Structure of the Coronary Circulation

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest /arrangement or affiliation with the organization(s) listed below

Affiliation/Financial Relationship	Company
Grant/ Research Support:	St. Jude Medical/Medtronic
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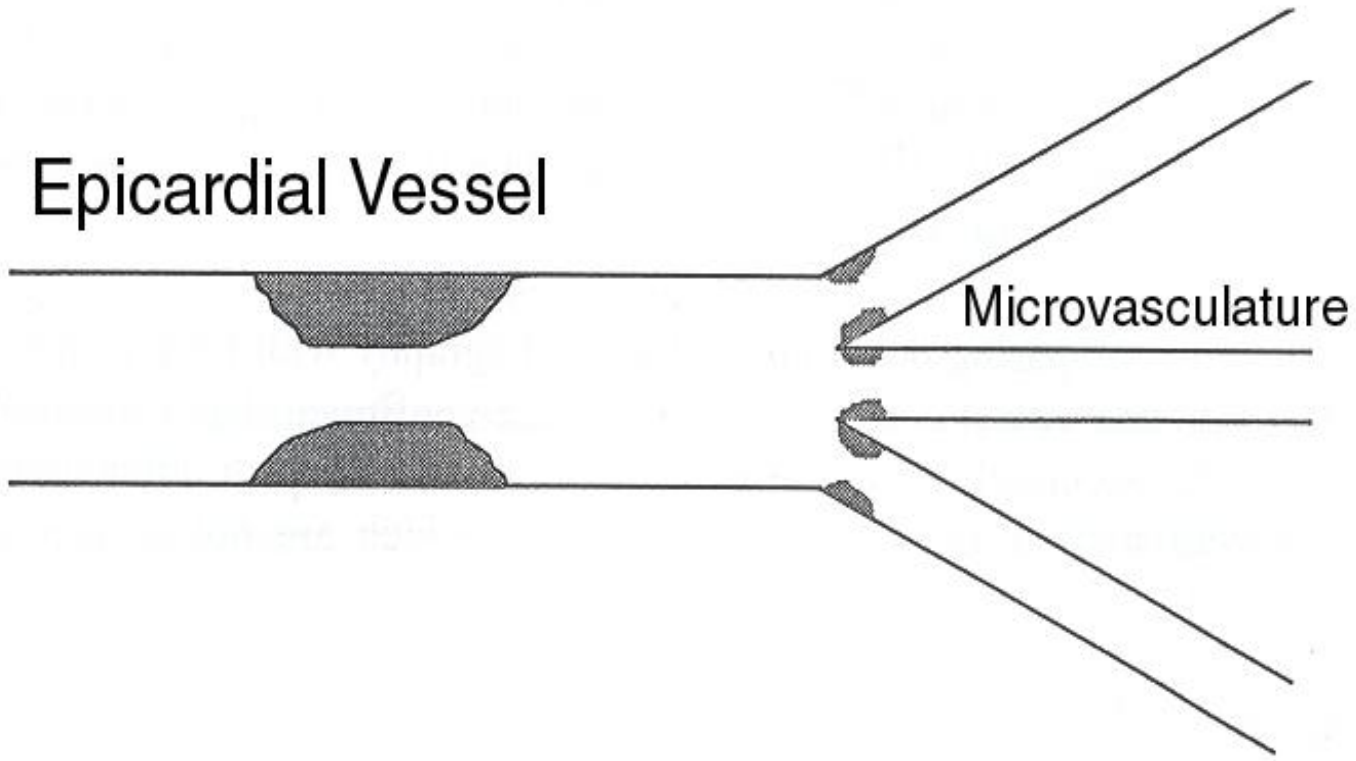
Consulting Fees/Honoraria:	Medtronic
Major Stock Shareholder/Equity Interest:	
Royalty Income:	
Ownership/Founder:	
Salary:	NIH-R01 HL093475 (PI)
Intellectual Property Rights:	
Other Financial Benefit (minor stock options):	HeartFlow

Outline:

- Coronary Anatomy
- Myocardial Mass and Coronary Flow
- Coronary Resistance
- Pathophysiology of Atherosclerosis

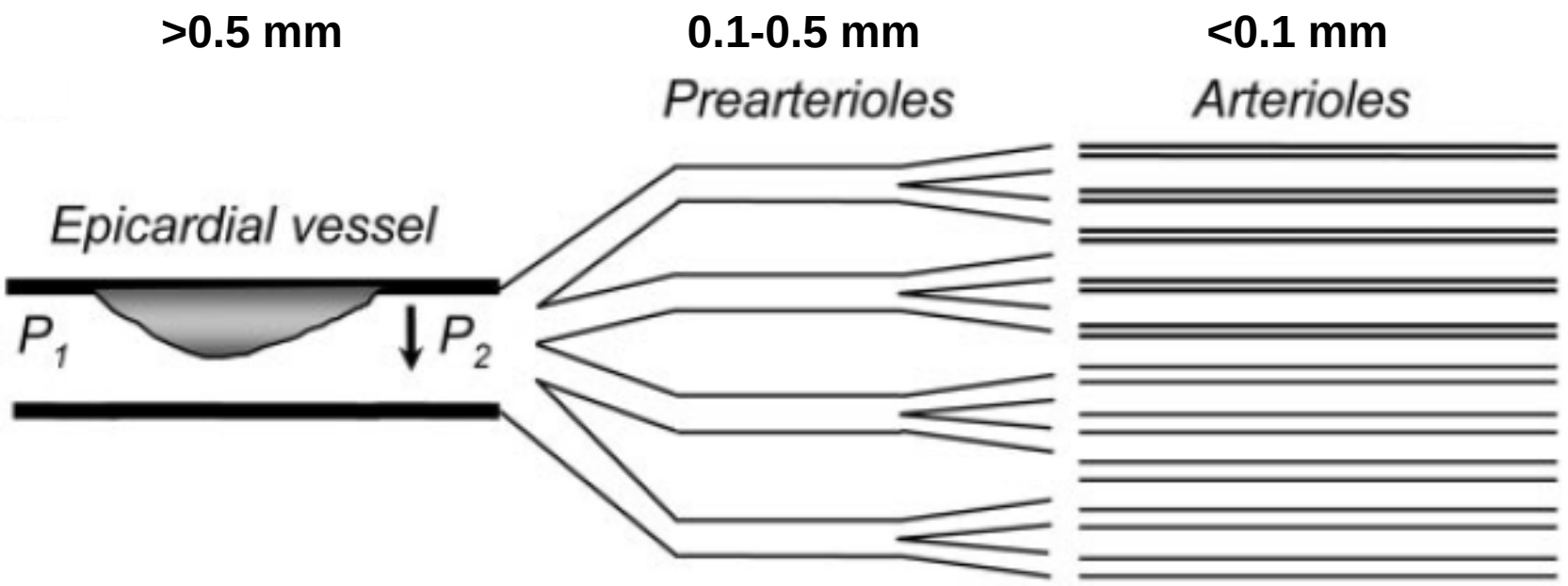
Coronary Circulation:

Two Compartment Model



Coronary Circulation:

Three Compartment Model

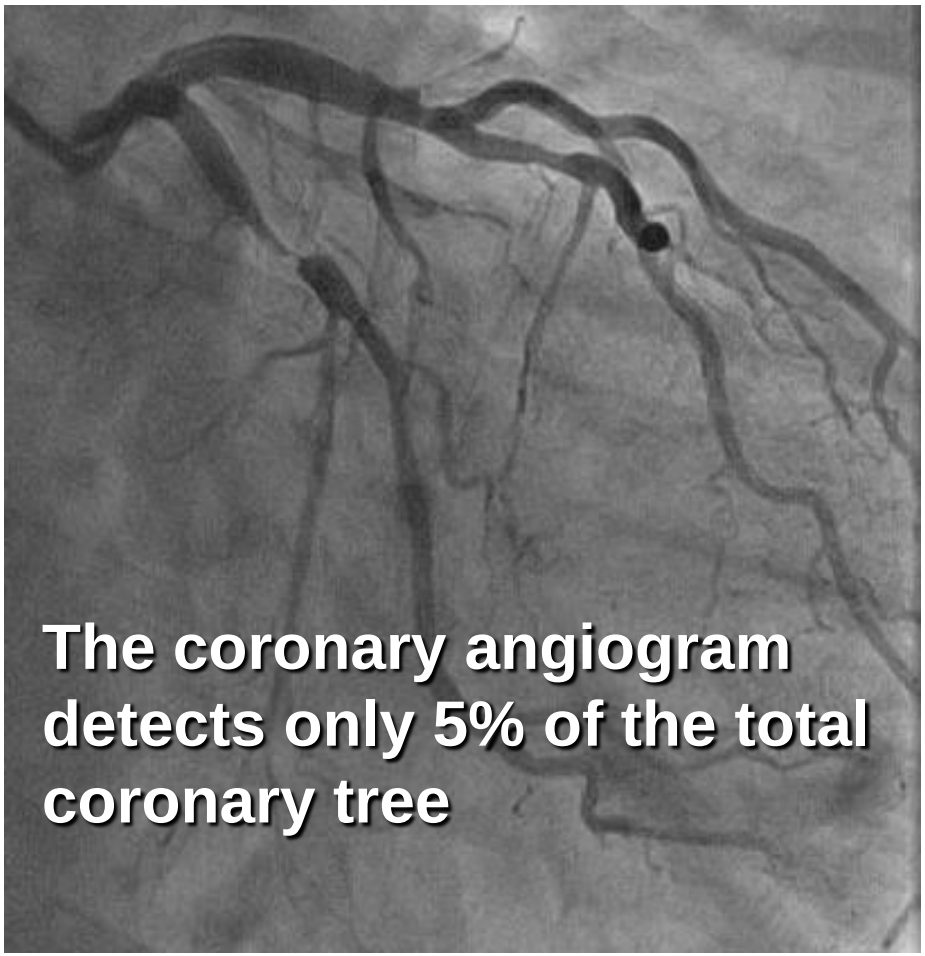


Sympathetic Innervation
Endothelium-Dependent
Shear Stress

Metabolic Milieu
Autoregulation
Myogenic Control

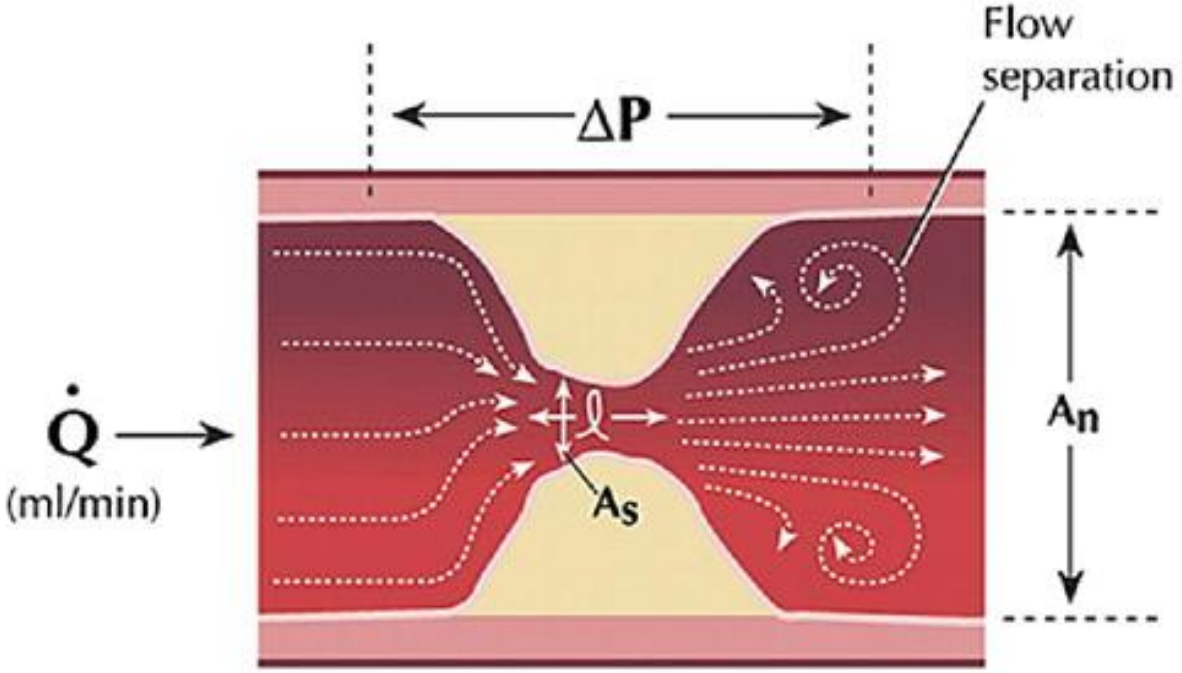
Adapted from: Lanza and Crea. Circulation 2010;121:2317-2325.

Coronary Circulation:



Courtesy of Bernard De Bruyne, MD,PhD

Determinants of a Pressure Gradient

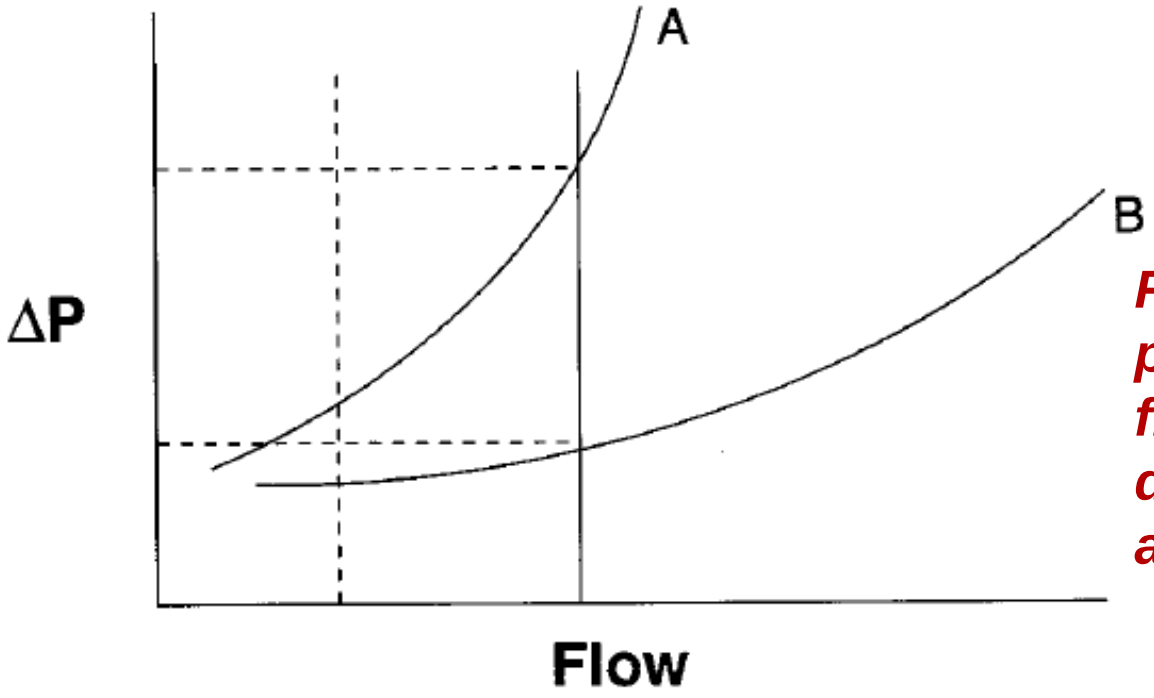


$$\Delta P = \underbrace{f_1(1/A_s^2, \ell, \dot{Q})}_{\text{Viscous}} + \underbrace{f_2(1/A_s^2, 1/A_n^2, \dot{Q}^2)}_{\text{Separation}}$$

Braunwald's Heart Disease 2005, 7th edition, vol.2, p.1112.

