblinded "eyebolling"

	Number of Patients	Delay Angio-MI
Ambrose et al *JACC* 1988	23	1 month to 7 years
Little et al *Circulation* 1988	42	4 days to 6.3 years
Giroud et al *AJC* 1992	92	1 month to 11 years
Moise et al. AJC 1984	116	39 months
Webster et al JACC 1990	30	55 months
Hackett et al AJC 1989	10	21 months
Total	**313**	**A few days to 11 years (average 3.9 years !!!)**



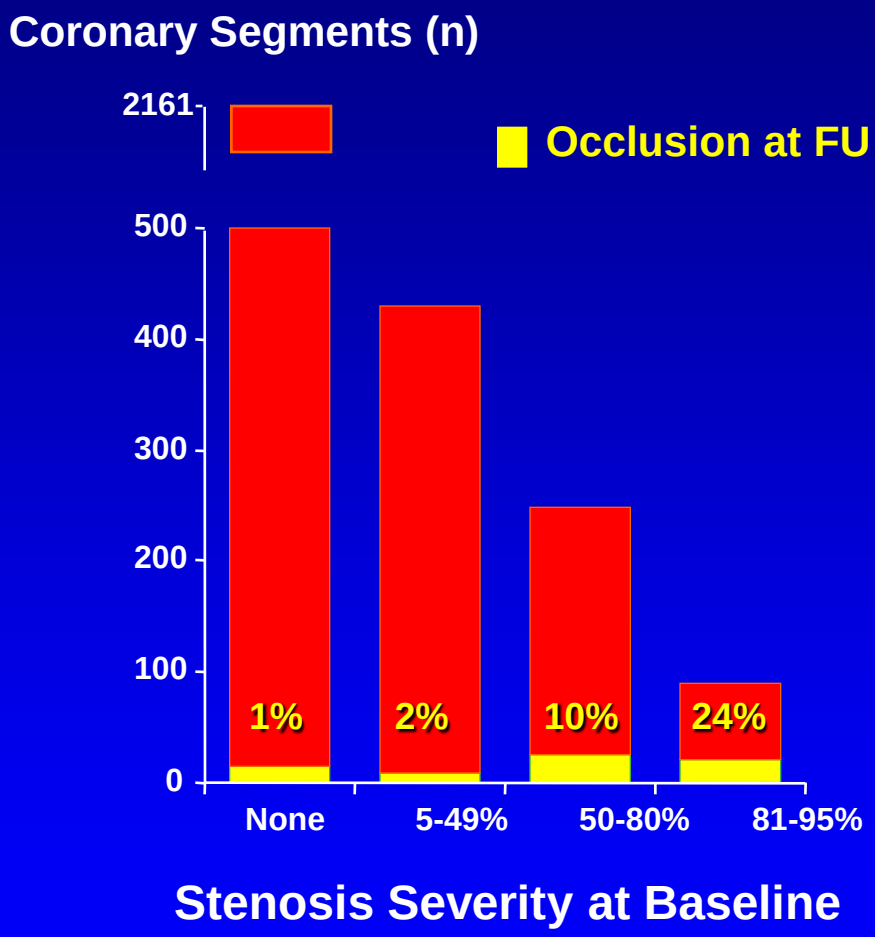
THE MYTHE OF THE "DANGEROUS" PLAQUE

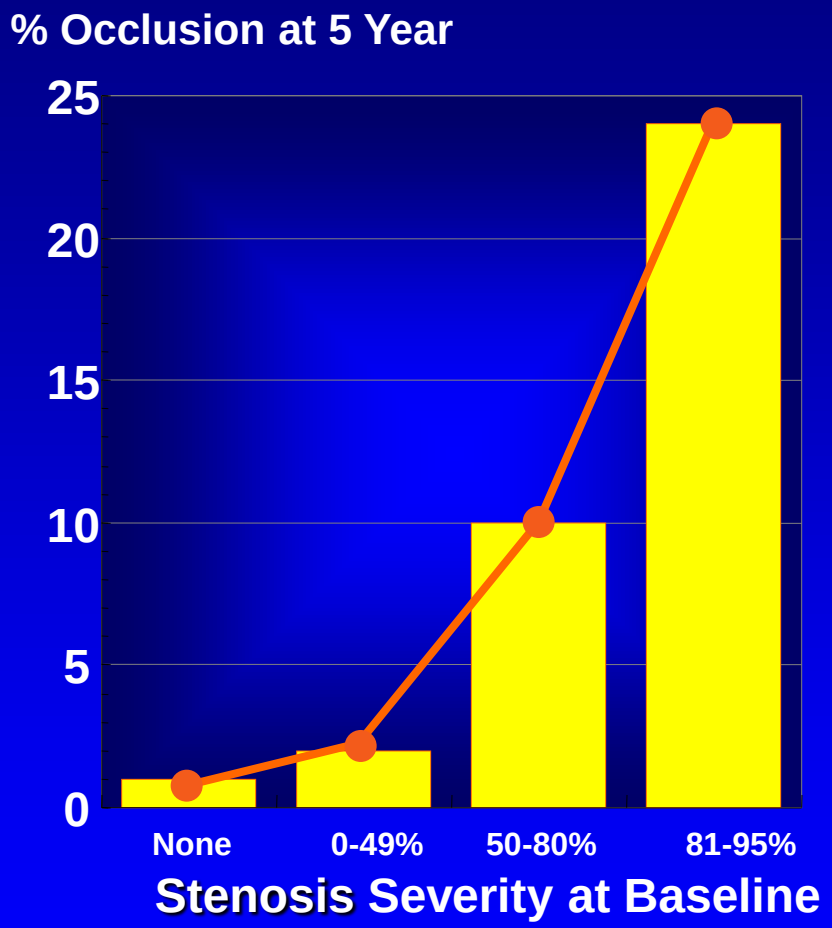
The hypothesis of the occurrence of acute MI on such previously non-significant plaque is based upon

- **6 small retrospective studies**
- **with a total of 313 patients**
- in whom the "index" catherization was performed an average of ***3.9 years*** before the acute event

All other literature (21 "meta-analyses" and hundreds of references), refer to these 6 studies !!!

Coronary Occlusion at 5 Years as a Function of Stenosis Severity

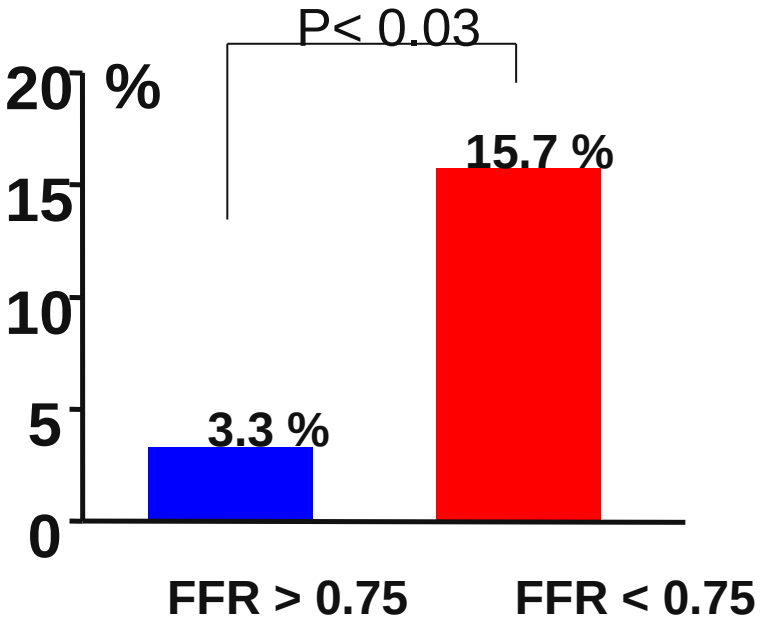




Adapted from Alderman et al. J Am Coll Cardiol 1993

DEFER study (N=325) :

Cardiac death and Acute MI after 5 years



- non-ischemic stenosis, treated medically
- ischemic stenosis, treatment by PCI & optimum R/x

→ ischemic lesion is much more dangerous than non-ischemic lesion

→ risk of individual non-ischemic lesion to cause death or AMI, is very small and < 1 % per year !!

