Coronary Pathophysiology & Microcirculation
ESC Working Group

Microvasculature Clinical Importance

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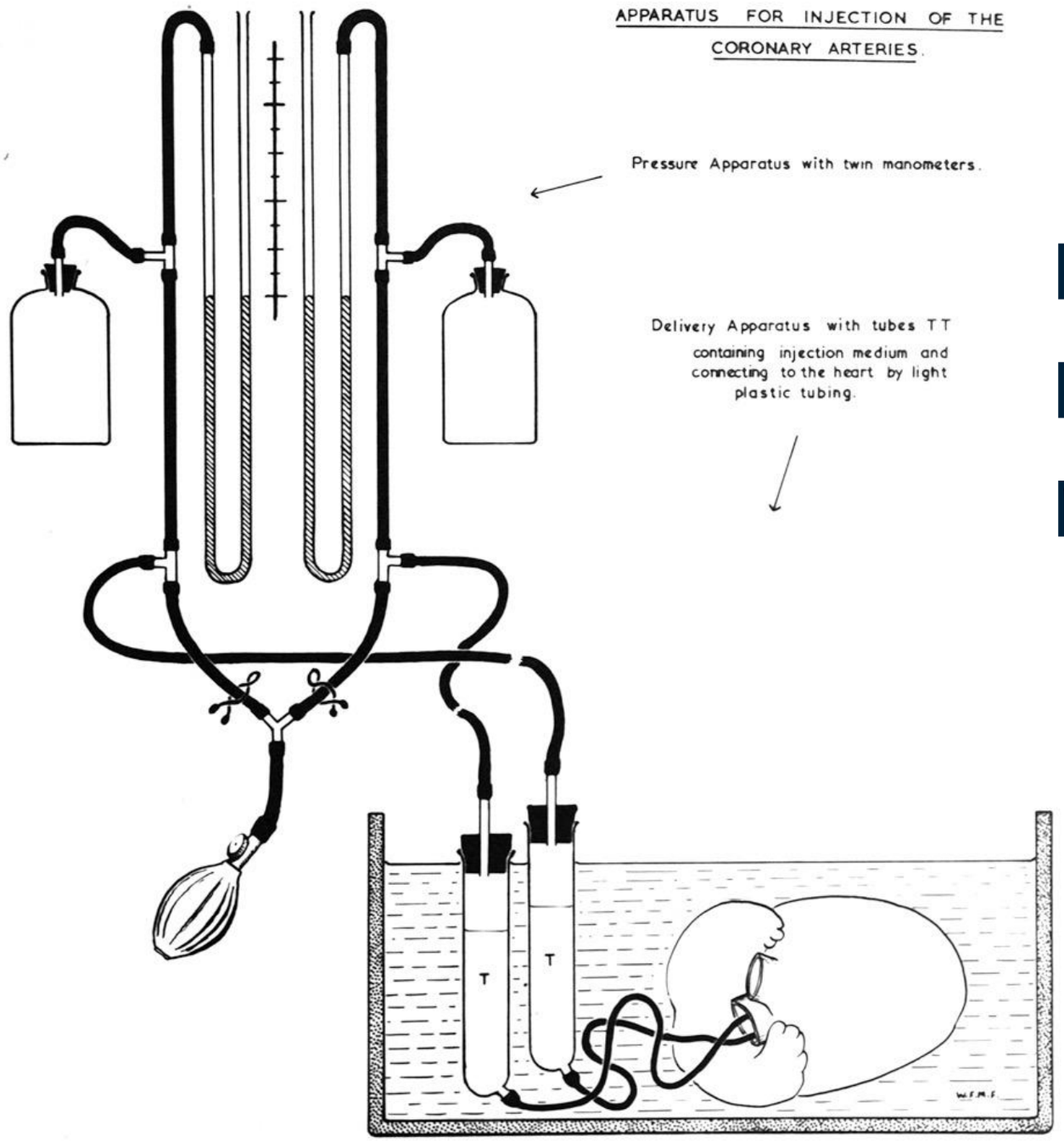