Pressure Gradients and Flow:

- The pressure gradient across a stenosis is related to the flow across the stenosis

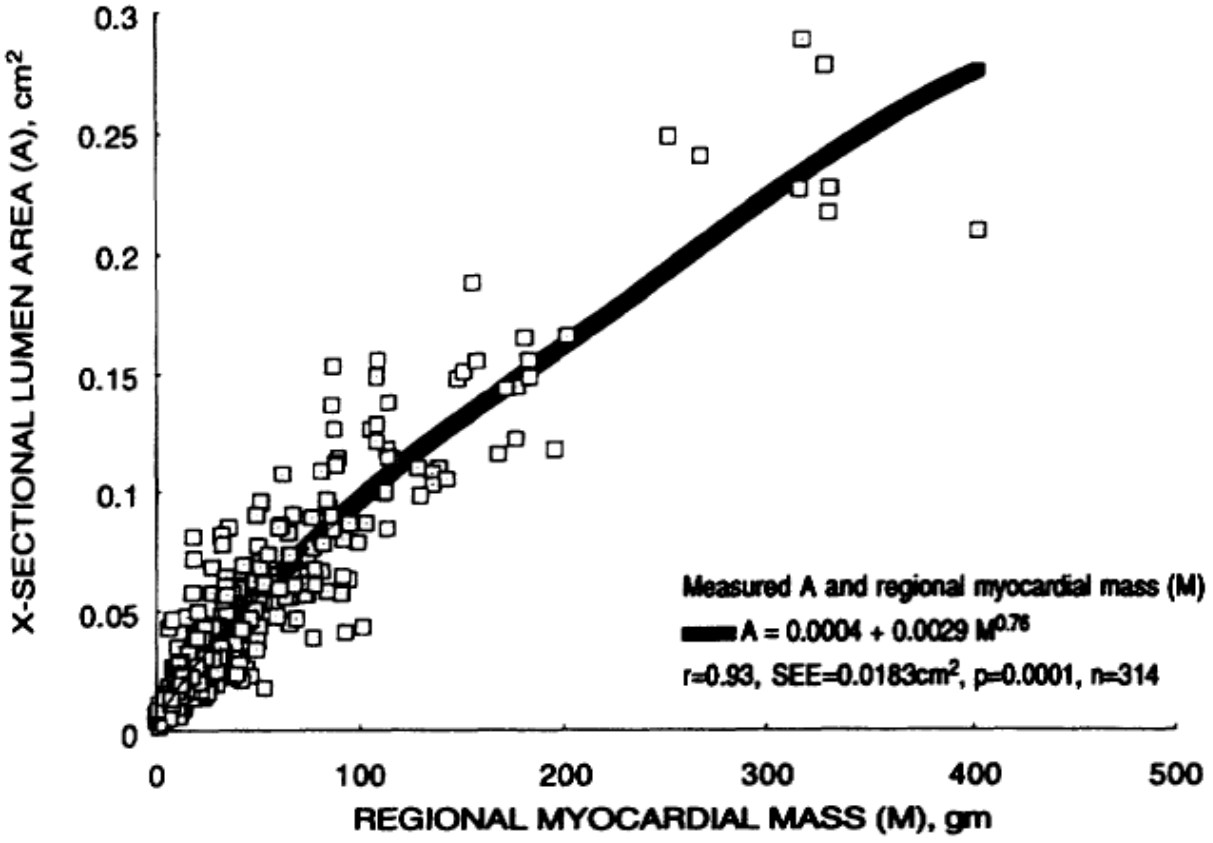


Relationship between pressure drop and flow across two different stenoses, A and B

Kern MJ. Circulation 2000;101:1344

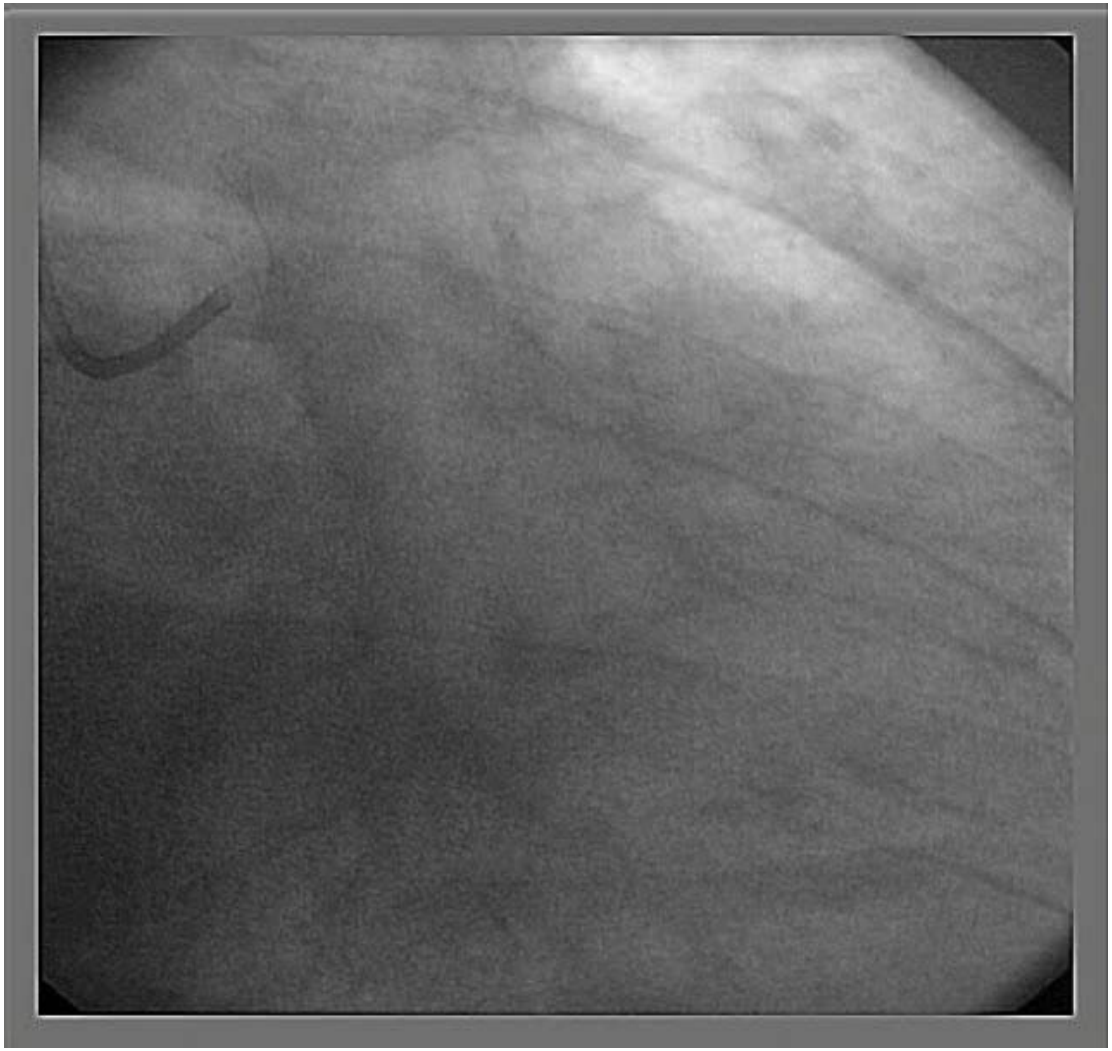
Relation Between Vessel Size and Perfusion Area

Cross-Sectional Area (≈ Flow) and Myocardial Mass



Seiler, et al. Circulation 1992;85:1987-2003.

Disconnect between Anatomy and Physiology



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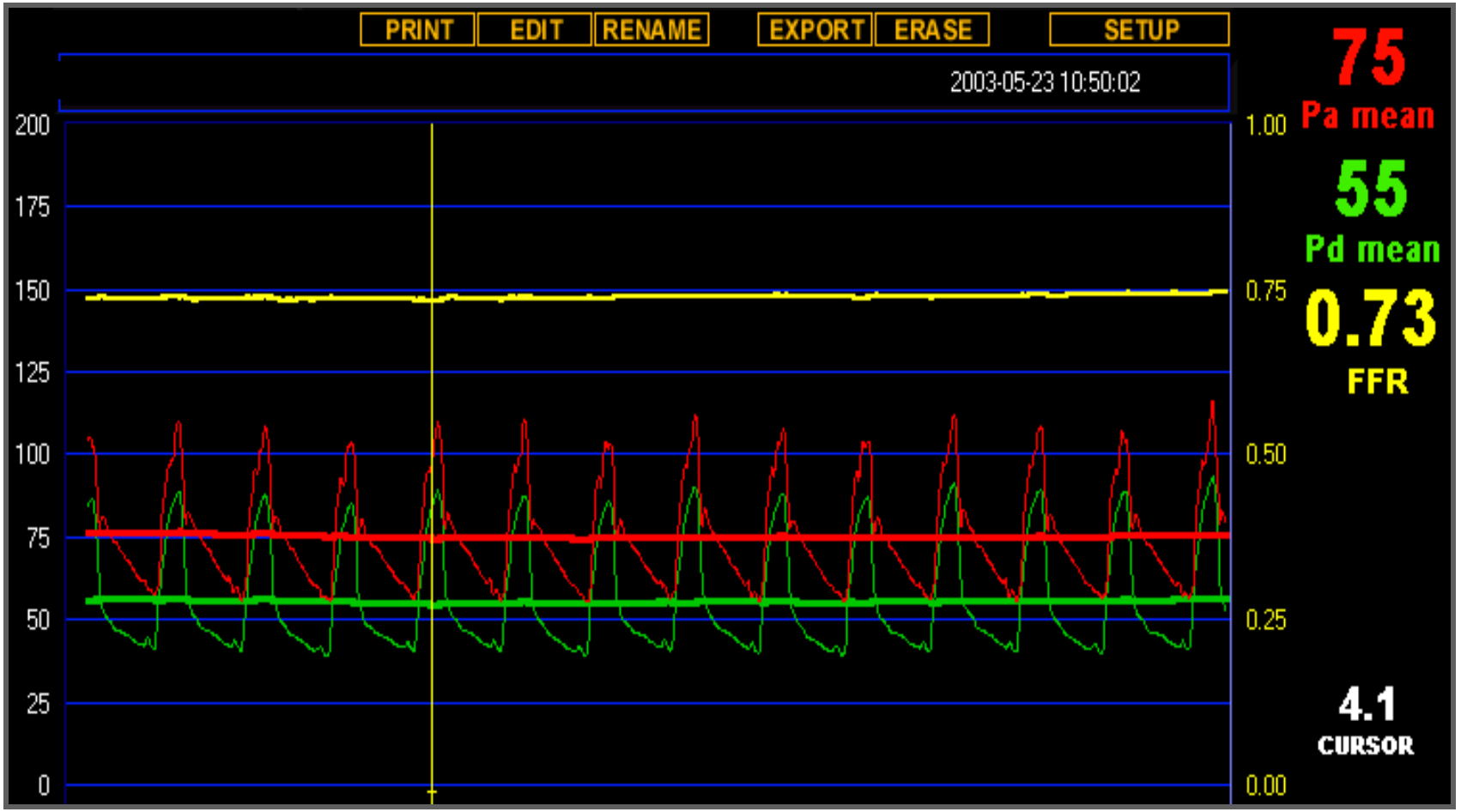

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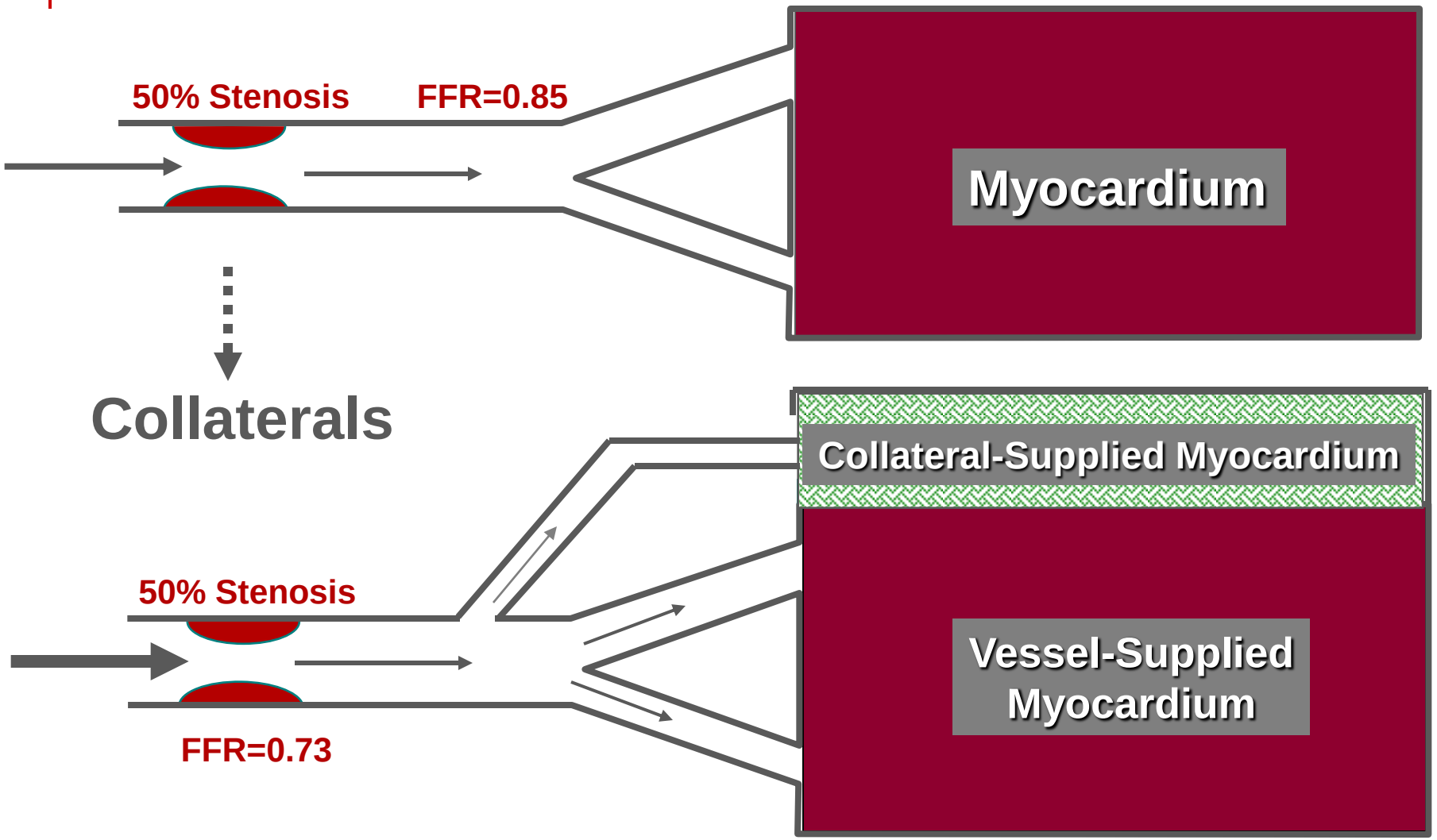