JACC 2007; 49: 2105-2111

250 consecutive patients with ST-elevation MI in the Catharina Hospital:

- underlying stenosis angiographically significant in 92 % of the cases
- *At meticulous anamnesis, 80 % of patients had recurrent chest pain in the year before the acute myocardial infarction occurred !!*

Frobert et al CCI, 2007, 70: 958-965

INCIDENCE OF CORONARY STENOSIS IN A GENERAL POPULATION

Incidence of coronary artery disease in *asymptomatic*, apparently healthy persons

> 50 years old : 25%
> 60 years old : 40%

Sims et al, Am Heart J 1983
Maseri, Ischemic Heart Disease 1995

What about the prognosis of these patients ?

⟶ **Related to inducibility of ischemia**

- structure of the coronary circulation
- relation between vessel size and perfusion area
- endothelium and development of atherosclerosis
- the 2 or 3 compartment model of the coron circulation
- collaterals
- why functional testing / FFR ?
- which lesions should be treated
- vulnerable plaques: facts & fiction
- ***ischemia & vulnerability: paradox or antithesis ?***

"The missing link"

Is there a link between vulnerabilty and ischemia ?

Hypothesis:

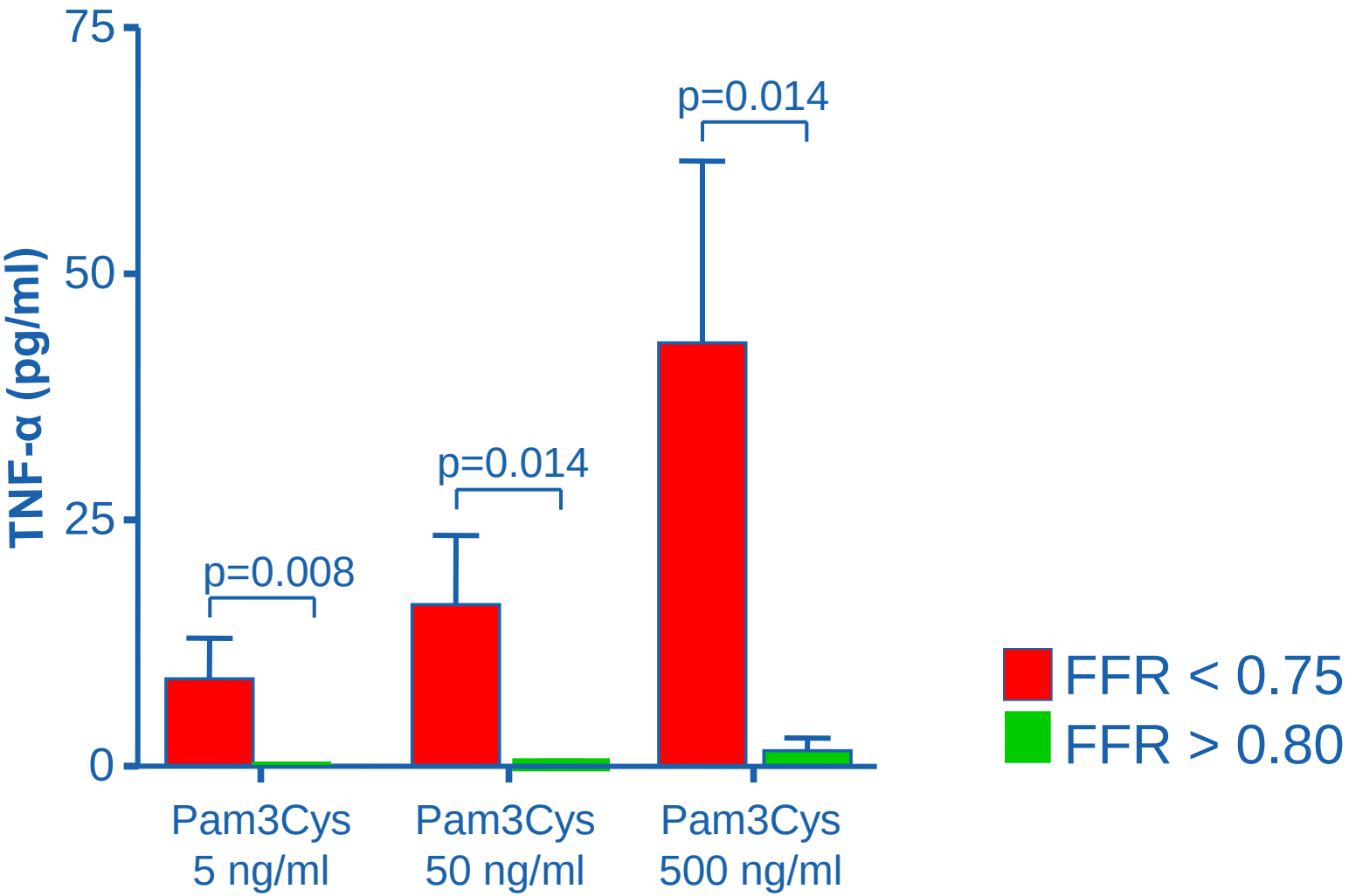
- repetitive ischemia *and*
- high shear stress / pressure gradients

induce vulnerability

→ *Supported by studies on the relation between vulnerability markers and low FFR: on-going work of Pasterkamp et.al.*