William Fulton, MD

Scottish Medical Journal, 1963

Fresh explanted human hearts

Physiological perfusion

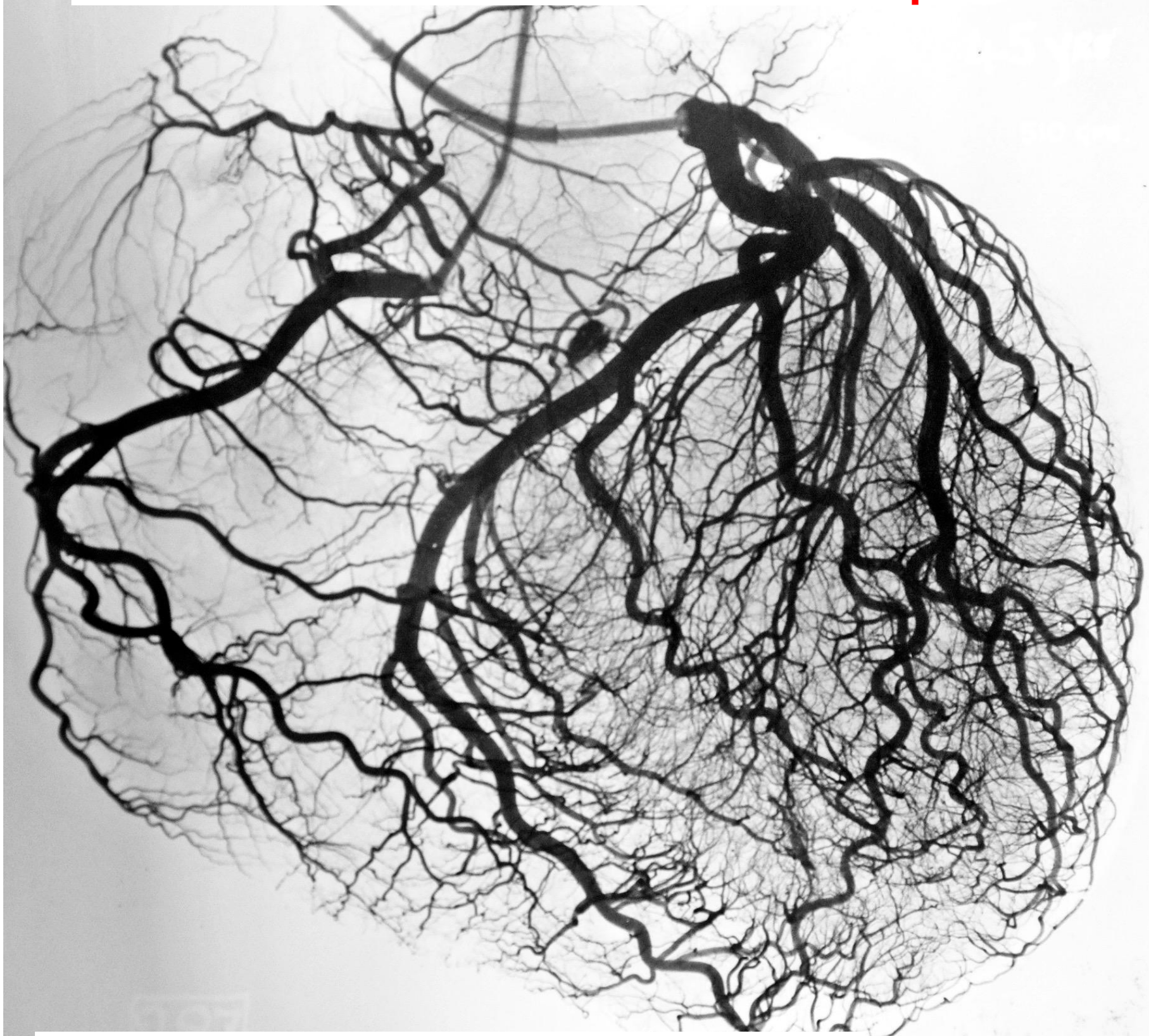
Microvascular anatomy

Collateral connections

1. Exist in the healthy heart

2. Microvascular density correlates with disease