…During Maximal Hyperemia

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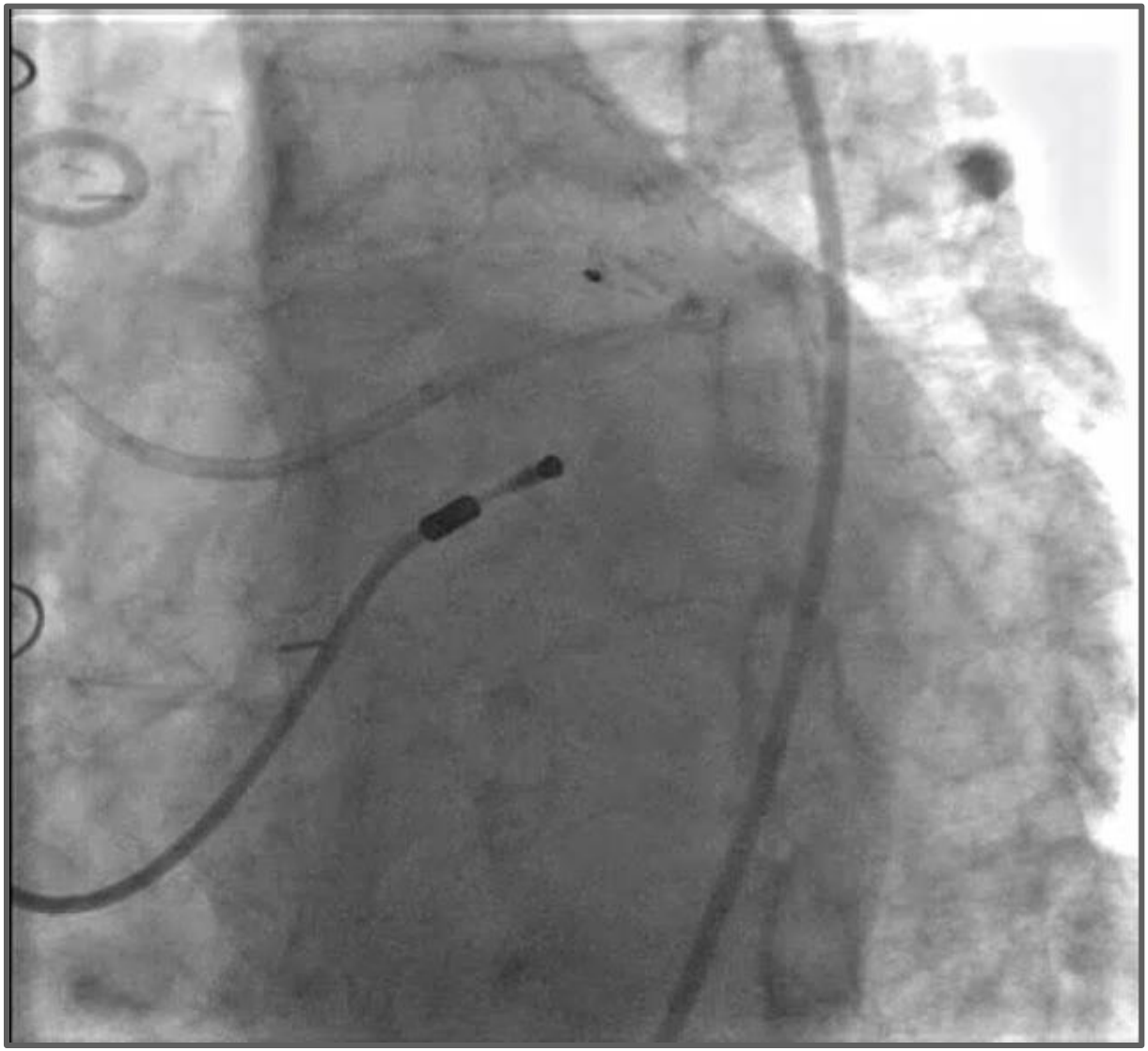

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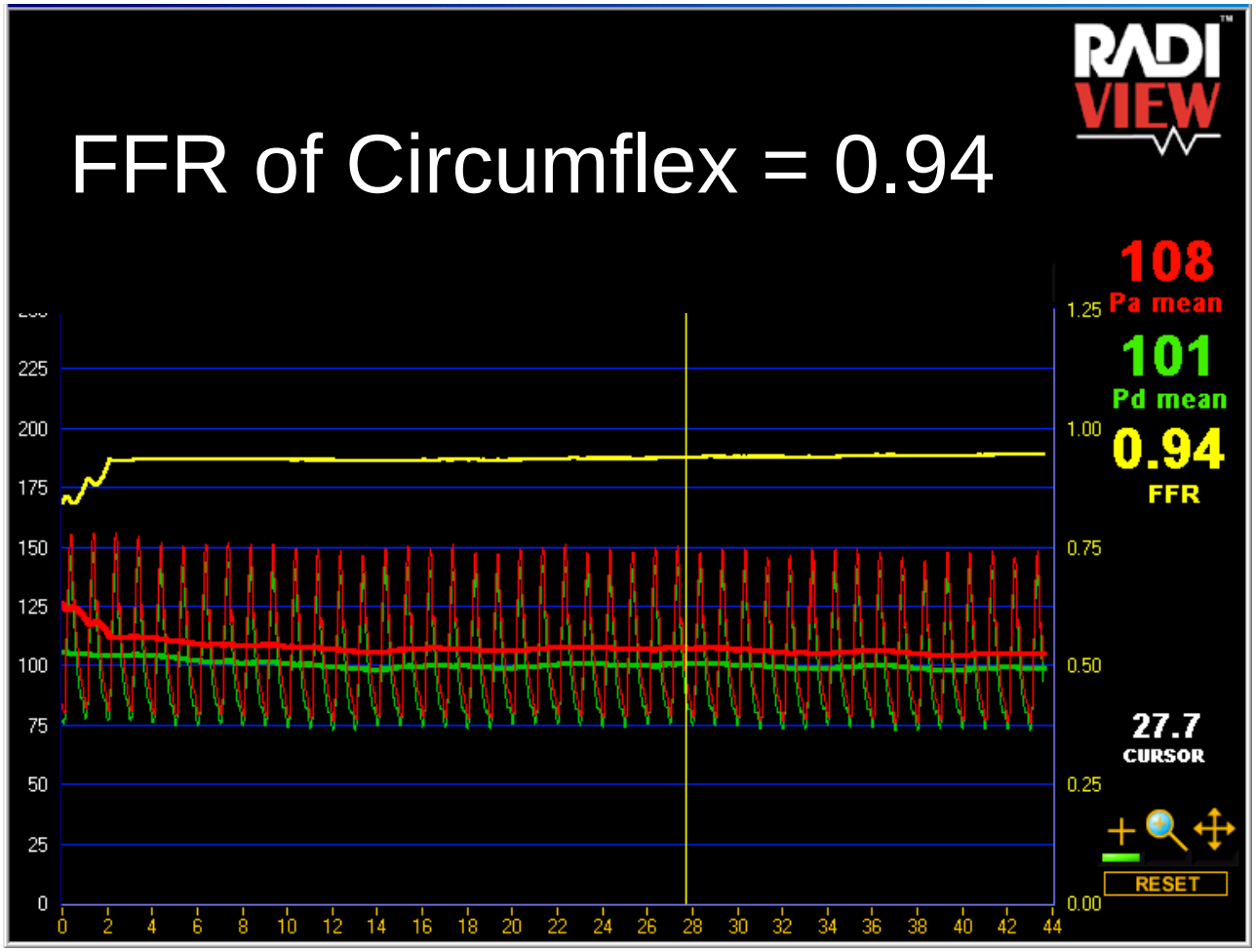

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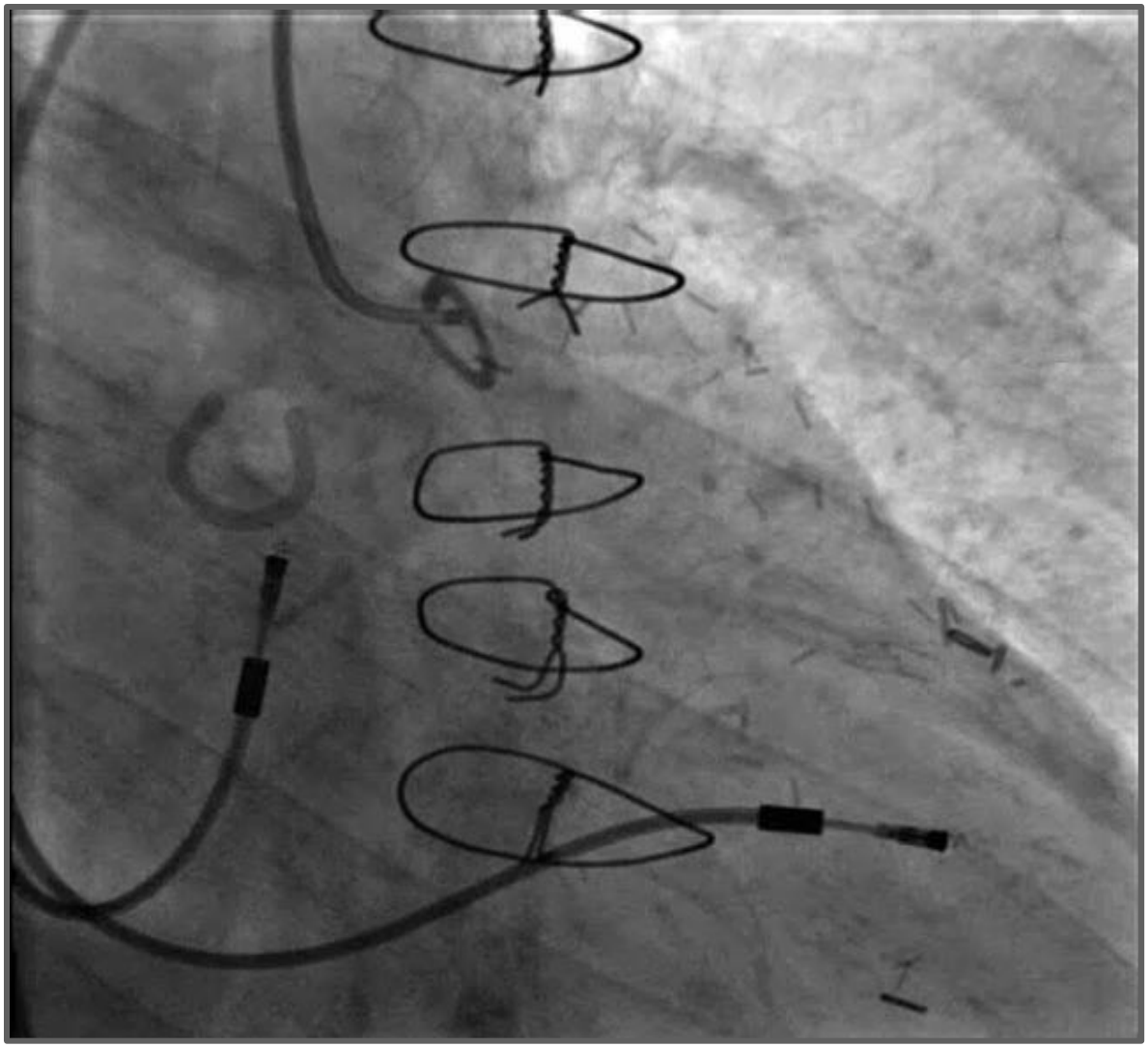

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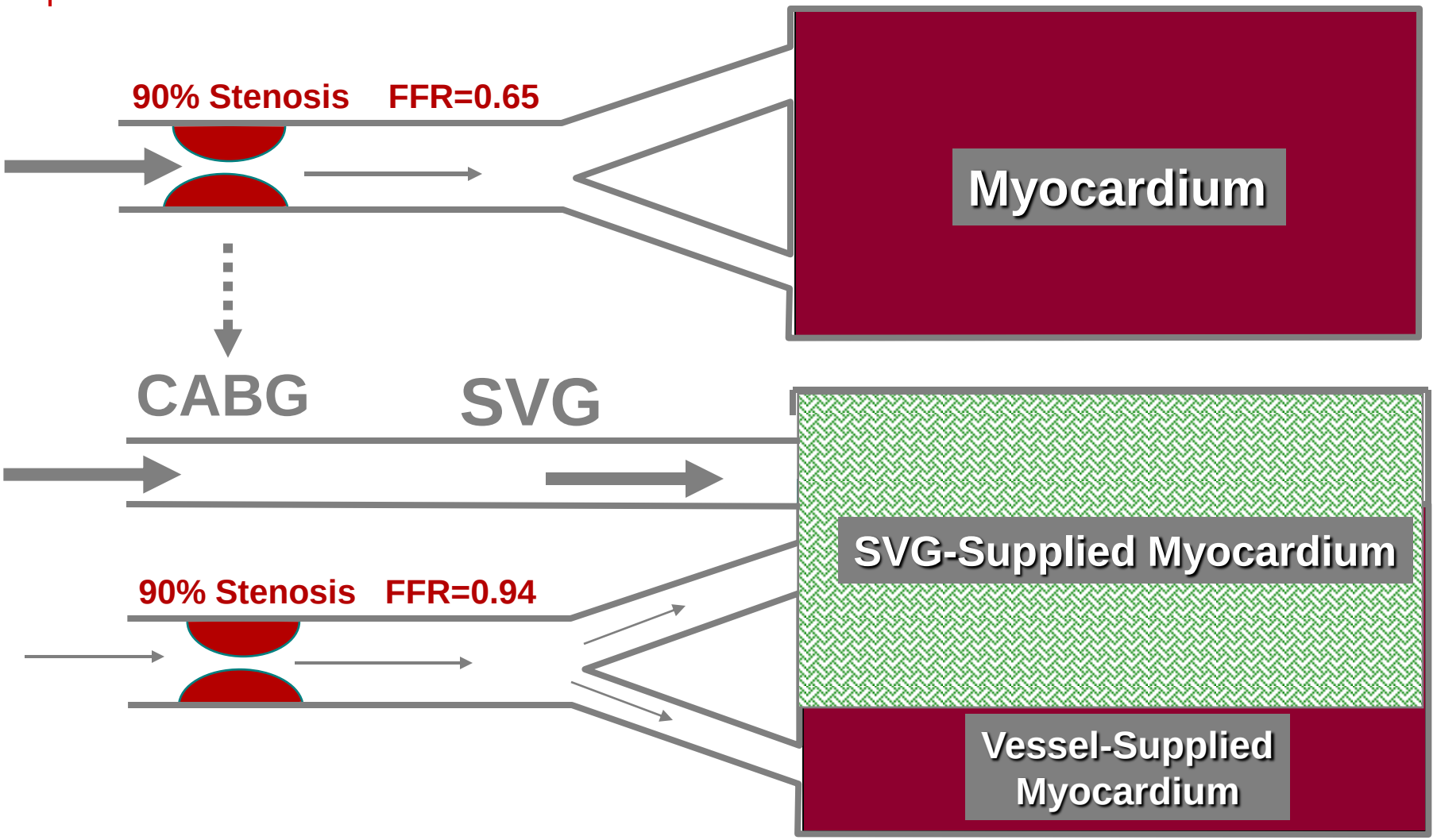

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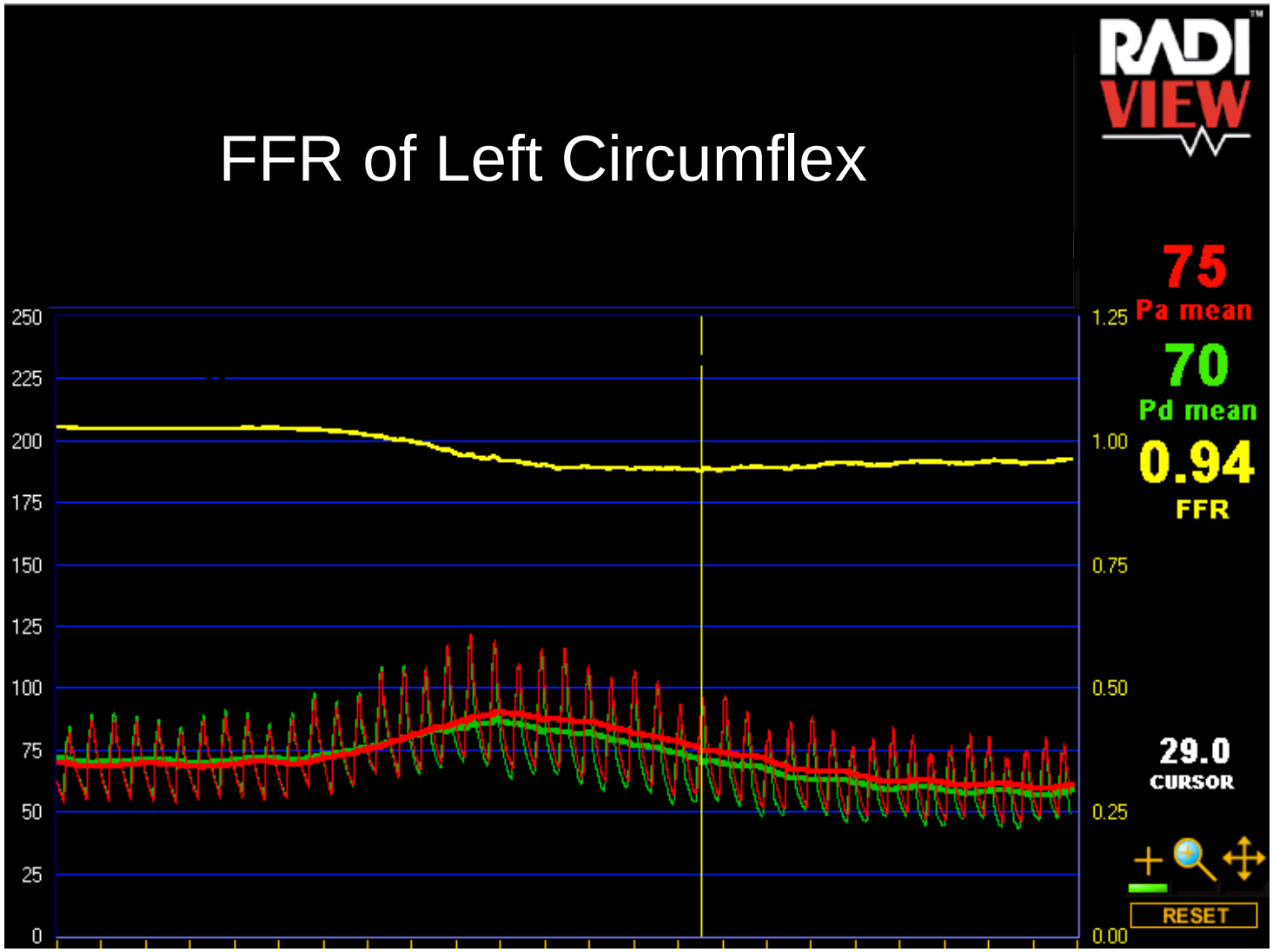