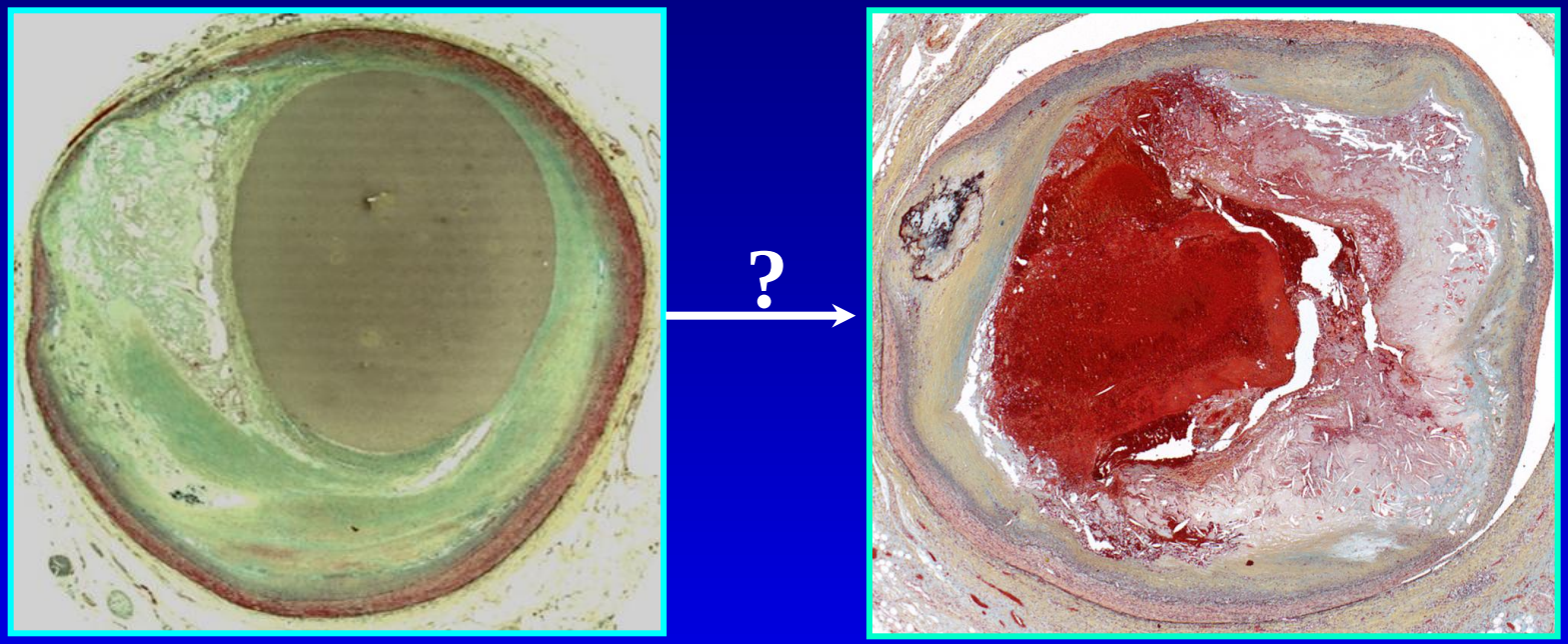
Heart 2007

TLR2 stimulation (Pam3Cys)



Versteeg et al, Heart 2007

Concept of Yesterday:



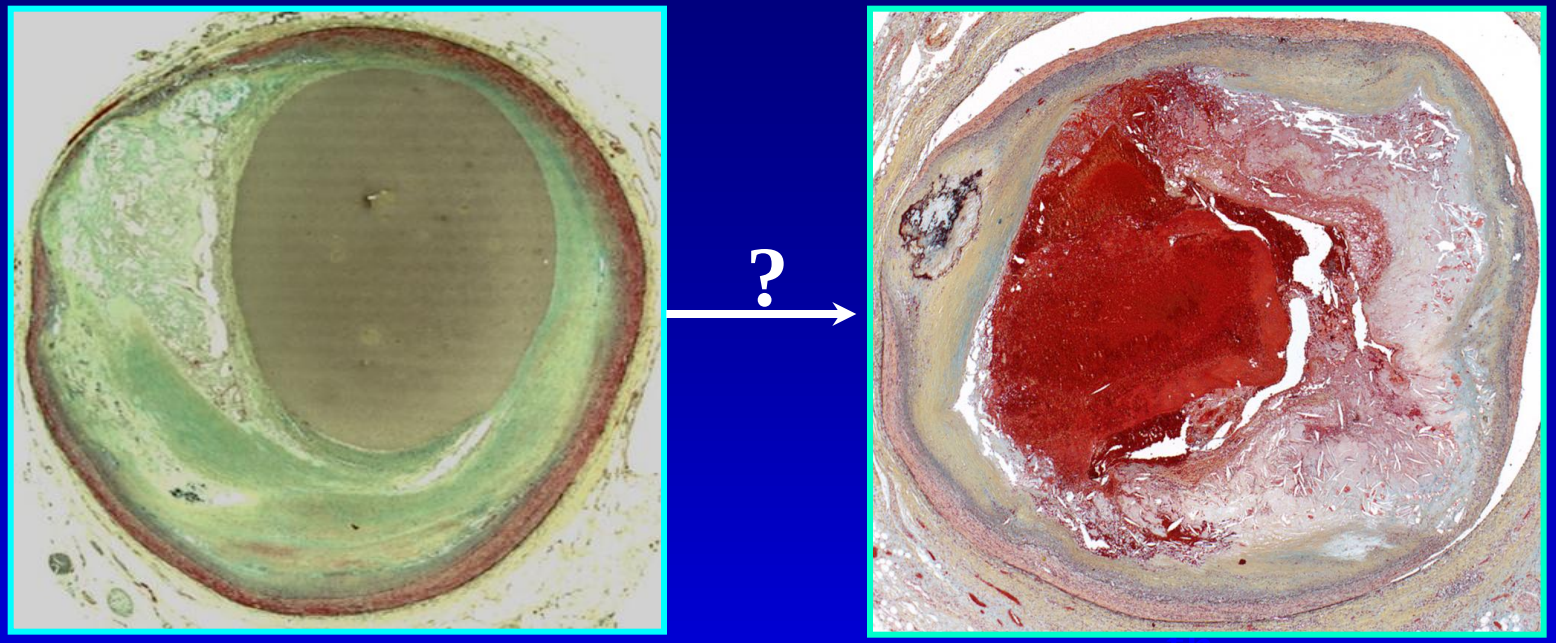
Pro-inflammatory cytokines,activated monocytes, etc

↓

Vulnerability

(“out of the blue”)

Concept of Tomorrow:



ischemic episodes

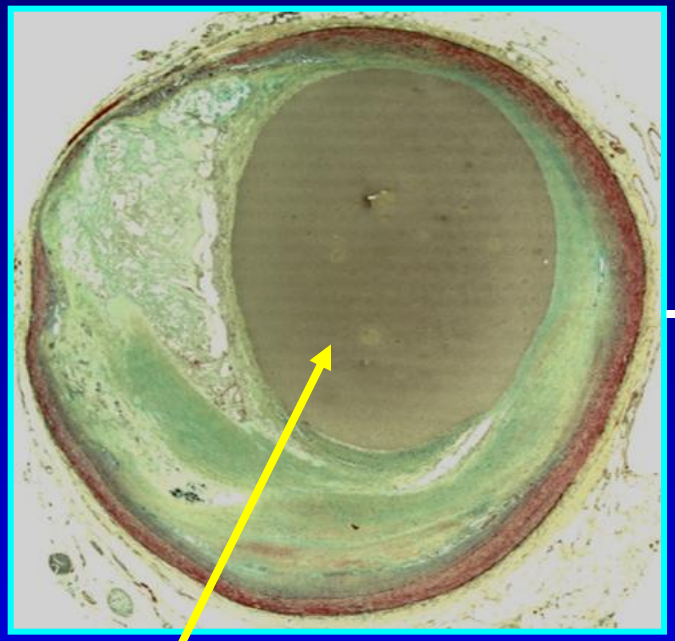
↓

Pro-inflammatory cytokines, activated monocytes, etc

↓

Vulnerability

Concept of today:



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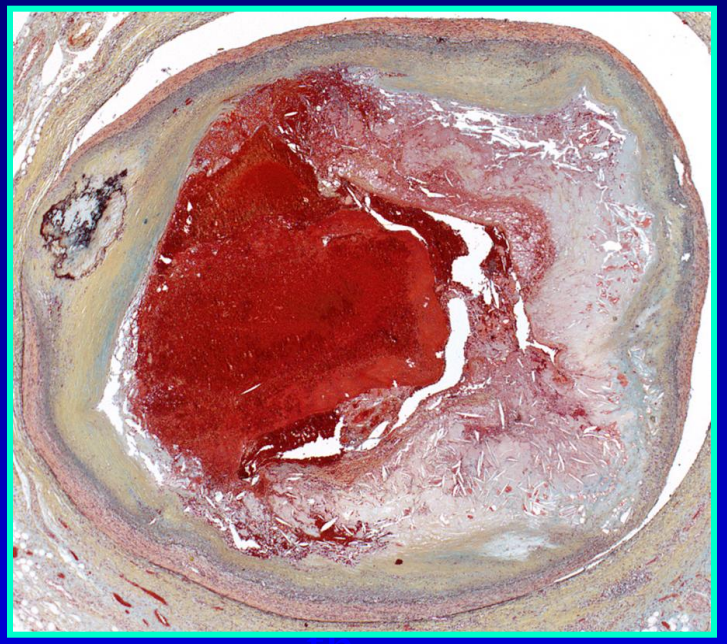


by the way:
70% area
Stenosis !!

ischemic episodes

↓

Pro-inflammatory cytokines etc

↓

Vulnerability

new paradigm:

Plaque / stenosis

↓

Ischemic episodes

↓

production of remodelling-promoting substances

↙ successful remodelling, decrease of ischemia

↘ overshoot, plaque rupture

Searching for vulnerability starts with searching for ischemia

Suppose aliens would visit us and would like to investigate the determinants of a fire.

"Substance X (also called "water") must be dangerous substance !"

FUNCTIONAL ASSESSMENT OF BOTH COMPARTMENTS TOGETHER:

- non-invasively
  (exercise testing, stress echo, Mibi)

- invasively: intracoronary Doppler, absolute flow

FUNCTIONAL ASSESSMENT OF THE MICROCIRCULATION:

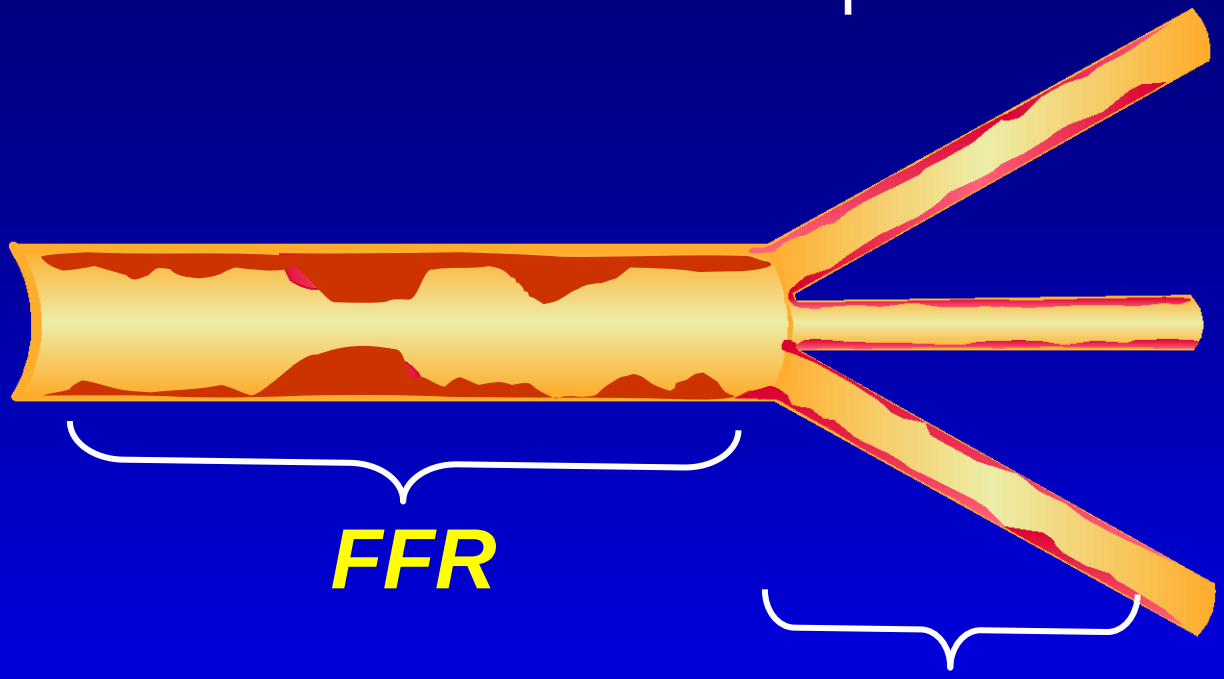
- Index of Microcirculatory Resistance (IMR)

The coronary microcirculation:

Still a black box ??