3D stereo-arteriography resolves: Collateral connections vs. 2D overlap



Adult, ‘normal’ coronary arteries

Fulton WF

Acute MI

Chronic MI

Infarct scar
↓ vascularity

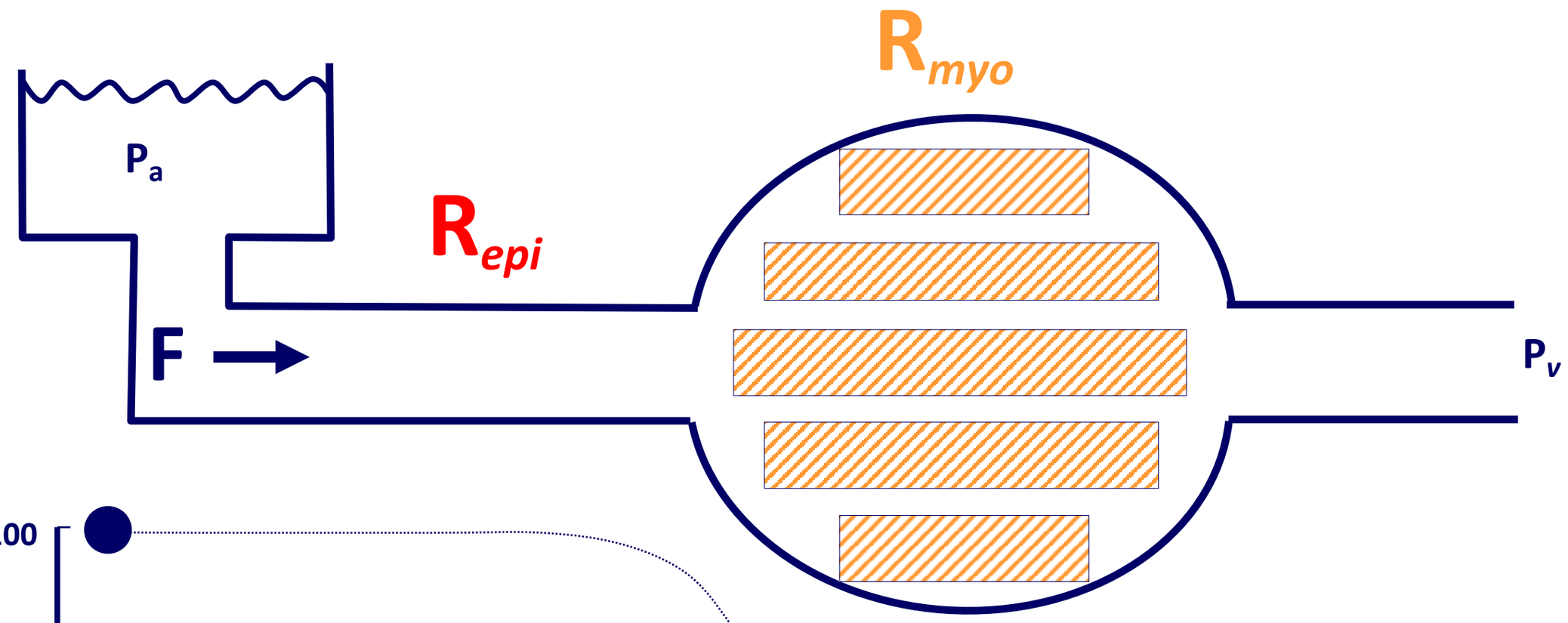
Remodelling
↑ vascularity

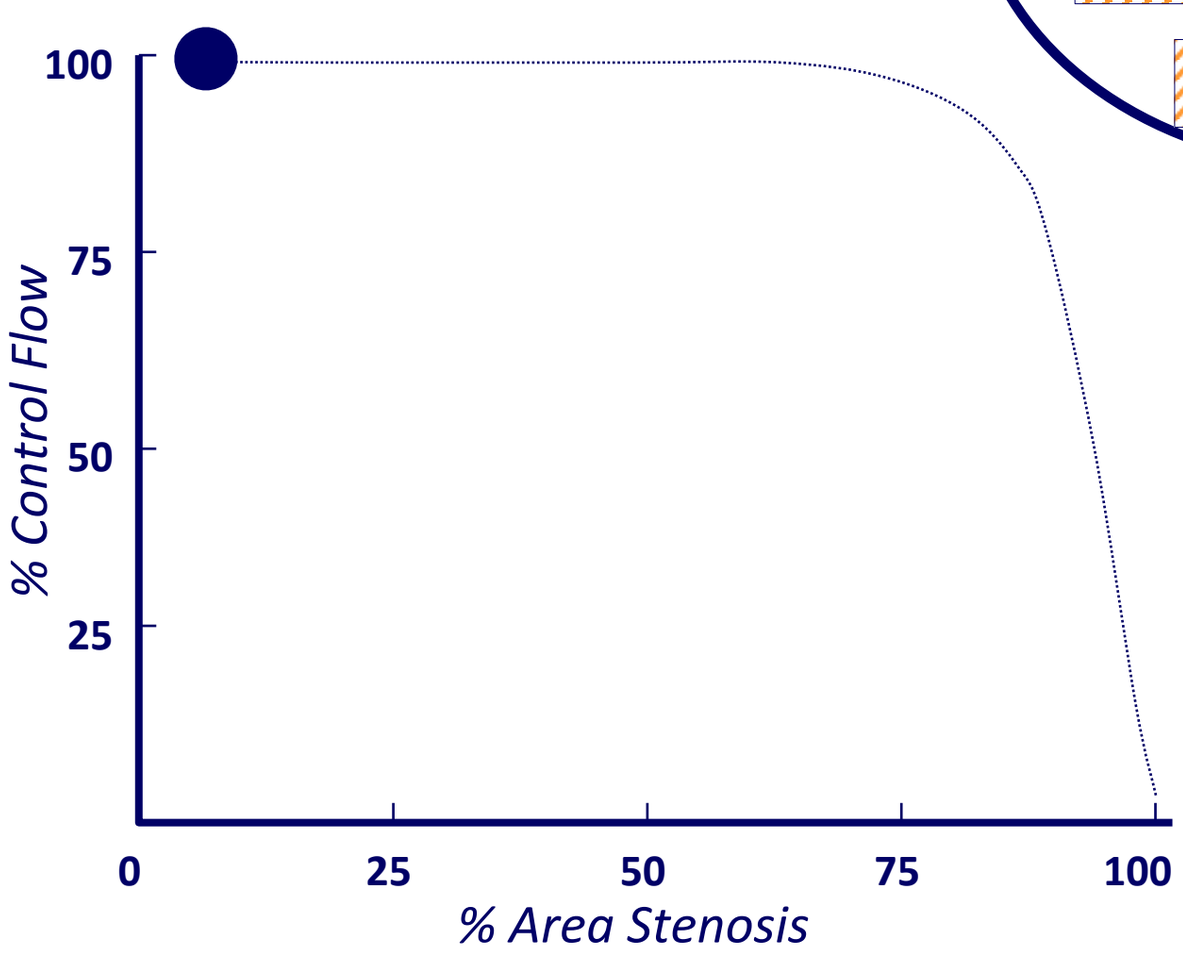
Remodelling