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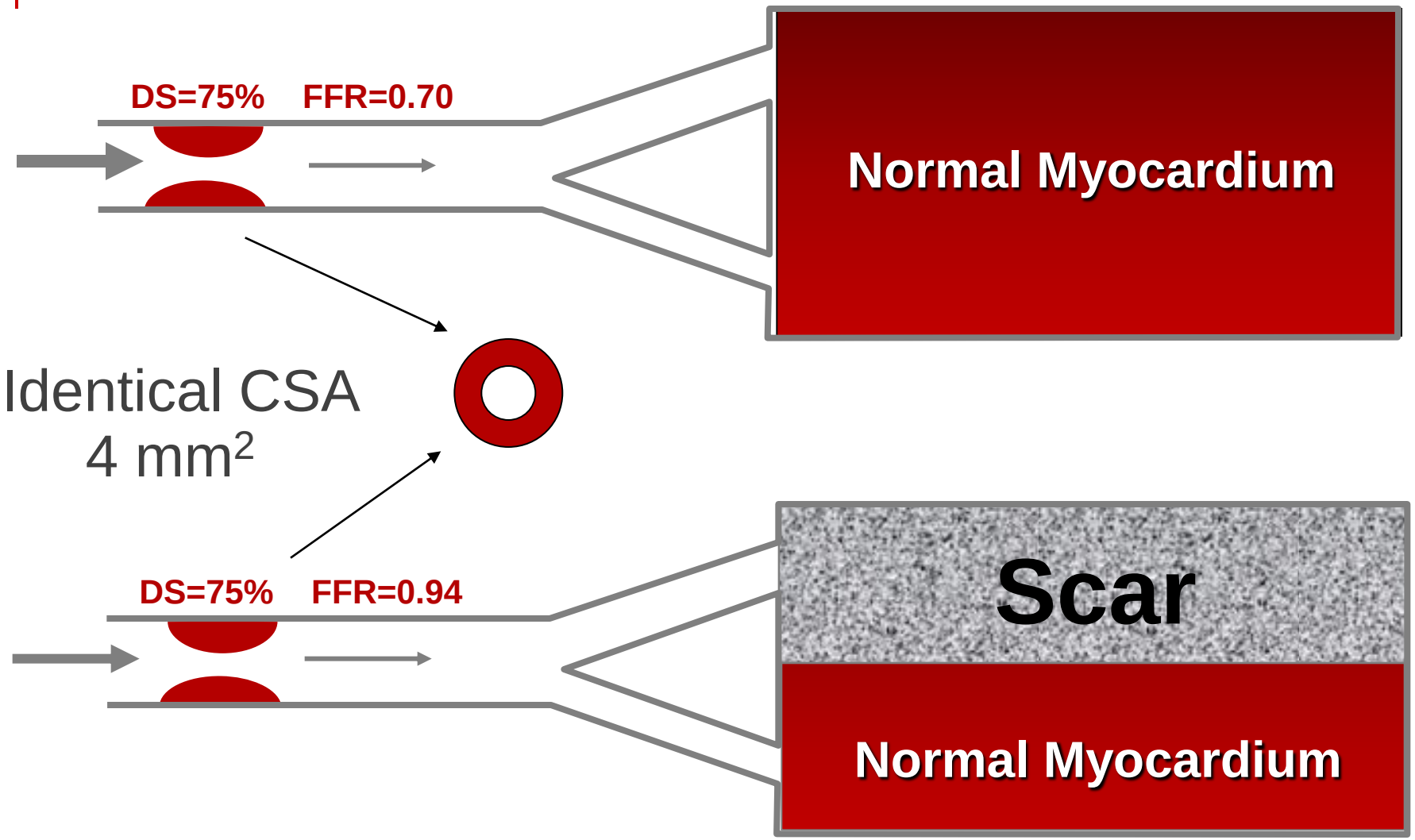
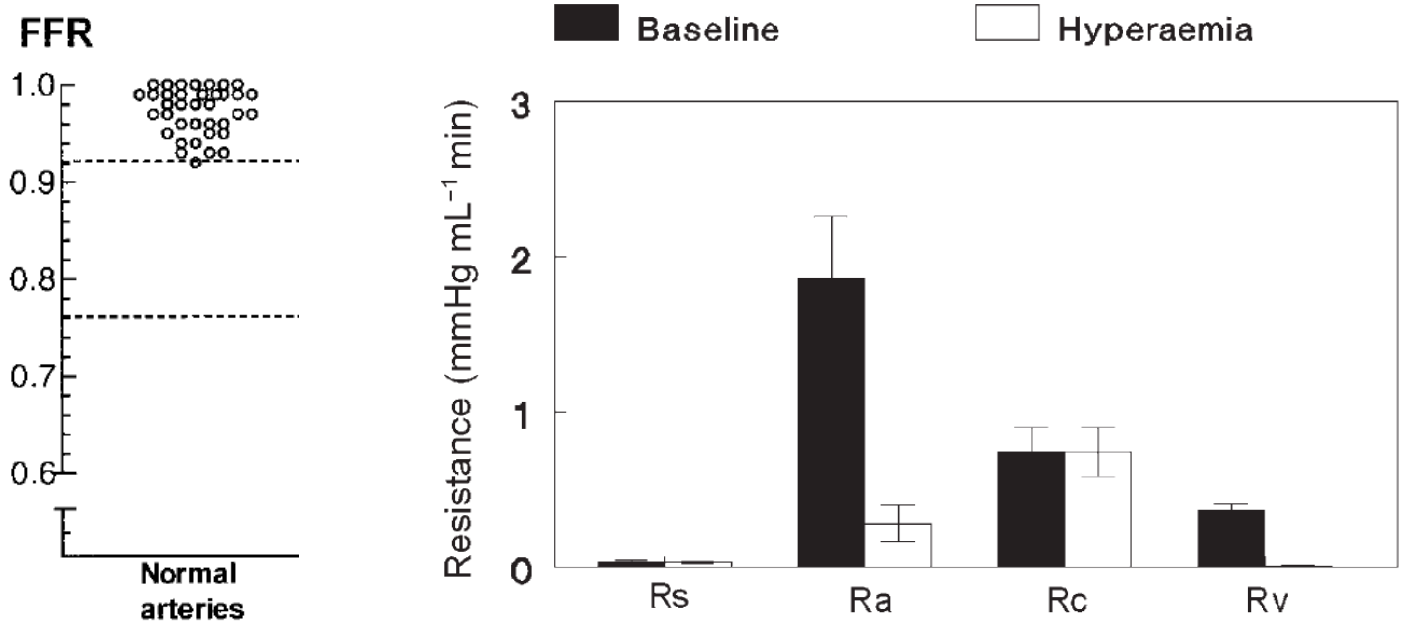


Outline:

- Coronary Anatomy
- Myocardial Mass and Coronary Flow
- Coronary Resistance
- Pathophysiology of Atherosclerosis

Coronary Artery Resistance:

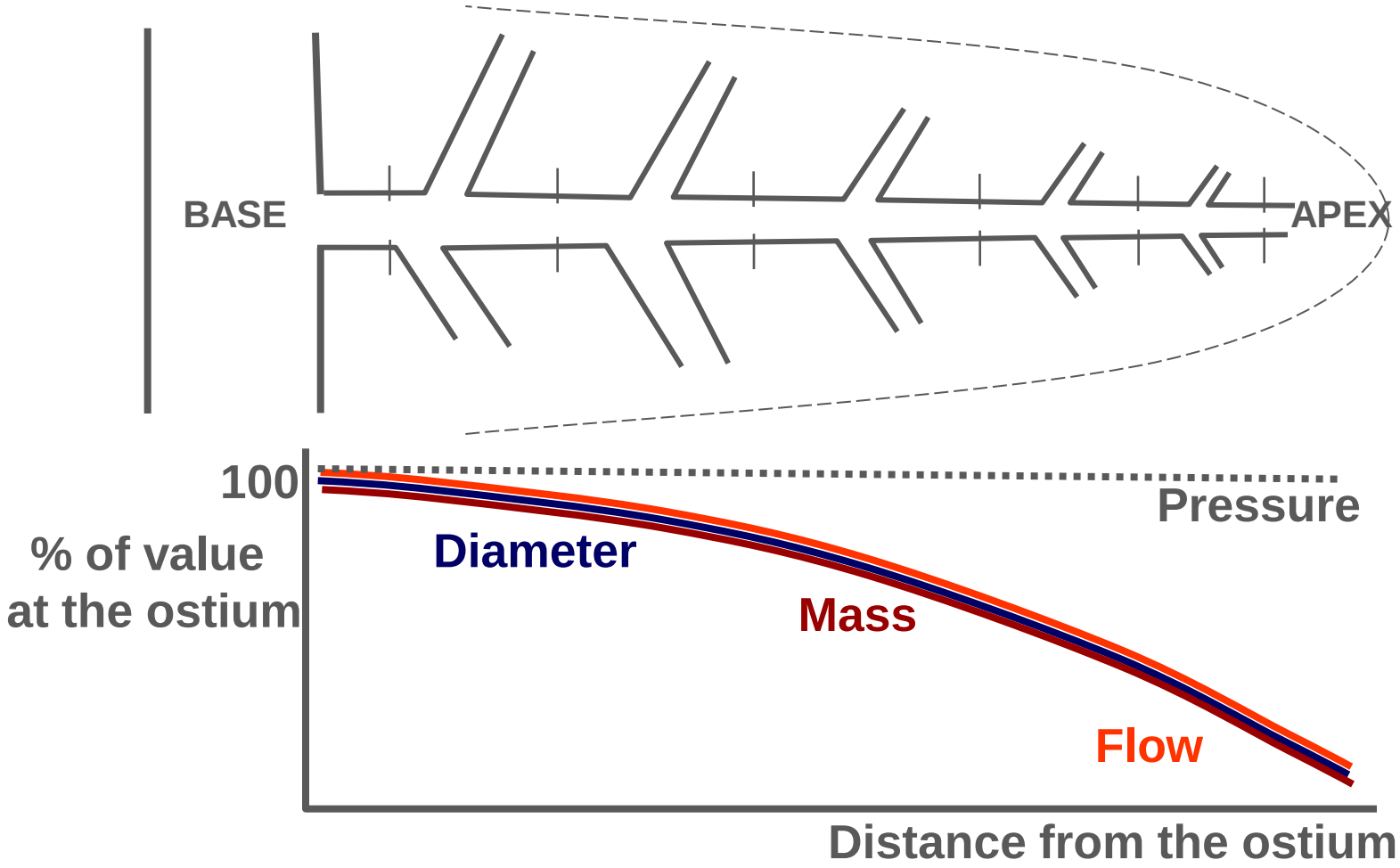
- There is little if any resistance in the normal epicardial artery; most of the resistance occurs in the microvasculature, at the level of the arteriole (100-300 um)



De Bruyne, et al. Circulation 2001;104:401 Kaul, et al. Eur Heart J 2006;27:2272-74.

Epicardial Coronary Pressure:

Pressure, Flow, Resistance and Vessel Size

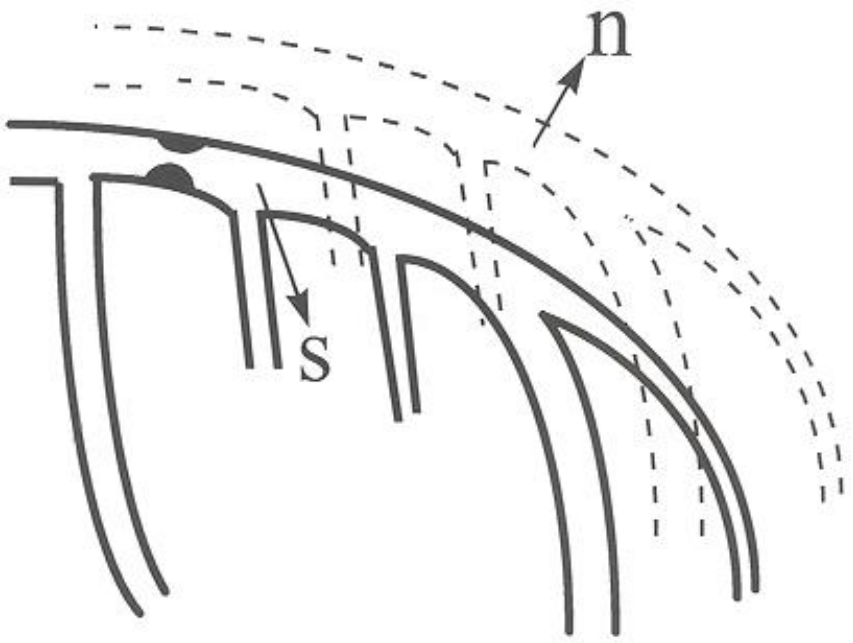


Courtesy of Bernard De Bruyne

Fractional Flow Reserve (FFR)

Maximum flow down a vessel in the presence of a stenosis…

…compared to the maximum flow in the hypothetical absence of the stenosis



Pijls and De Bruyne, Coronary Pressure
Kluwer Academic Publishers, 2000

Derivation of FFR

- $\text{FFR} = \dfrac{\text{Coronary Flow (Stenosis)}}{\text{Coronary Flow (Normal)}}$
- $\text{Coronary Flow} = \dfrac{\text{Pressure}}{\cancel{\text{Resistance}}}$
- ***at maximal hyperemia*** $\text{Coronary Flow} \approx \text{Pressure}$

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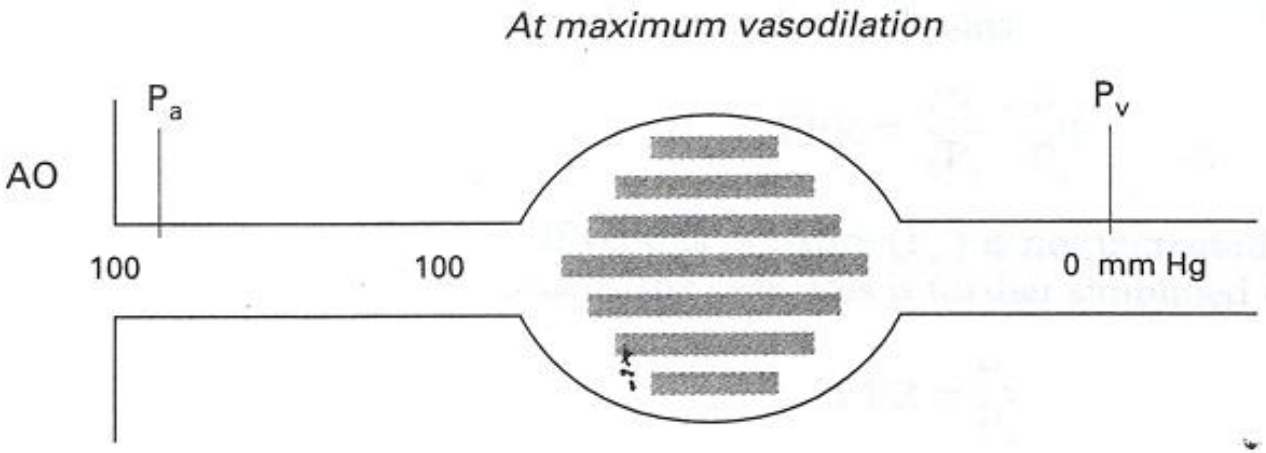