focal and diffuse
Epicardial disease

microvascular
compartment

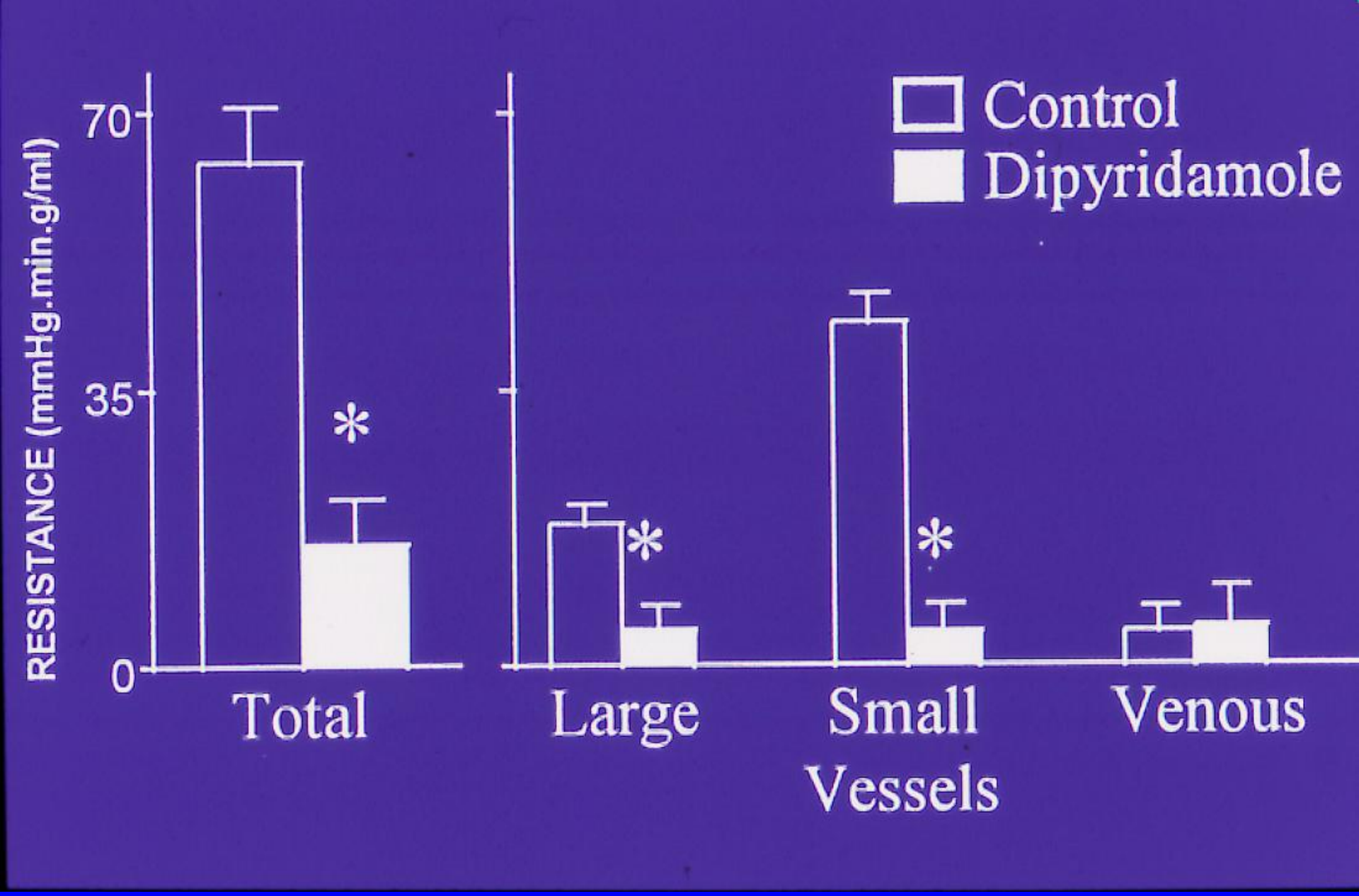


→ ***Invasive indexes*** *(saturday morning):*

IMR *(Bill Fearon)*

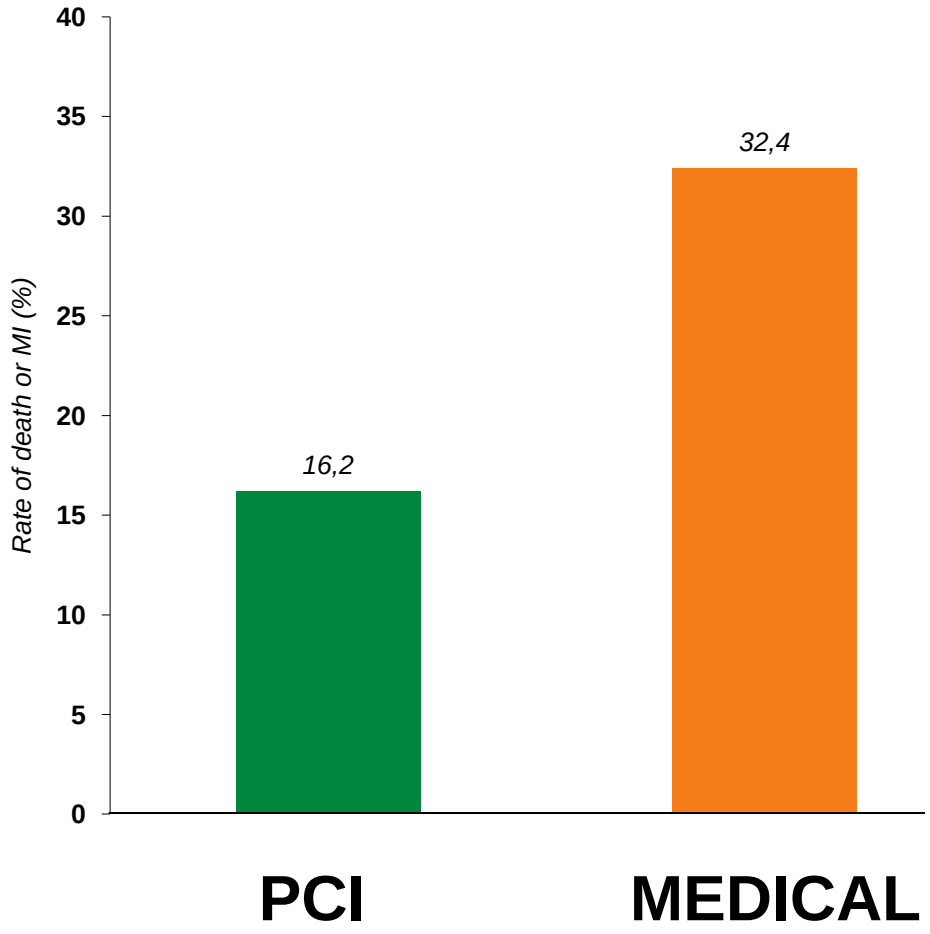
absolute resistance *(Nico Pijls)*

! We cannot understand the physiologic significance of a stenosis without taking into account the distal perfusion territory !

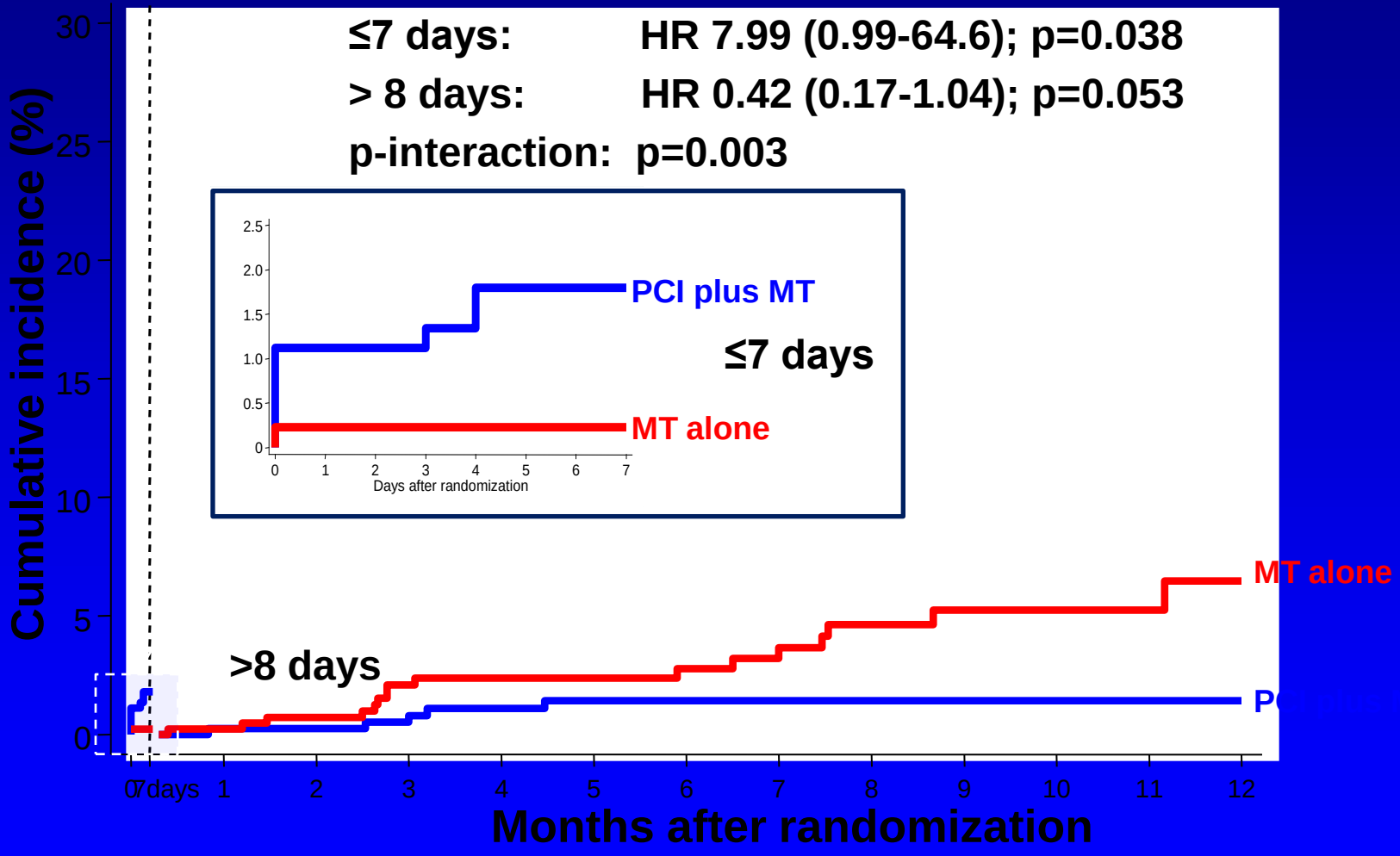


majority of resistance located in arterioles (100-400 µm)