↑ vascularity

Fulton WF

The Clinical Importance of the Microcirculation

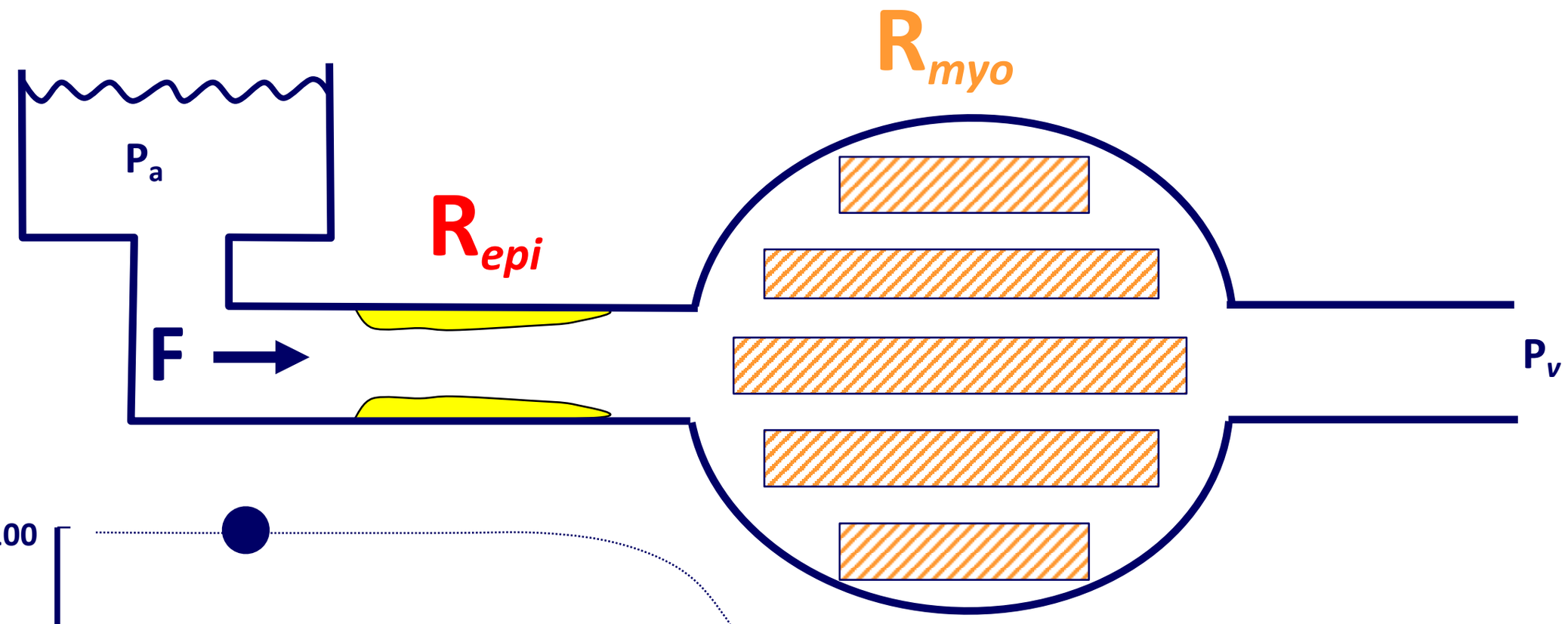
- **Major determinant of myocardial blood flow and therefore maximal hyperaemia**
- Significant impact on prognosis - FFR/CFR discordance
- Critically important in shock states