Adapted from: Pijls and De Bruyne, Coronary Pressure
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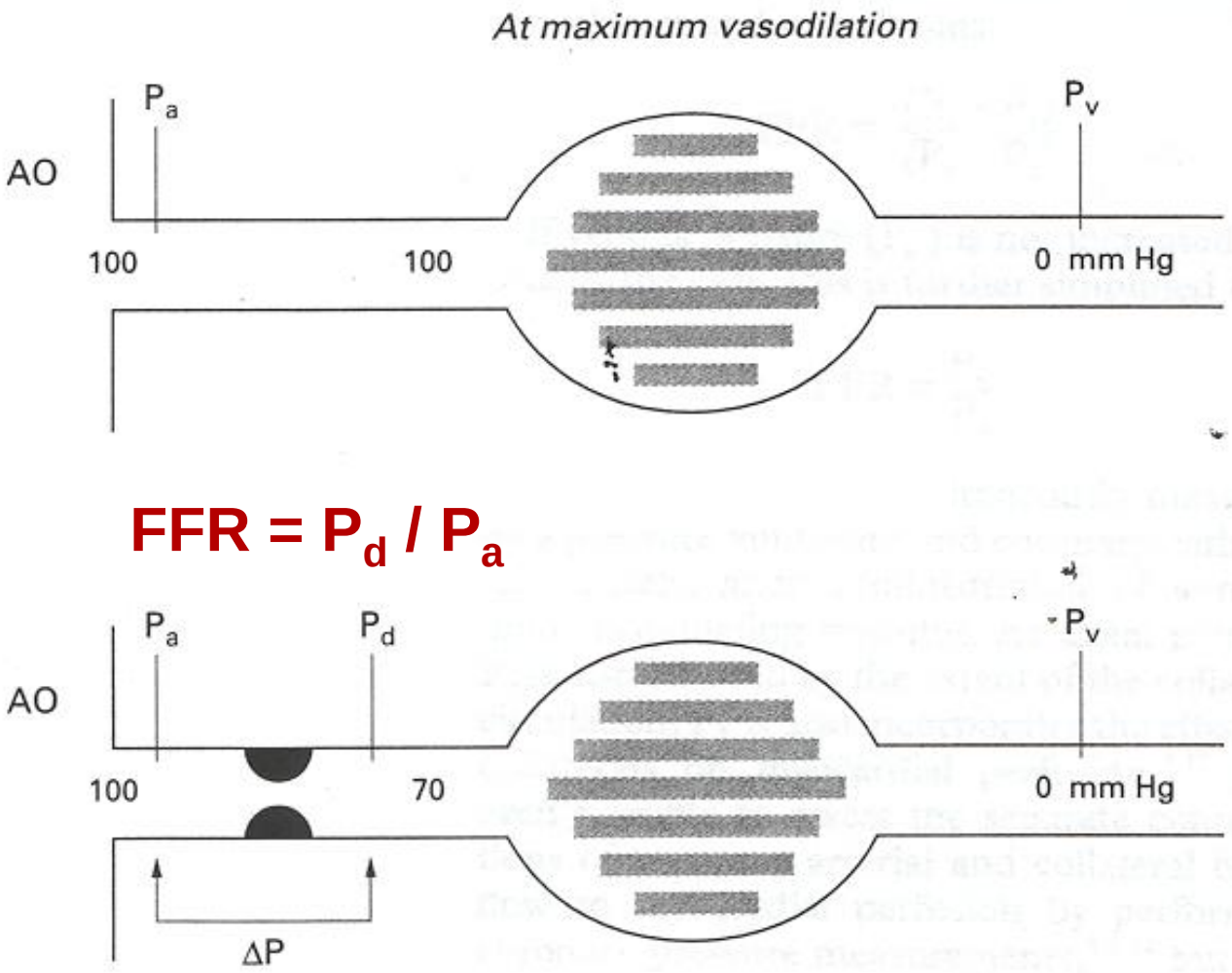

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Kluwer Academic Publishers, 2000

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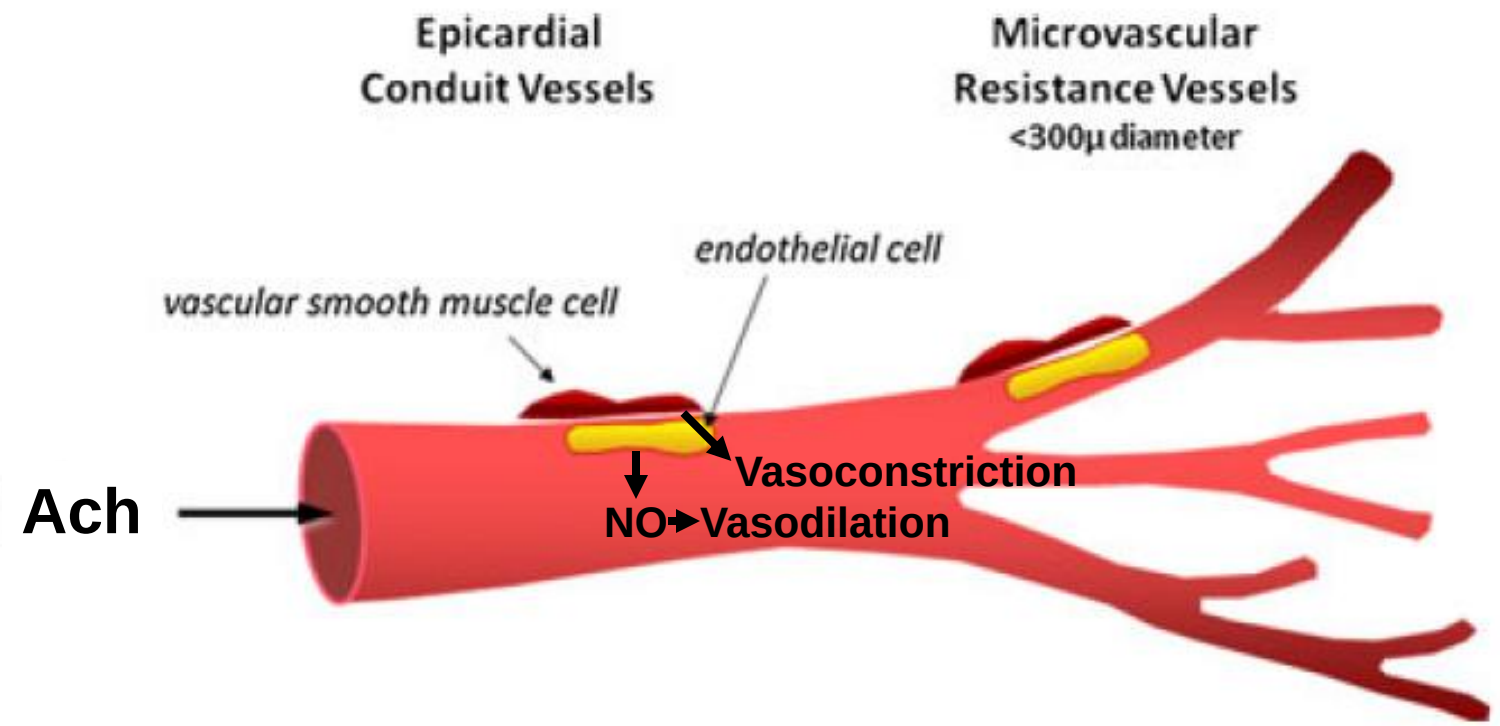
Determinants of Myocardial Flow

- Epicardial Coronary Flow
  - Functional Impairments → **Ach Testing**
    - Endothelial dysfunction (Variant Angina, CAD)
  - Structural Impairments → **FFR**
    - Obstructive coronary stenosis (CAD)
- Microvascular Flow
  - Functional Impairments → **Ach Testing**
    - Endothelial dysfunction (DM, dyslipidemia)
  - Structural Impairments → **IMR**
    - Atherosclerosis, fibrosis, decreased vessel density (MI)

Determinants of Myocardial Flow

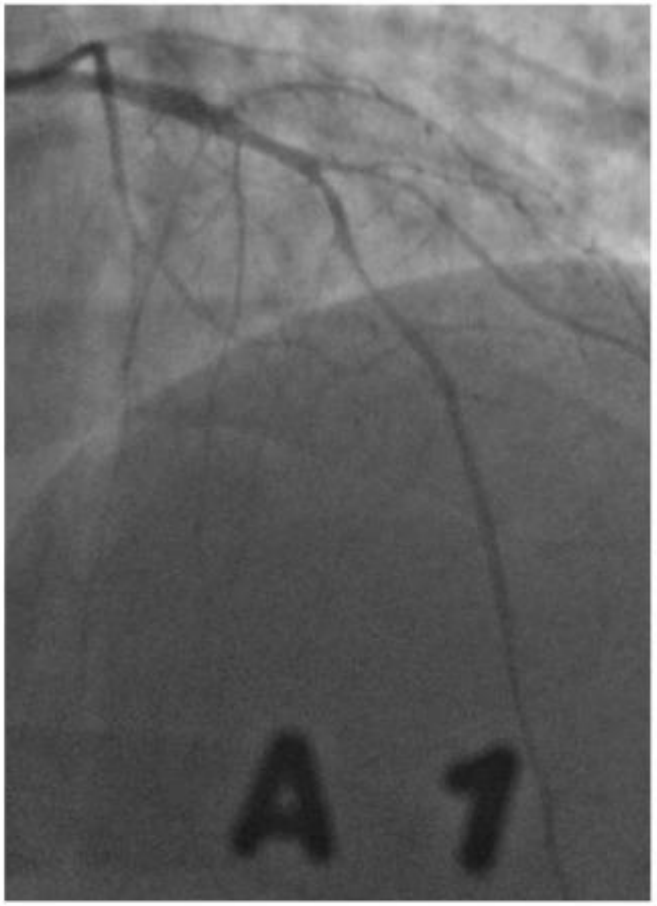
Endothelial (Dys)Function



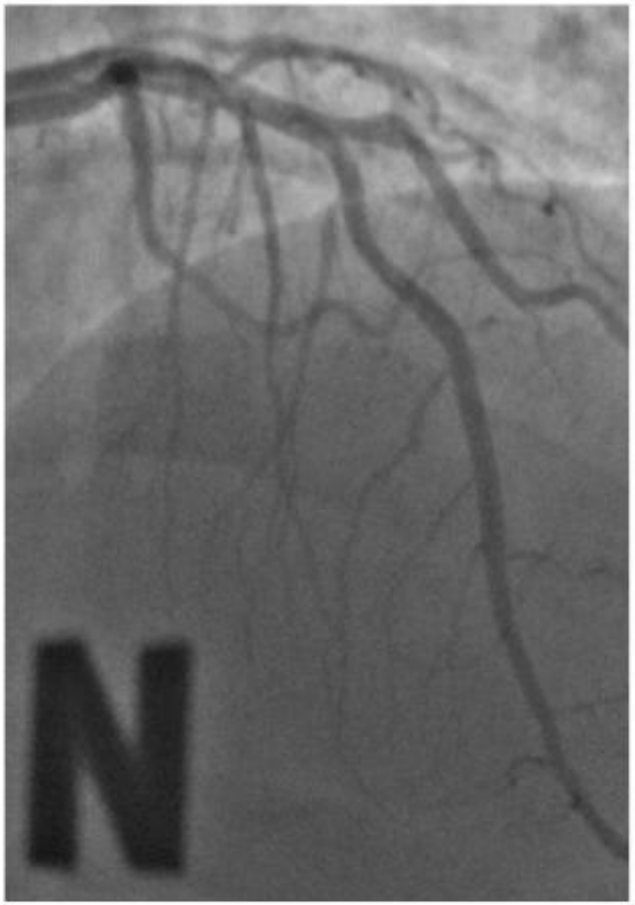
Adapted from J Nuc Cardiol 2010;17:545-54.

Endothelial Dysfunction:

After Acetylcholine



After Nitroglycerin



Mild Lesions Cause Most MIs

Smoking Gun Theory

Angiographically Normal or Mild Coronary Plaque as a Cause of Myocardial Infarction

Jason C. Kovacic, MD, PhD; Valentin Fuster, MD, PhD

of this disease. Thanks to a series of pivotal observations, we now appreciate that MI rarely arises because of progressive vessel narrowing that culminates in a critical flow-limiting stenosis. Rather, it is now understood that an atherosclerotic

MI, when in 1988 we showed with Ambrose et al[3] that MI frequently develops from previously nonsevere lesions. In a

Circulation 2012;126:2918-20.

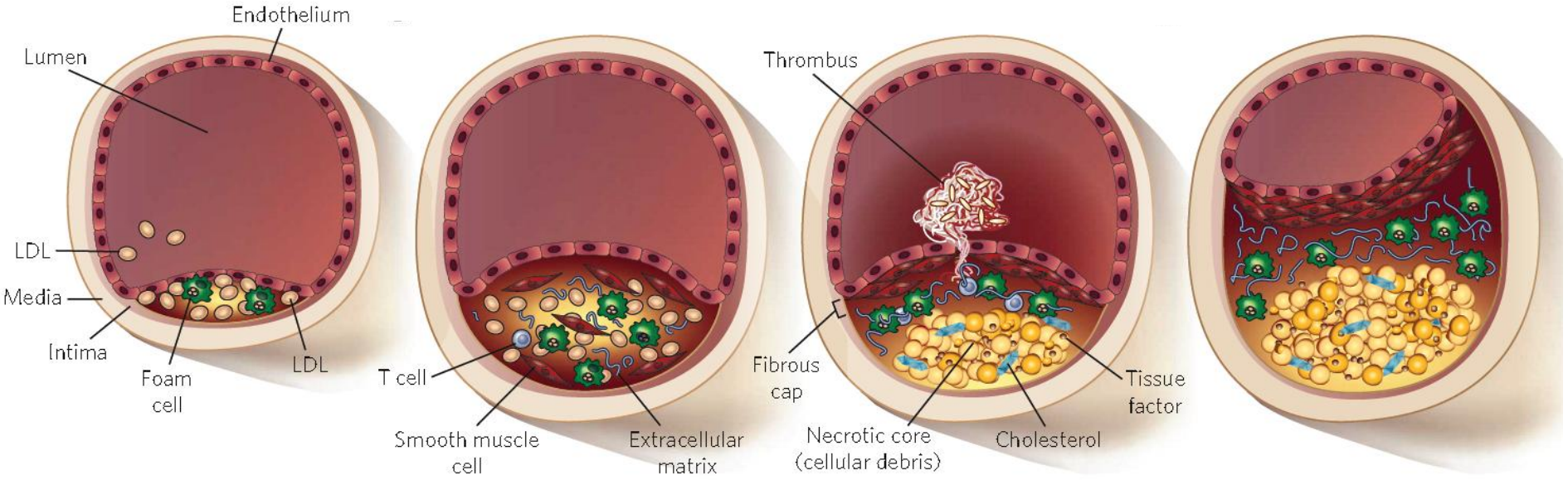
Do Mild Stenoses Cause Most MIs?