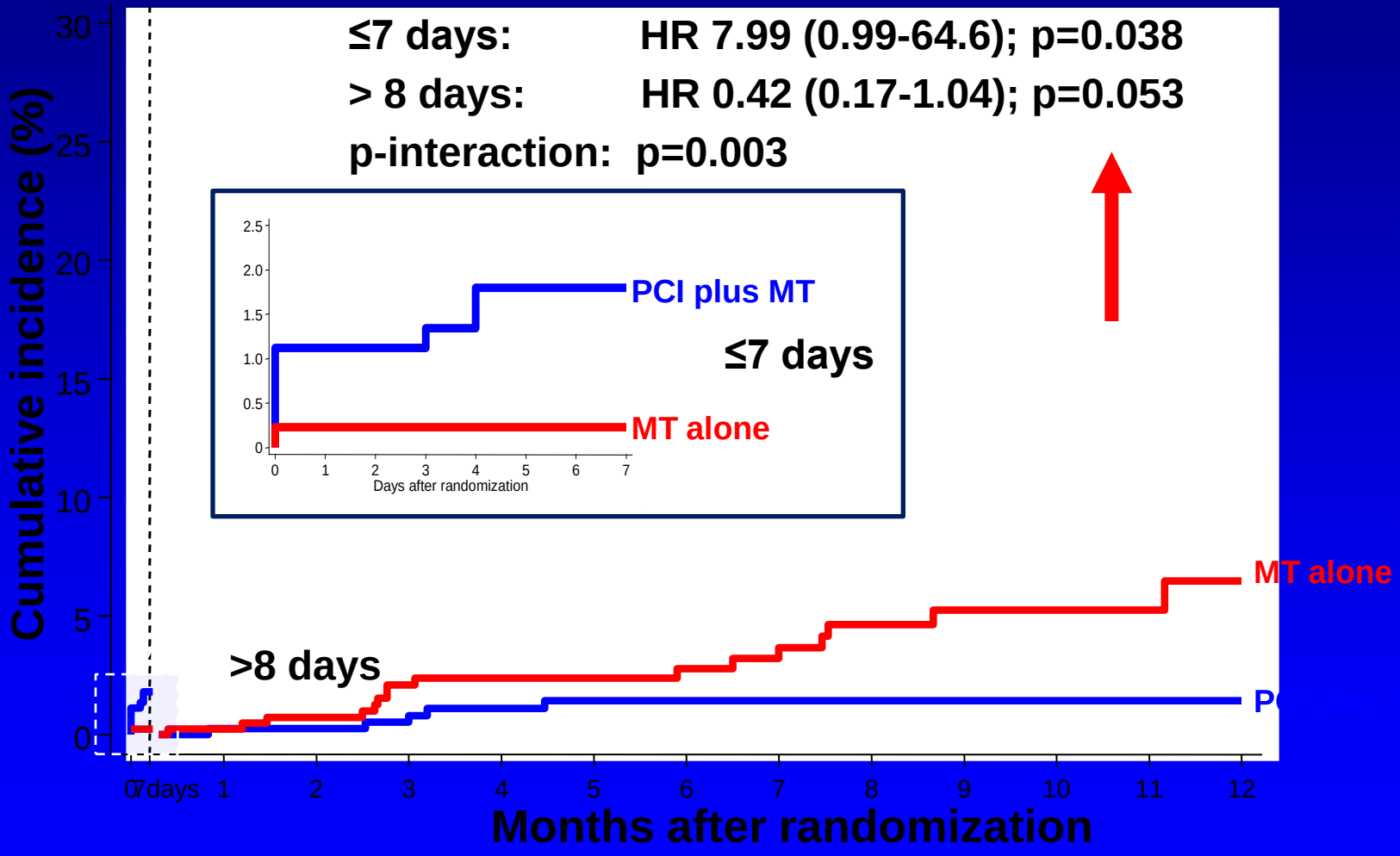
ISCHEMIC



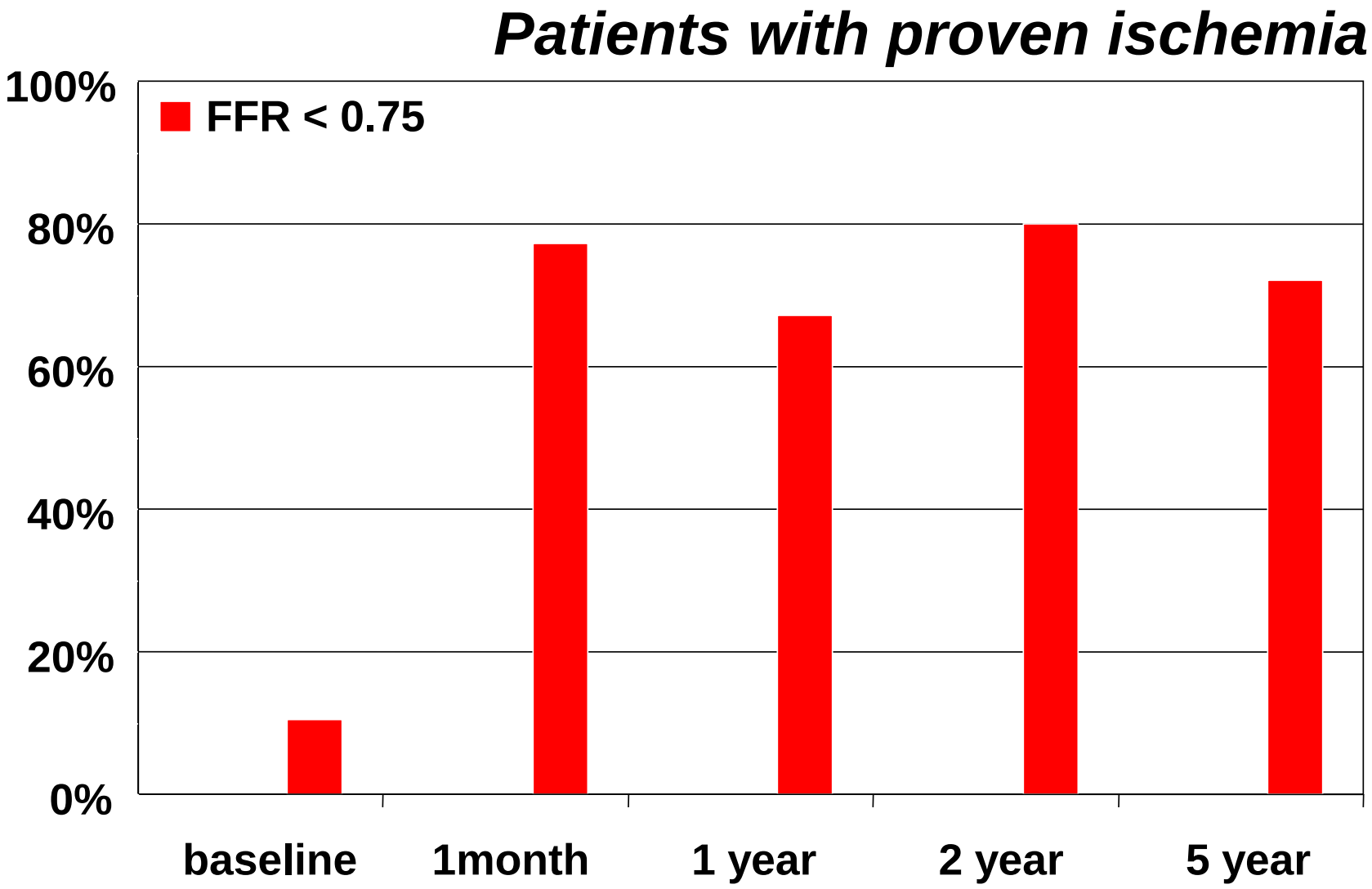
Kaplan-Meier plots of Landmark Analysis of *Death or MI*