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

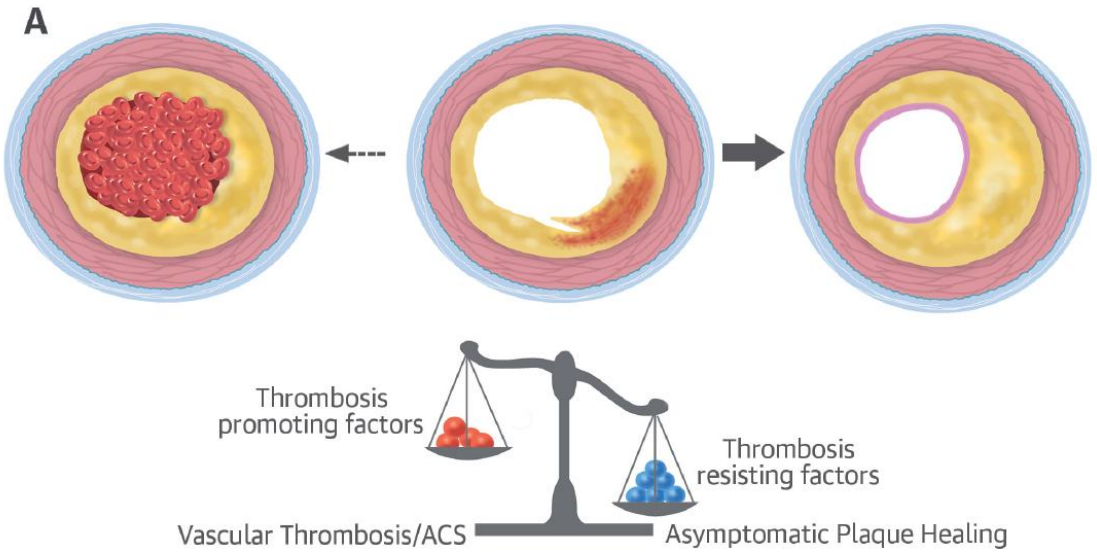
	Number of Patients	Delay Angio -MI
Ambrose et al *JACC* 1988	23	1 month to 7 years
Little et al. *Circulation* 1988	42	4 days to 6.3 years
Giroud et al. *AJC* 1992	92	1 month to 11 years
Moise et al. AJC 1984	116	39 months
Webster et al JACC 1990 abstr	30	55 months
Hackett et al AJC 1989	10	21 months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

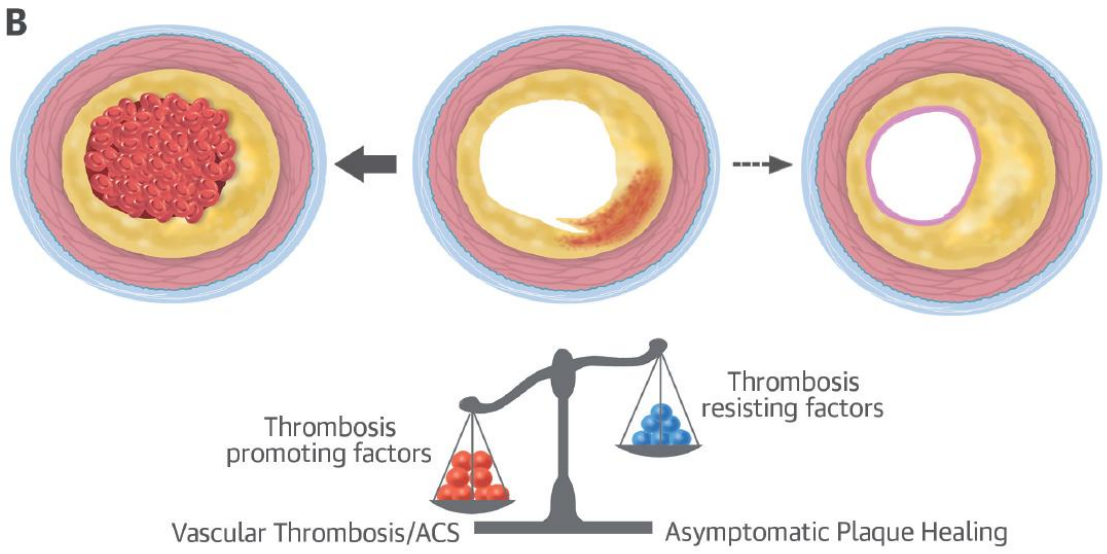
Progression of Atherosclerosis

Repetitive episodes of plaque rupture/erosion and healing lead to an increasingly severe stenosis and a greater chance for AMI.



Rader D, Daugherty A. Nature 2008;451:904-13.

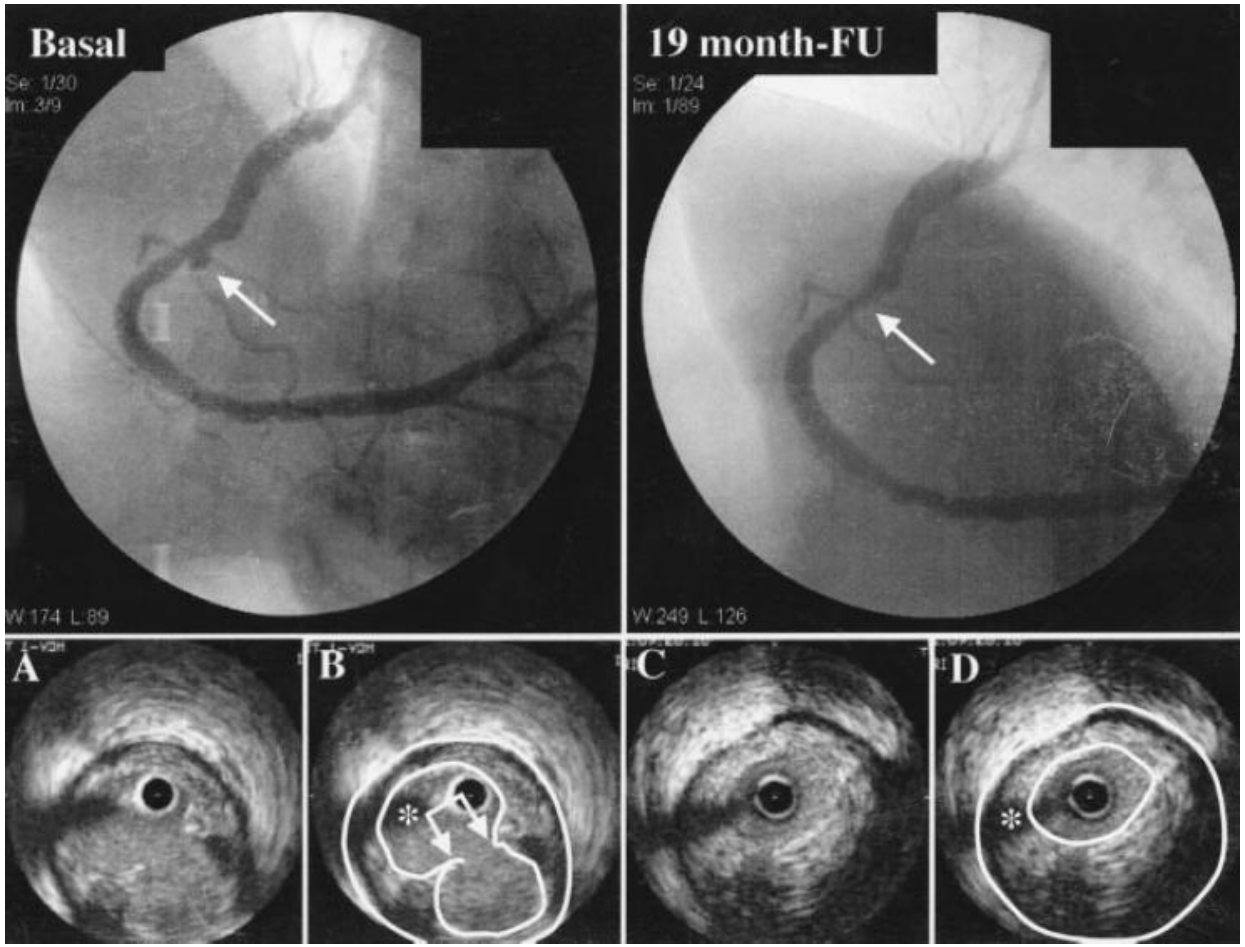




J Am Coll Cardiol 2015;65:846-55.

Healing of Non-Culprit Ruptured Plaques

28 non-culprit ruptured plaques without significant stenosis were identified by IVUS at time of ACS and treated medically without events out to 2 years



Rioufol, et al. Circulation 2004;110:2875-2880.

Do Mild Stenoses Cause Most MIs?

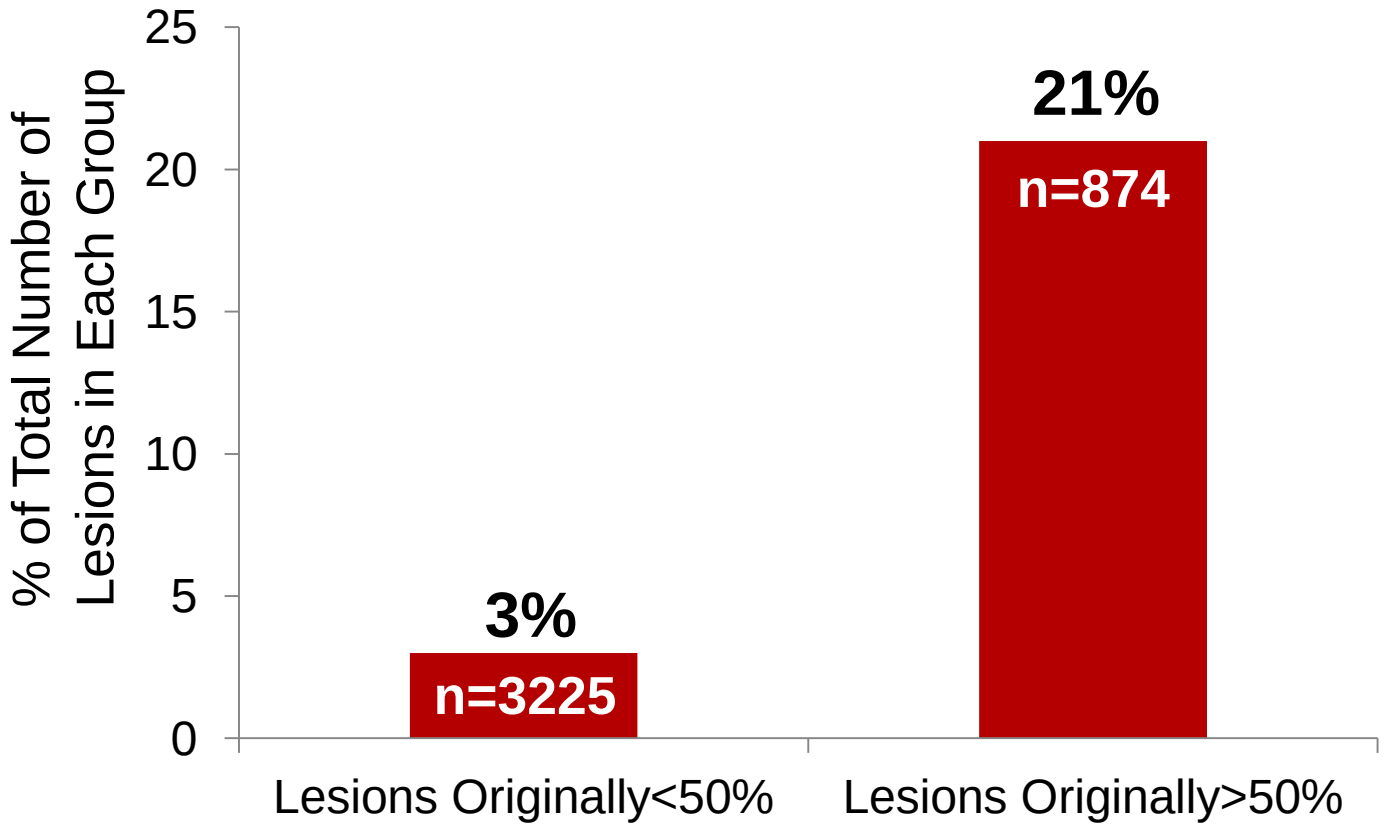
In 164 patients who died of AMI had 184 vessels with plaque rupture. The mean diameter stenosis by pre-existing atherosclerotic plaque was 91%.

Coronary Artery	No. (%)	% Stenosis by Atheroma
LAD	79 (43)	90.5 ±5.8
LCx	38 (21)	90.7 ±6.1
RCA	67 (36)	90.4 ±7.5

Qiao, et al. J Am Coll Cardiol 1991;17:1138-42.

Lesion Severity and ACS

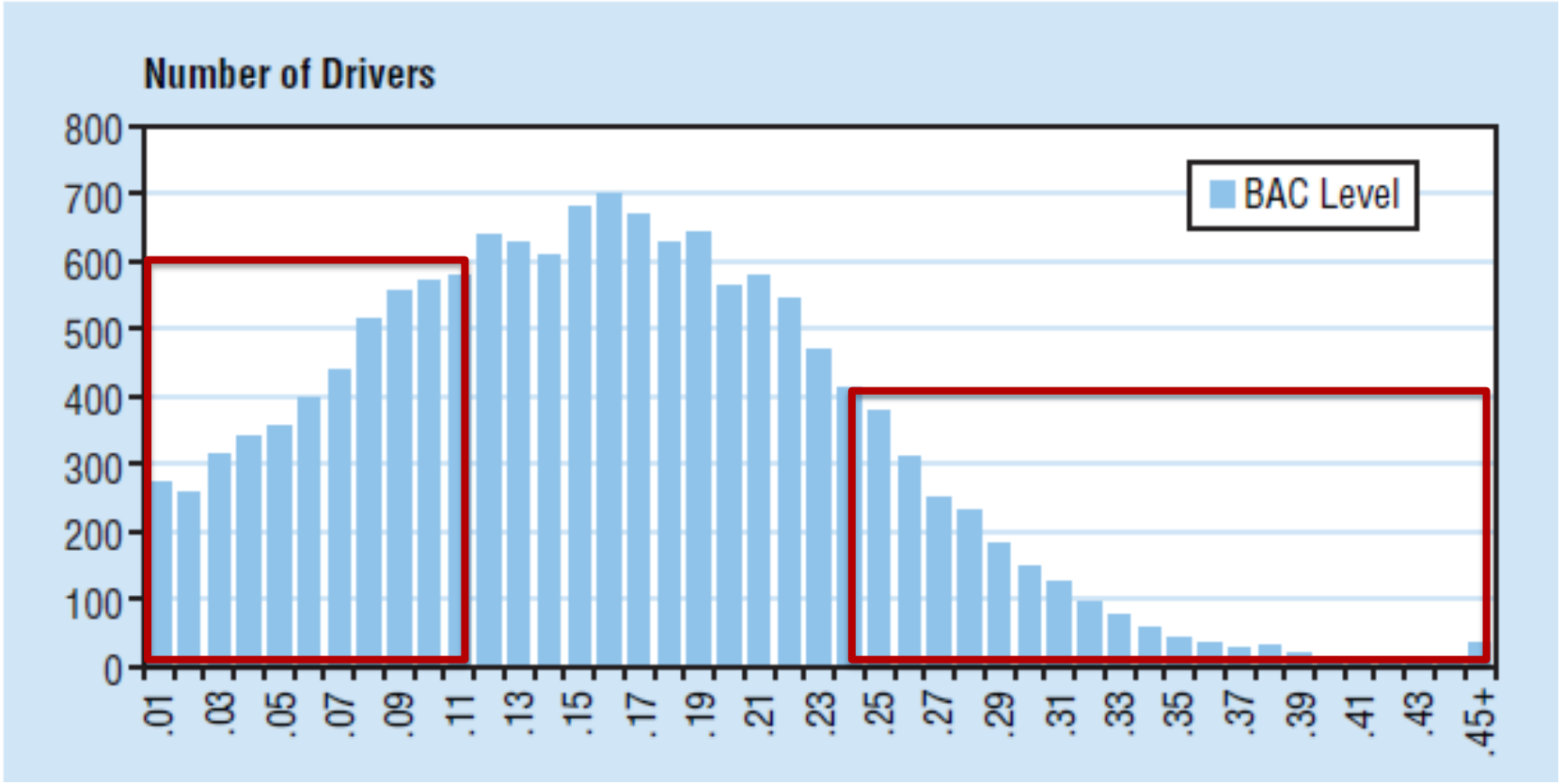
Likelihood of lesion subsequently causing ACS in the COURAGE Trial



Mancini, et al. Circ Cardiovasc Interv 2011;4:545-52.

Do Mild Stenoses Cause Most MIs?