Kaplan-Meier plots of Landmark Analysis of *Death or MI*

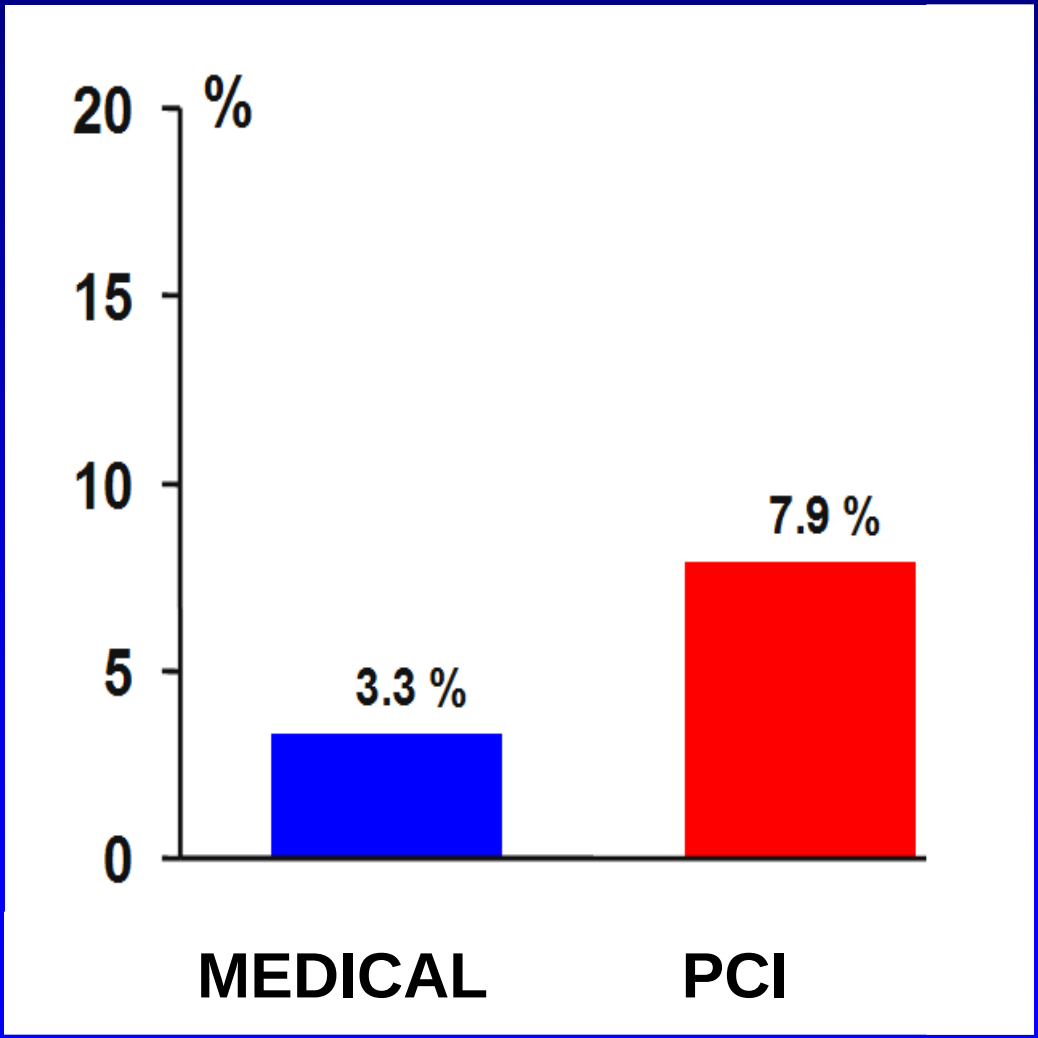


DEFER-study, JACC 2007; 49 : 2105-2111



freedom from angina after stenting ischemic stenosis

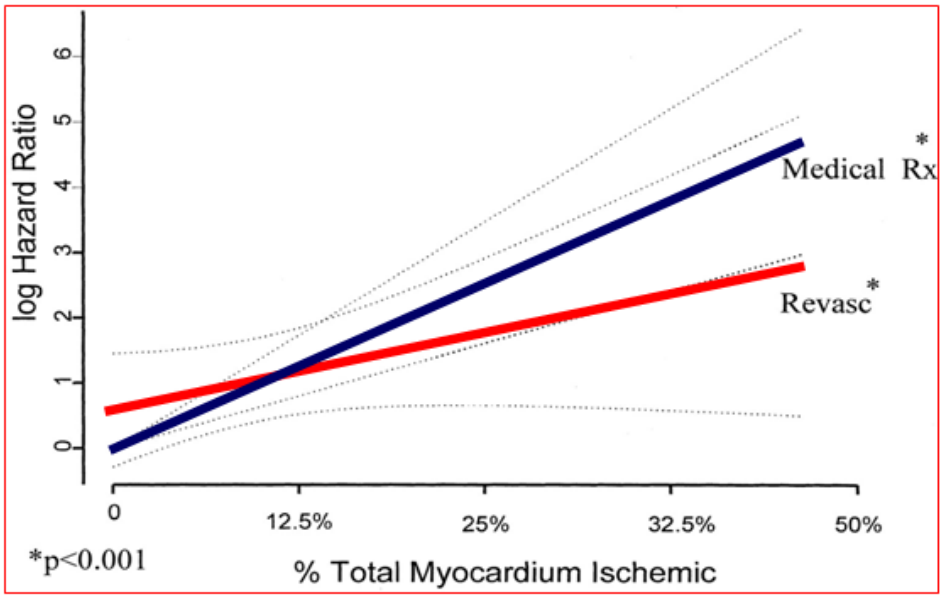
Death & MI 5 during 5 years of follow-up after PCI vs Medical Treatment in NON-ischemic stenosis



Pijls et al
JACC 2007

Is it important to detect ischemia ?