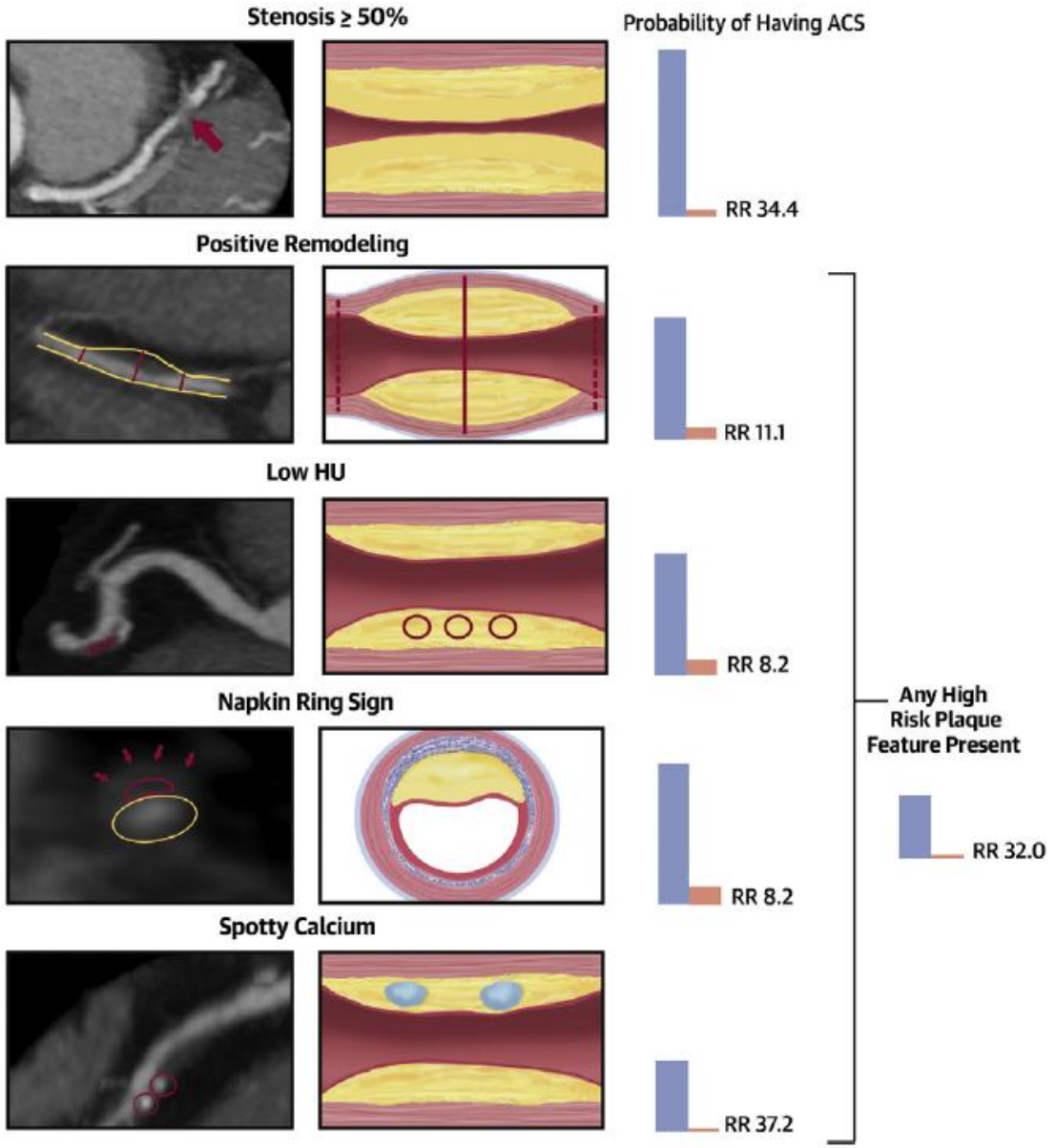
Distribution of blood alcohol content levels in drivers involved in fatal drunk driving accidents



www.nhtsa.gov

Lesion Severity and Vulnerability

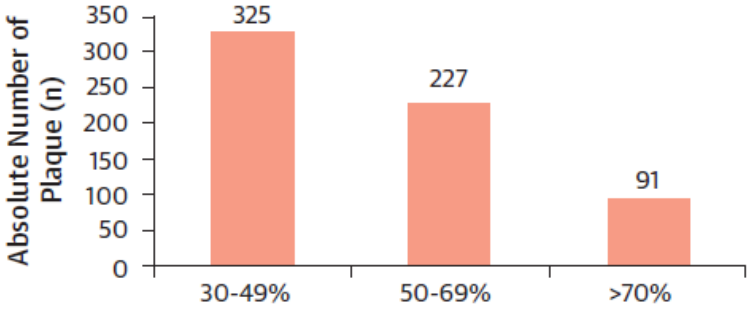
472 patients with chest pain and suspicion of ACS randomized to CTA arm of ROMICAT II trial underwent evaluation of stenosis severity and plaque vulnerability, based on CTA, and this was correlated with diagnosis of ACS.

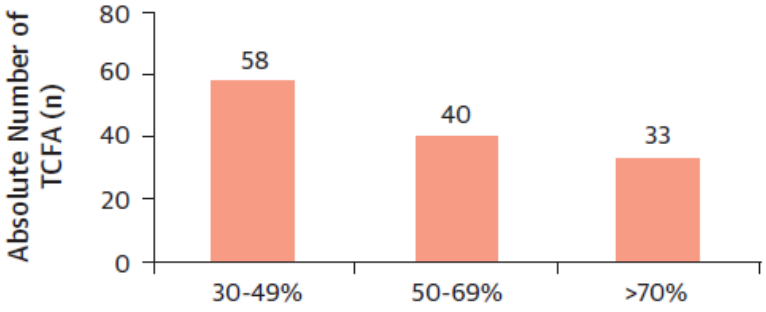


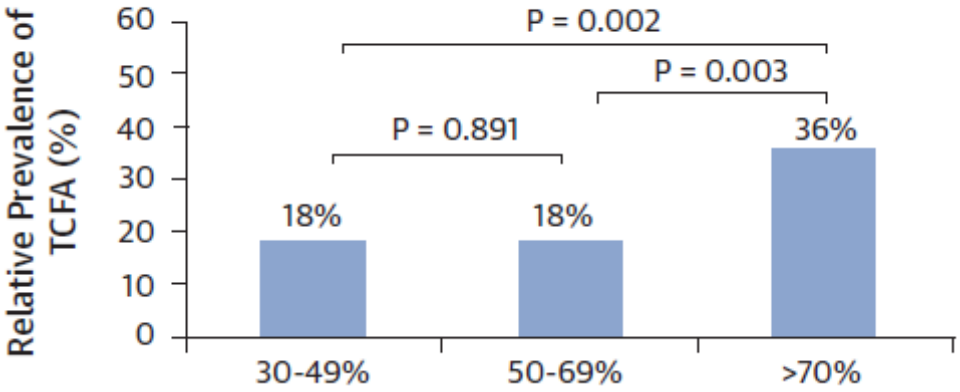
J Am Coll Cardiol 2014;64:684-92.

Lesion Severity and Vulnerability

IVUS and OCT performed in all three arteries in 255 subjects and identified 643 plaques





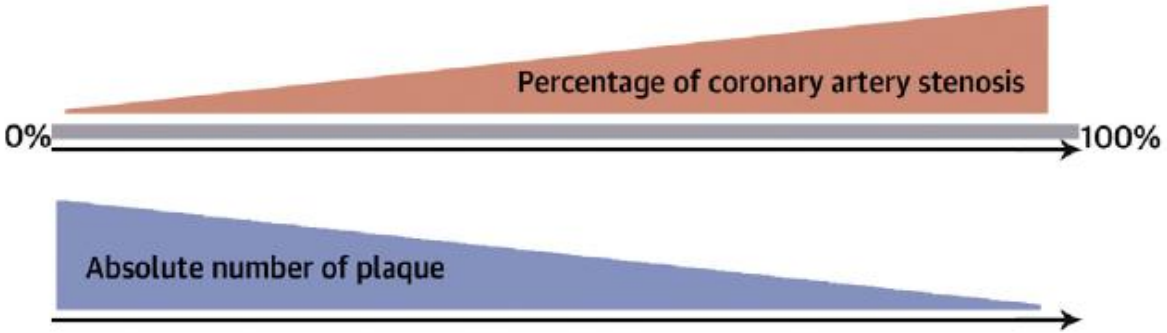


Fibrous cap thickness was thinnest in the most severe lesions, and remodeling index and plaque burden was greatest.

Tian, et al. J Am Coll Cardiol 2014;64:672-80.

Lesion Severity and Plaque Vulnerability

IVUS and OCT performed in all three arteries in 255 subjects and 643 plaques identified



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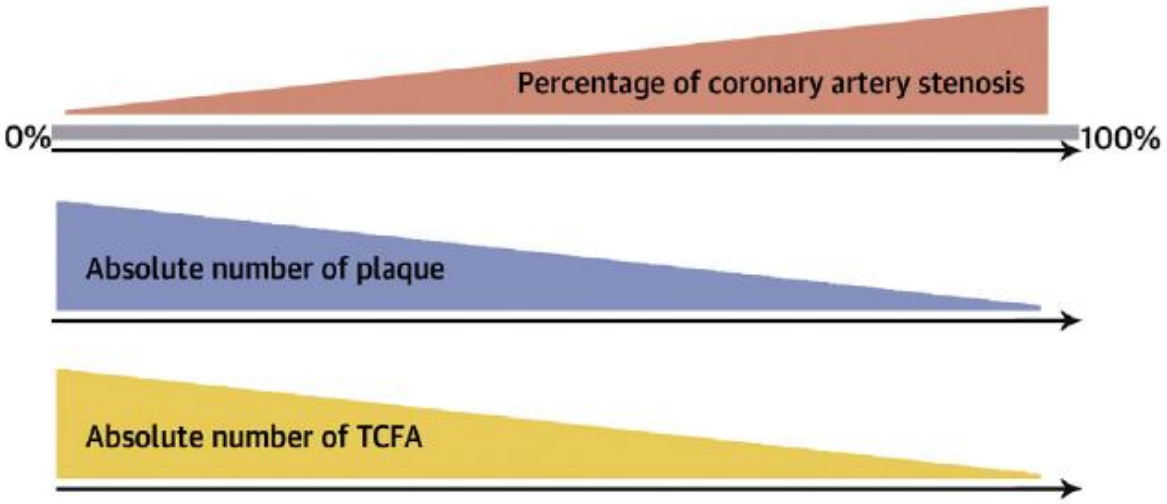

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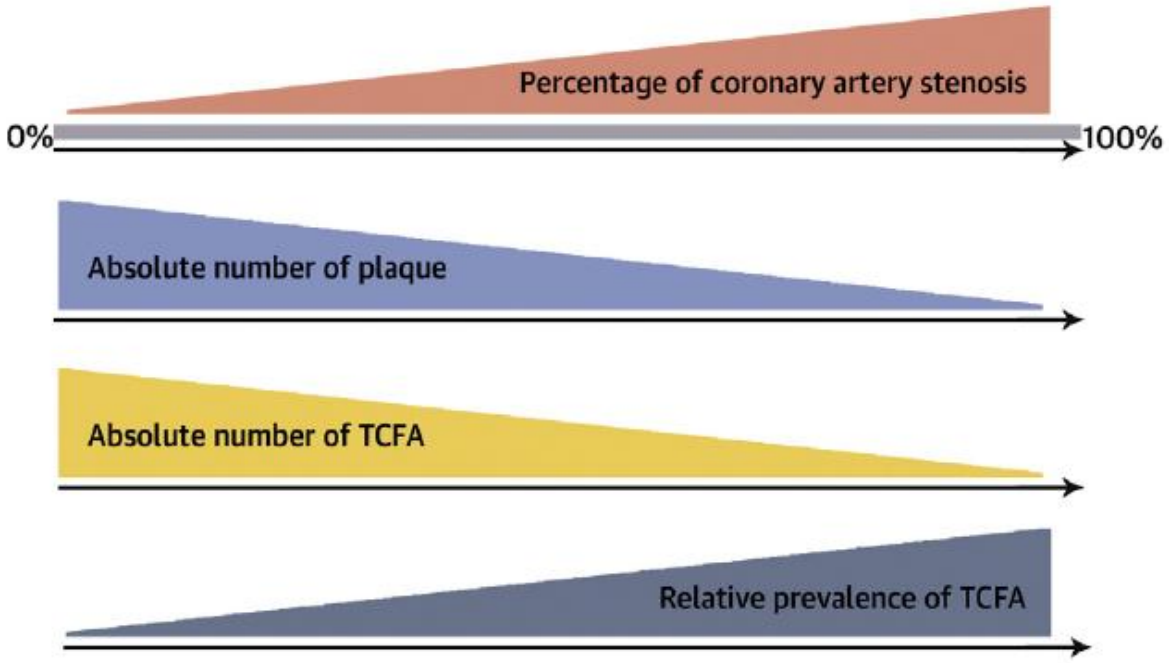

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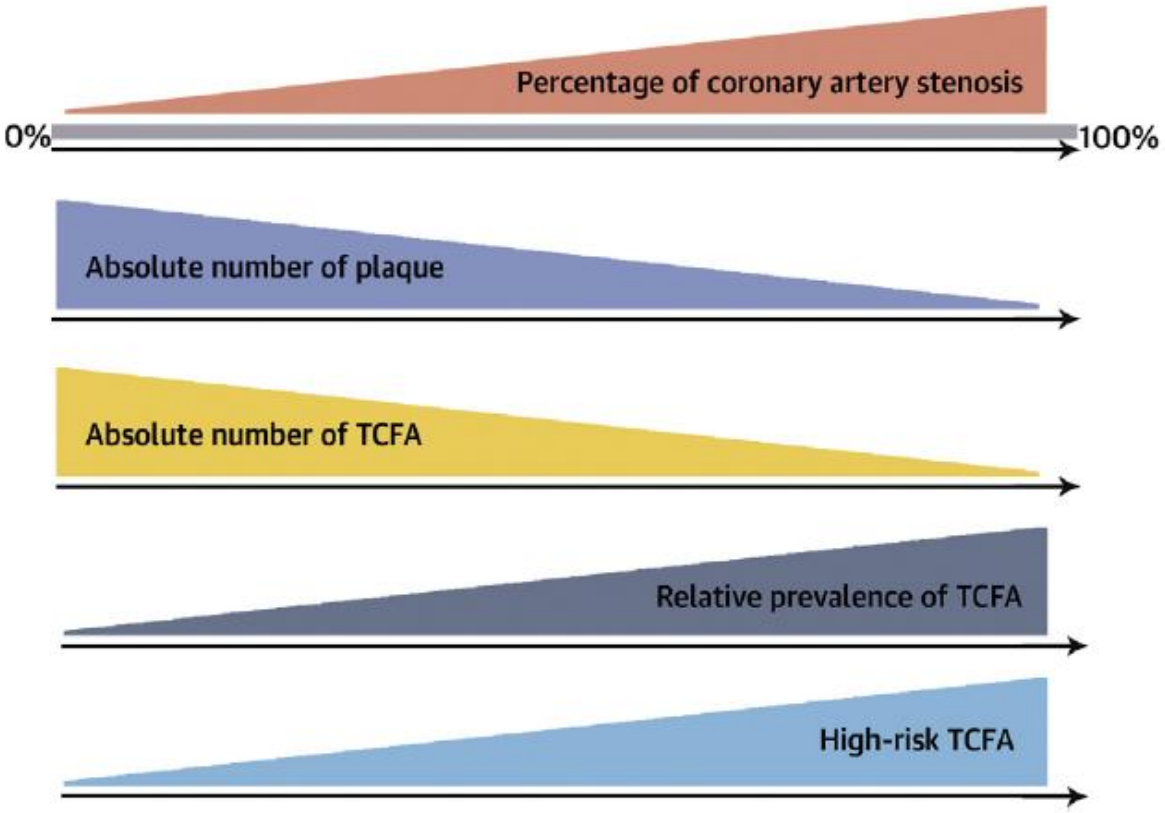
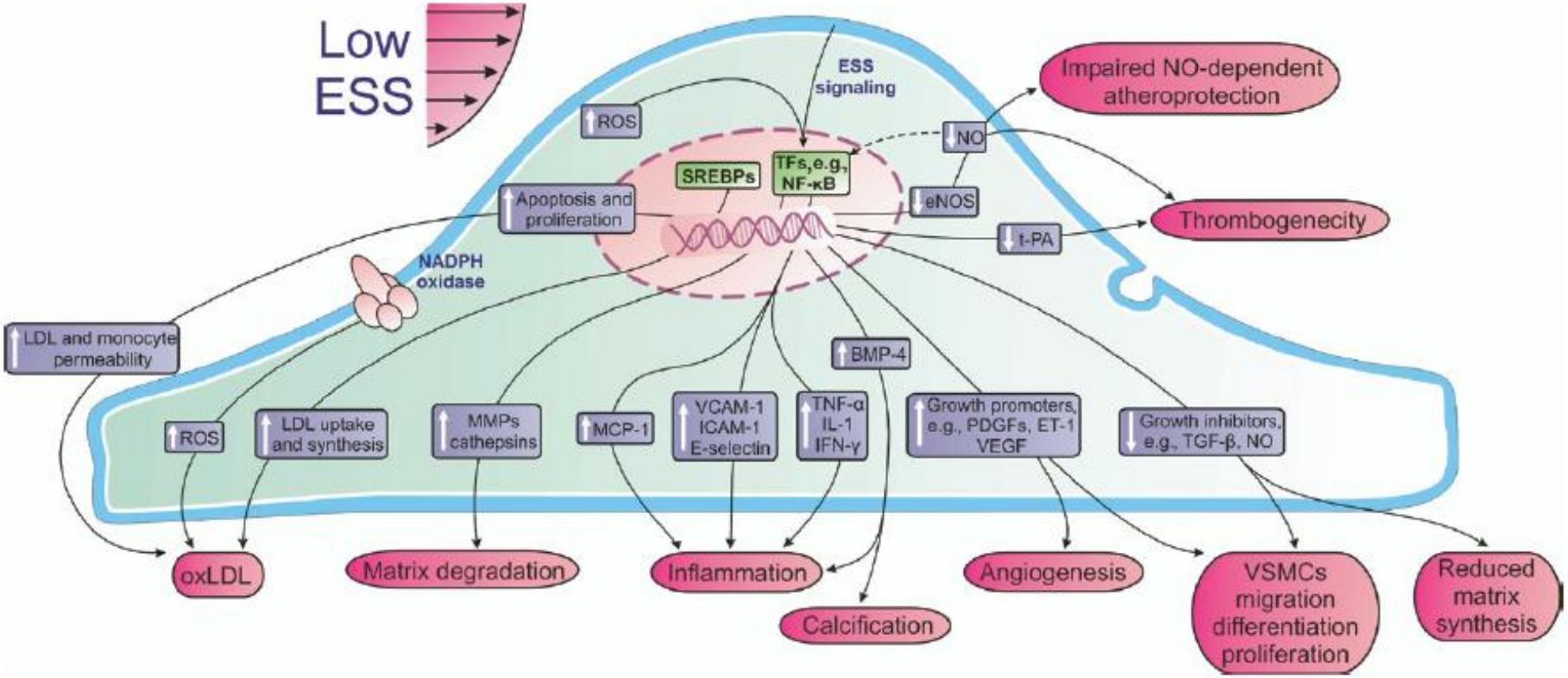


Tian, et al. J Am Coll Cardiol 2014;64:672-80

Why does FFR work?

Does Ischemia Lead to Plaque Vulnerability?

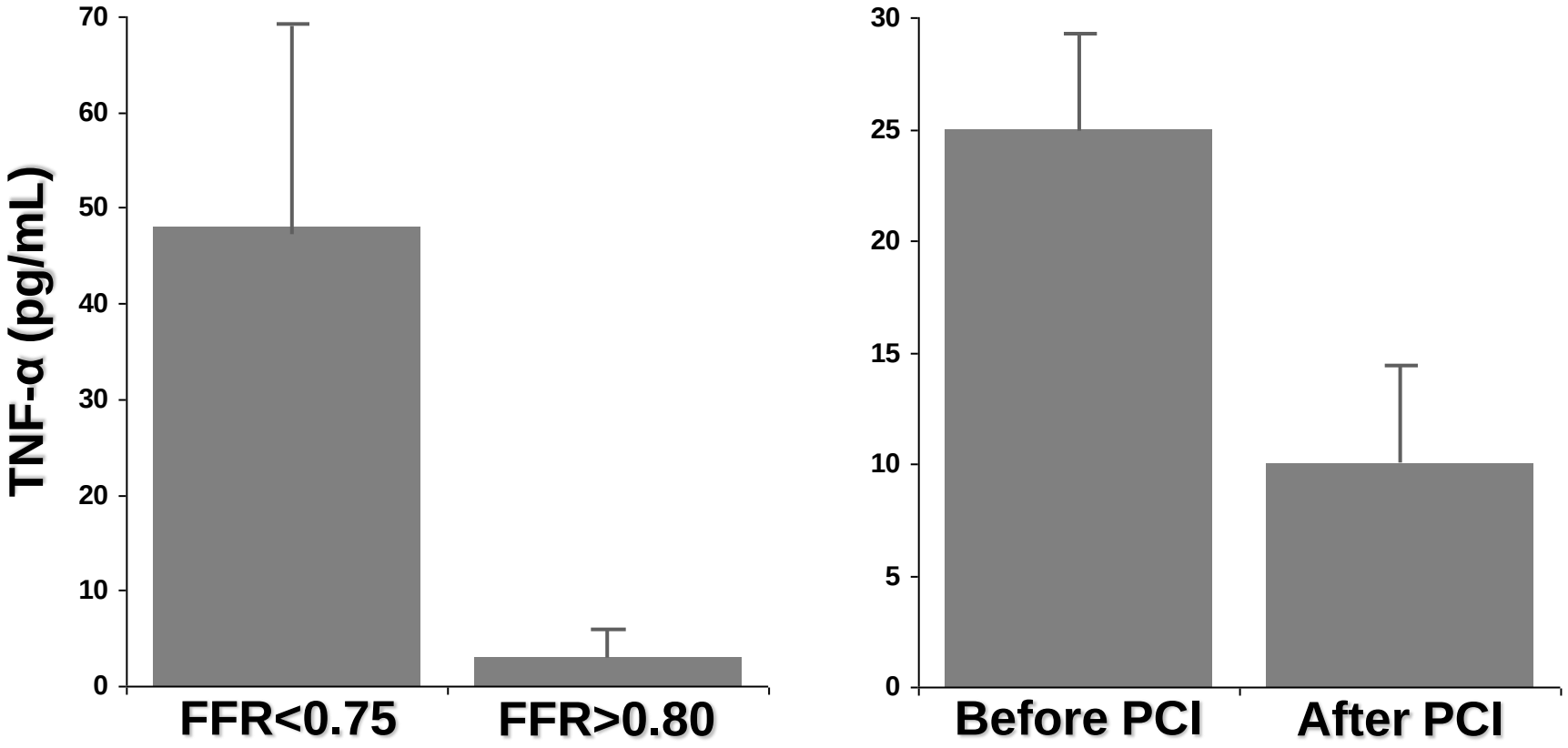
Low shear stress down-regulates vasoprotective factors and up-regulates inflammatory, oxidative stress, and thrombogenic factors



Chatzizisis, et al. J Am Coll Cardiol 2007;49:2379

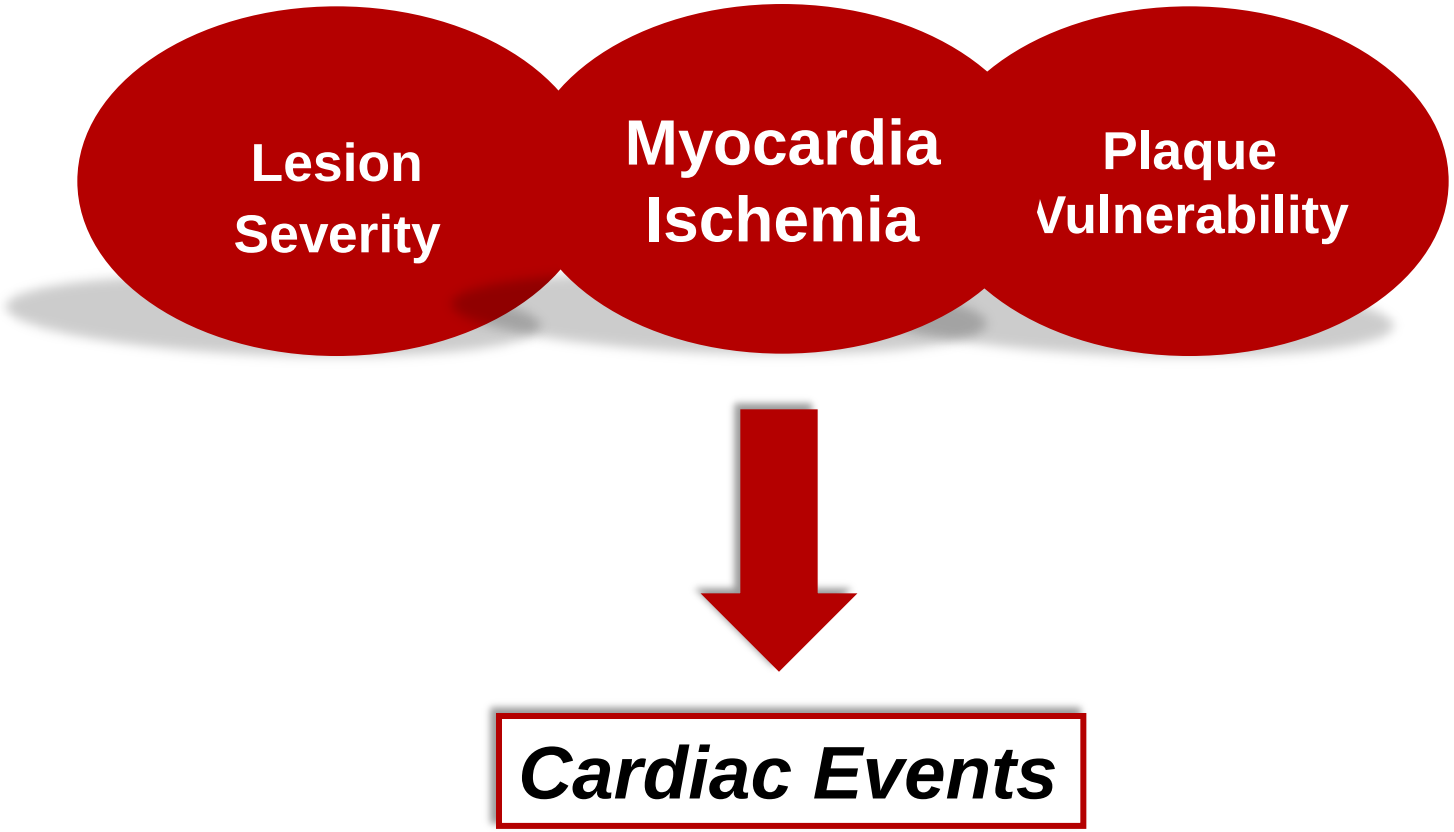
Ischemia and “vulnerability”

Increased production of TNF-α correlates with fractional flow reserve measured in 70 patients referred for PCI

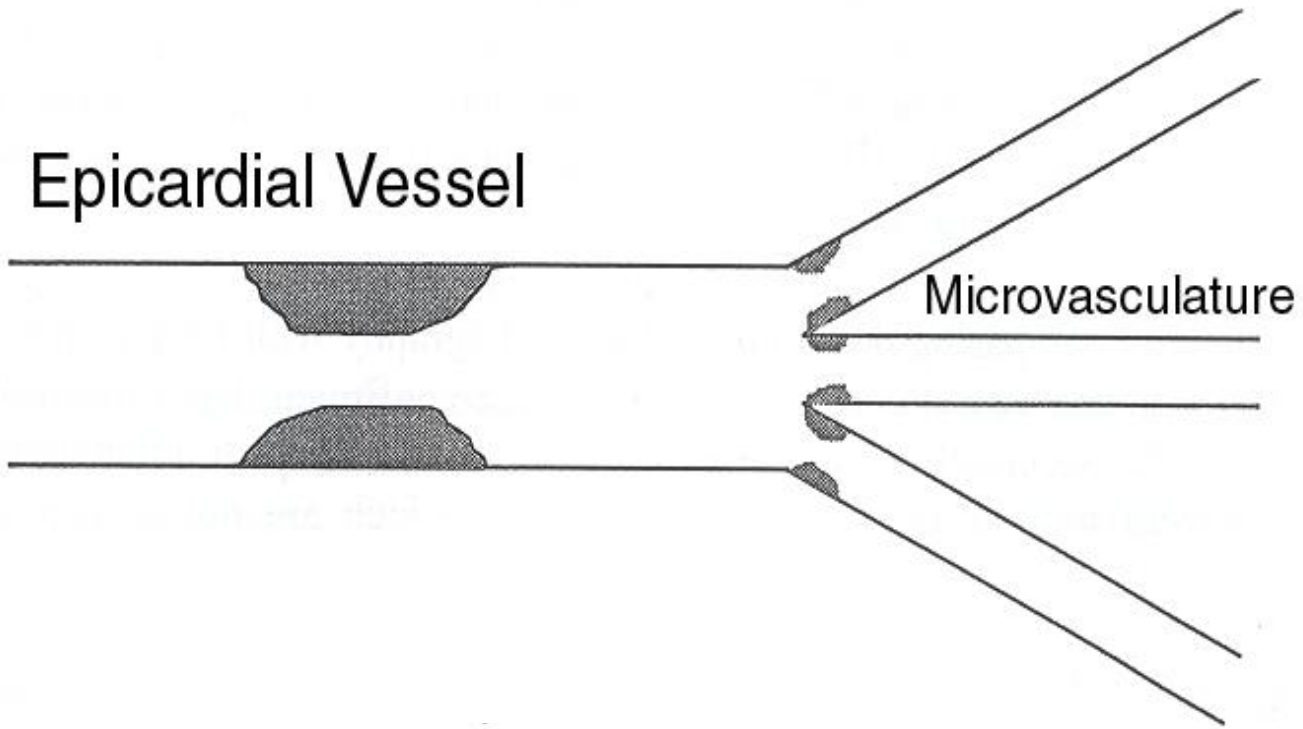


Adapted from Versteeg, et al. Heart 2008;94:770

Joining Anatomy and Morphology



Detecting Myocardial Ischemia in the Cath Lab:



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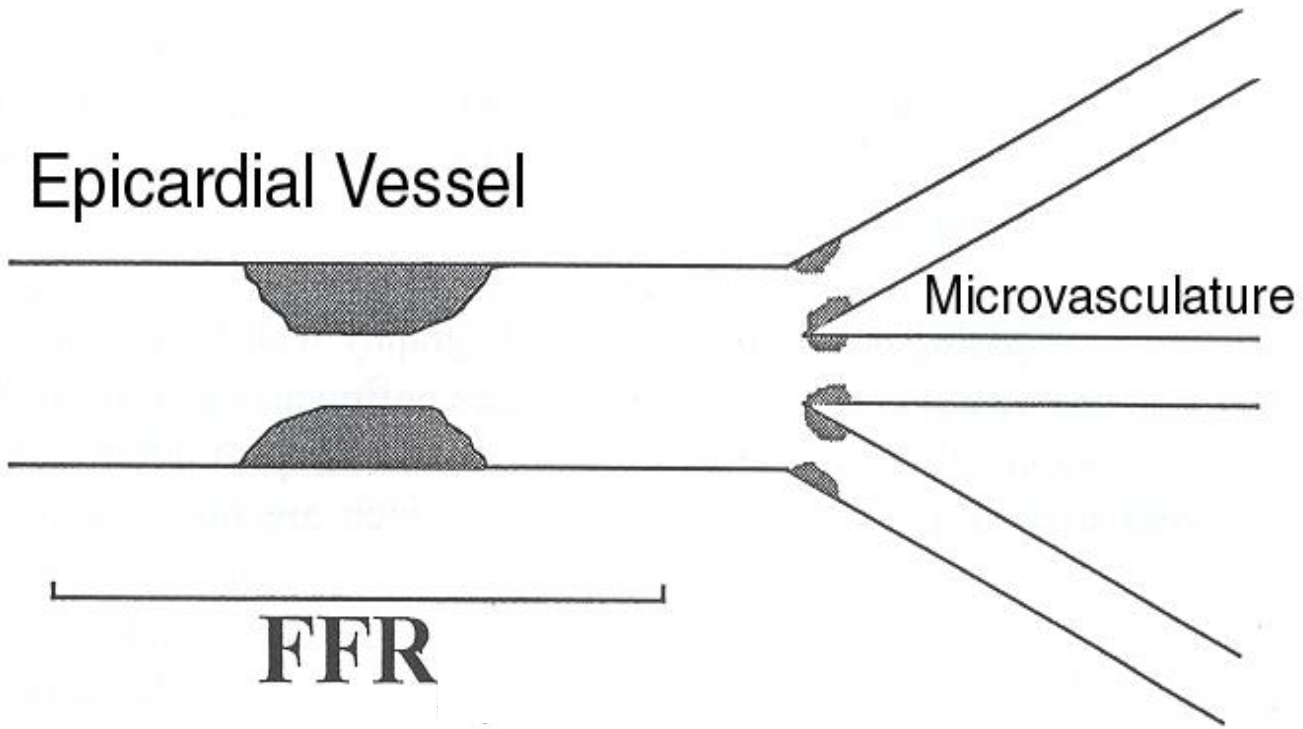

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