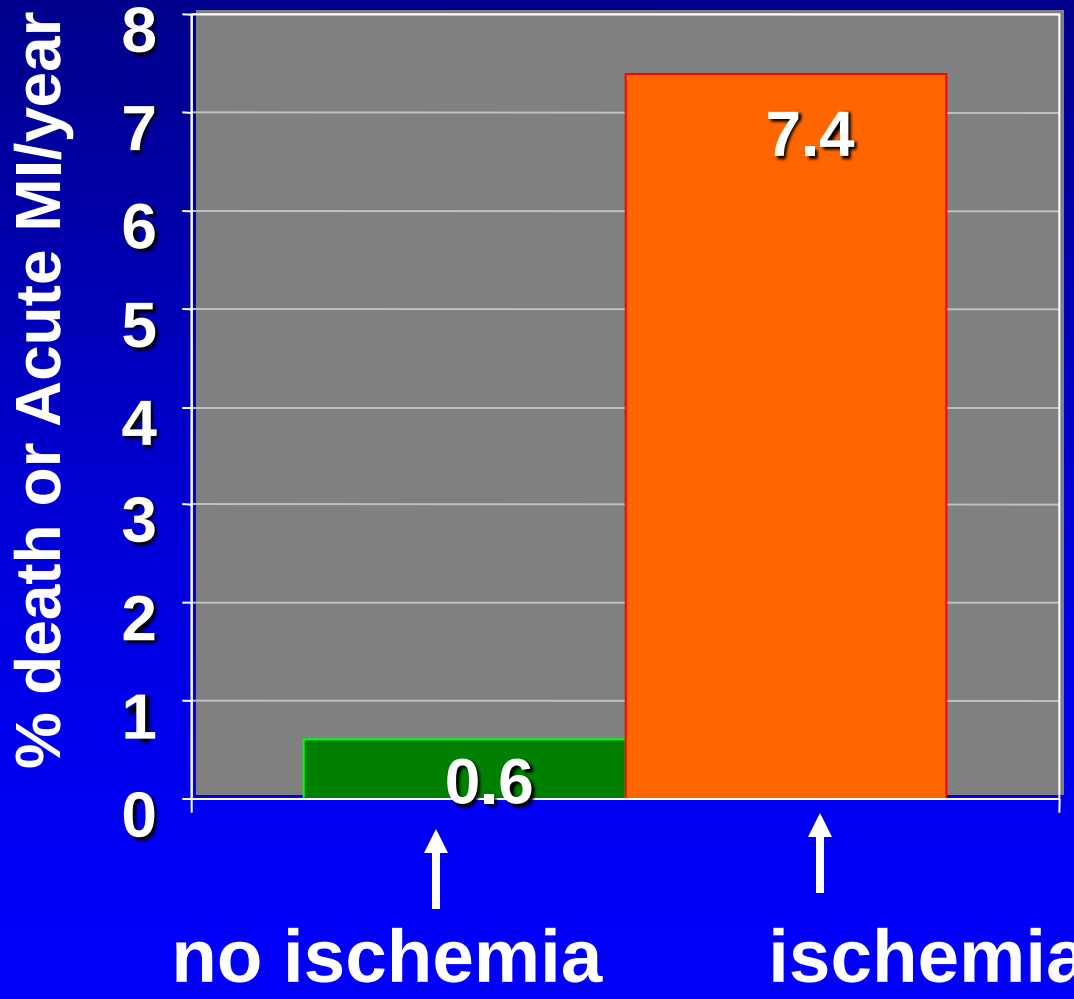
Log hazard ratio for revascularization (Revasc) vs medical therapy (Medical Rx) as a function of % myocardium ischemic based on final Cox proportional hazards model



Above 10% ischemic myocardium, the survival benefit from revascularisation increases with the extent of ischemia

Hachamovitch, R. et al. Circulation 2003

The risk for death or acute myocardial infarction in the next five years is 20 times higher for an ischemic lesion compared to a non-ischemic lesion !!!



12000 Patients (2 x 6000)

similar stenosis severity by coronary angio

Iskander S, Iskandrian A E JACC 1998

Risk to die or experience myocardial infarction in the next 5 years related to a coronary stenosis:

- **non-ischemic stenosis: < *1% per year ****
  (NUCLEAR studies, PET, MRI, DEFER, FAME)
- **ischemic stenosis, if left untreated: *5-10% per year***
  (Many historical registries, nuclear studies, ACIP, CCTA, MRI, FFR)
- **stented stenosis: *2-3% per year***
  (*e.g DEFER, FAME, SYNTAX,many large studies and registries)*

THE KEY ISSUE IN INTERVENTIONAL CARDIOLOGY IS TO DISCRIMINATE THOSE LESIONS RESPONSIBLE FOR INDUCIBLE ISCHEMIA

→ ***Fractional Flow Reserve***

THE EPICARDIAL COMPARTMENT IS RATHER EASY TO ASSESS:

IMAGING OF THE EPICARDIAL COMPARTMENT

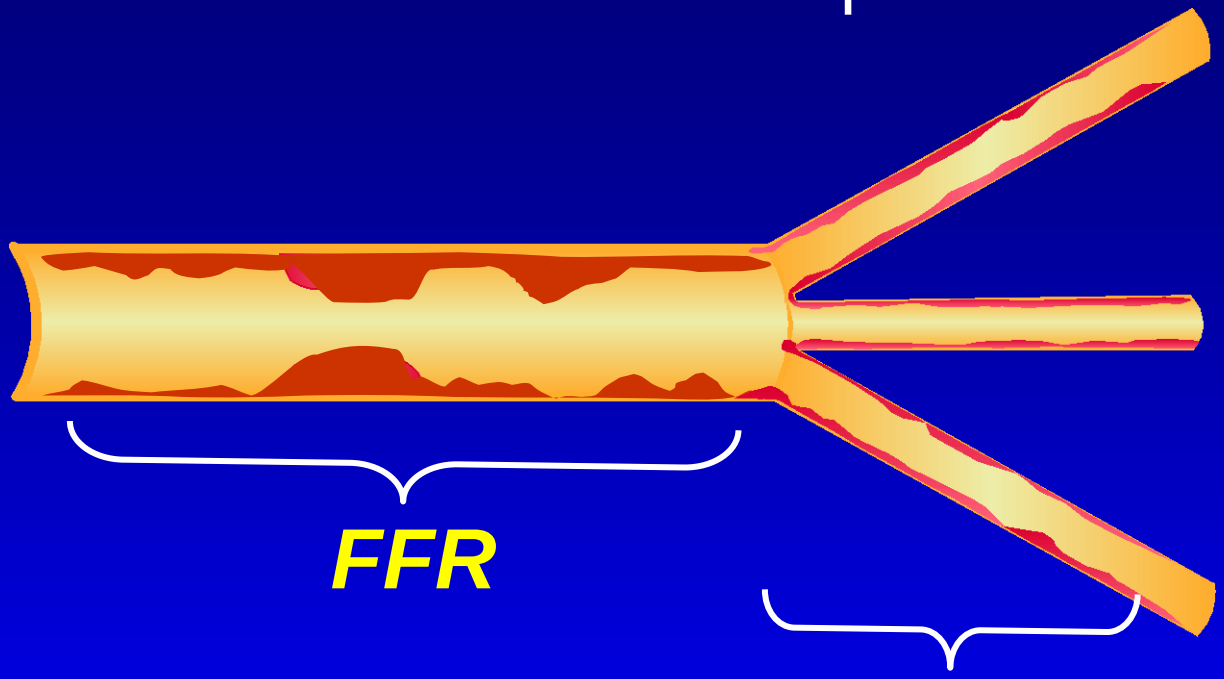
- non-invasively by CT, MRI
- invasively by angio, IVUS, OCT,and some newer techniques

FUNCTIONAL ASSESSMENT OF THE EPICARDIAL COMPARTMENT

- coronary pressure & FFR

focal and diffuse
Epicardial disease

microvascular
compartment



→ ***Invasive indexes***:

IMR*(Bill Fearon,Bernard De Bruyne)*

absolute flow & resistance *(Gabor Toth, Inge wijnbergen)*