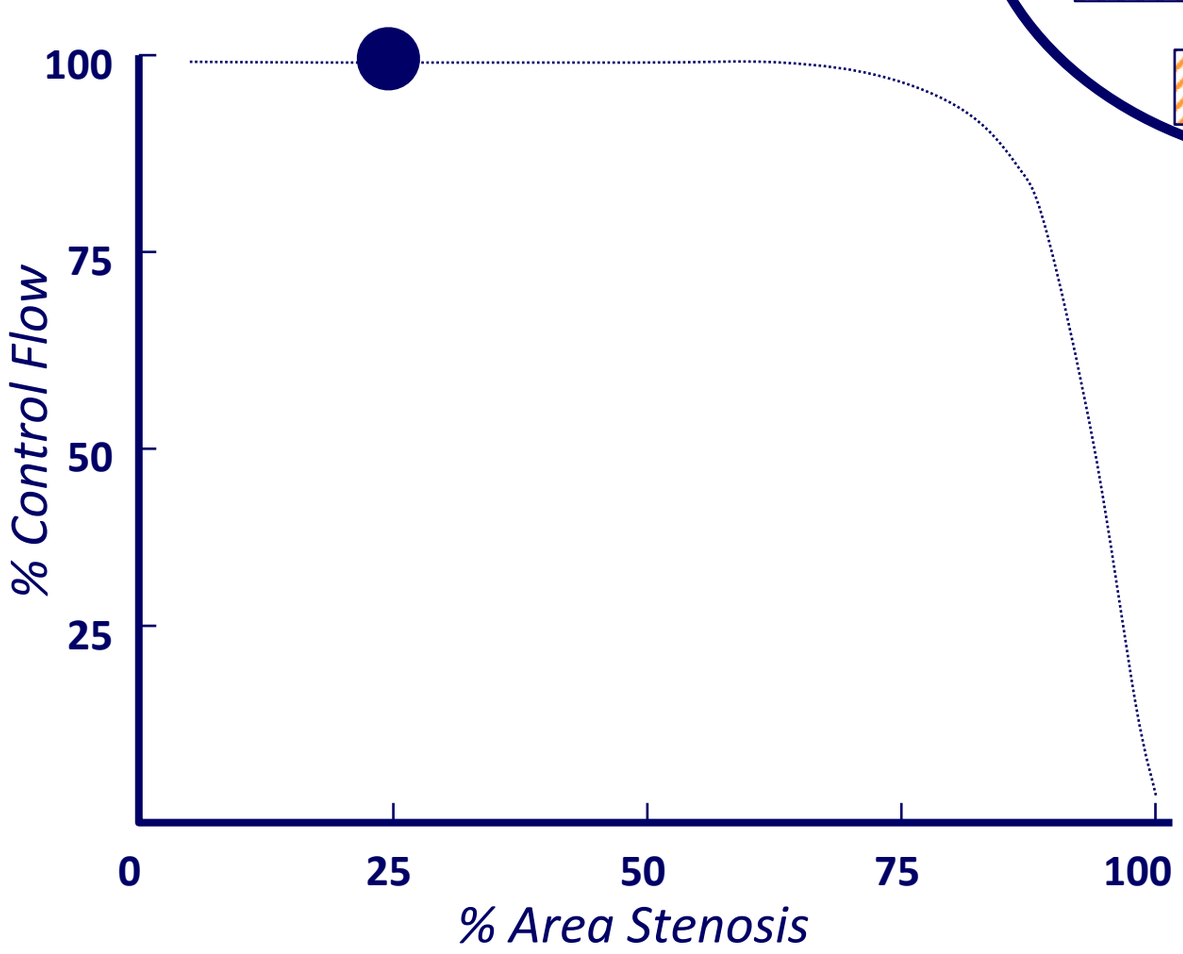




$$F = \frac{\otimes P}{R_{epi} + R_{myo}}$$

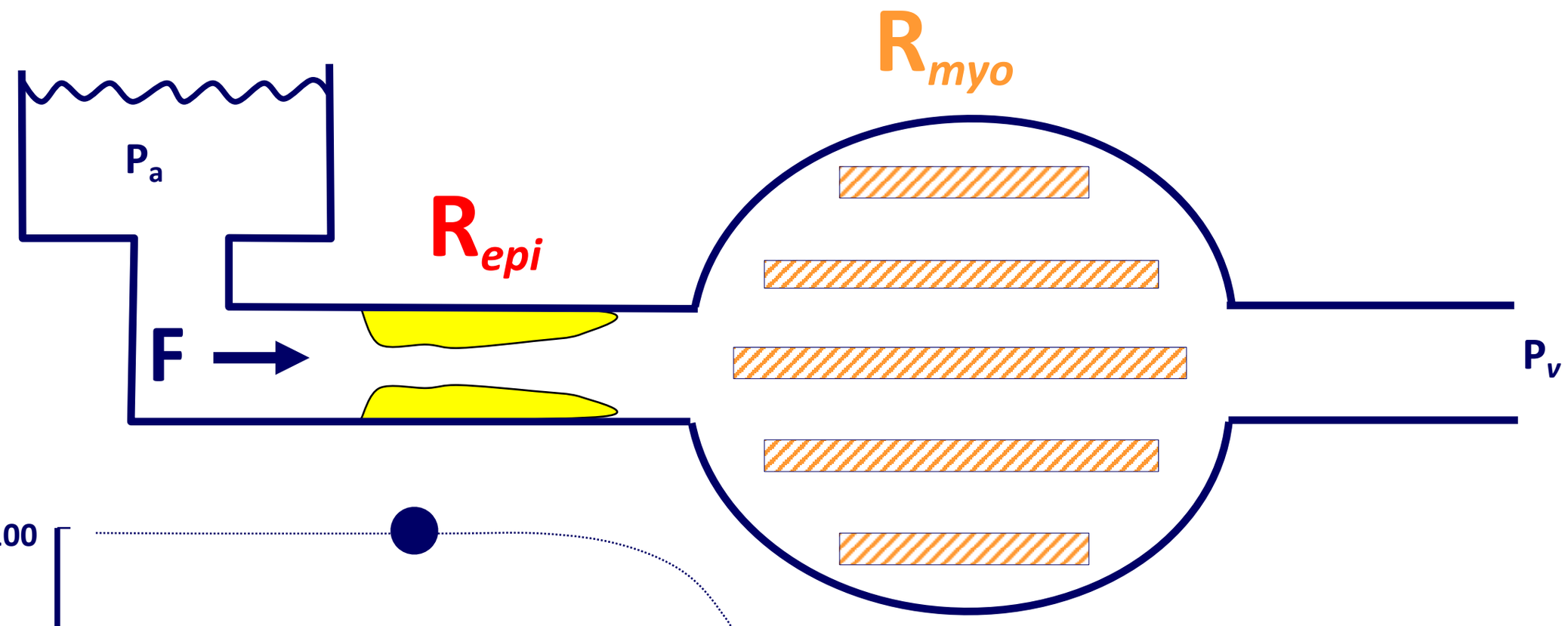
K. Lance Gould, 1974

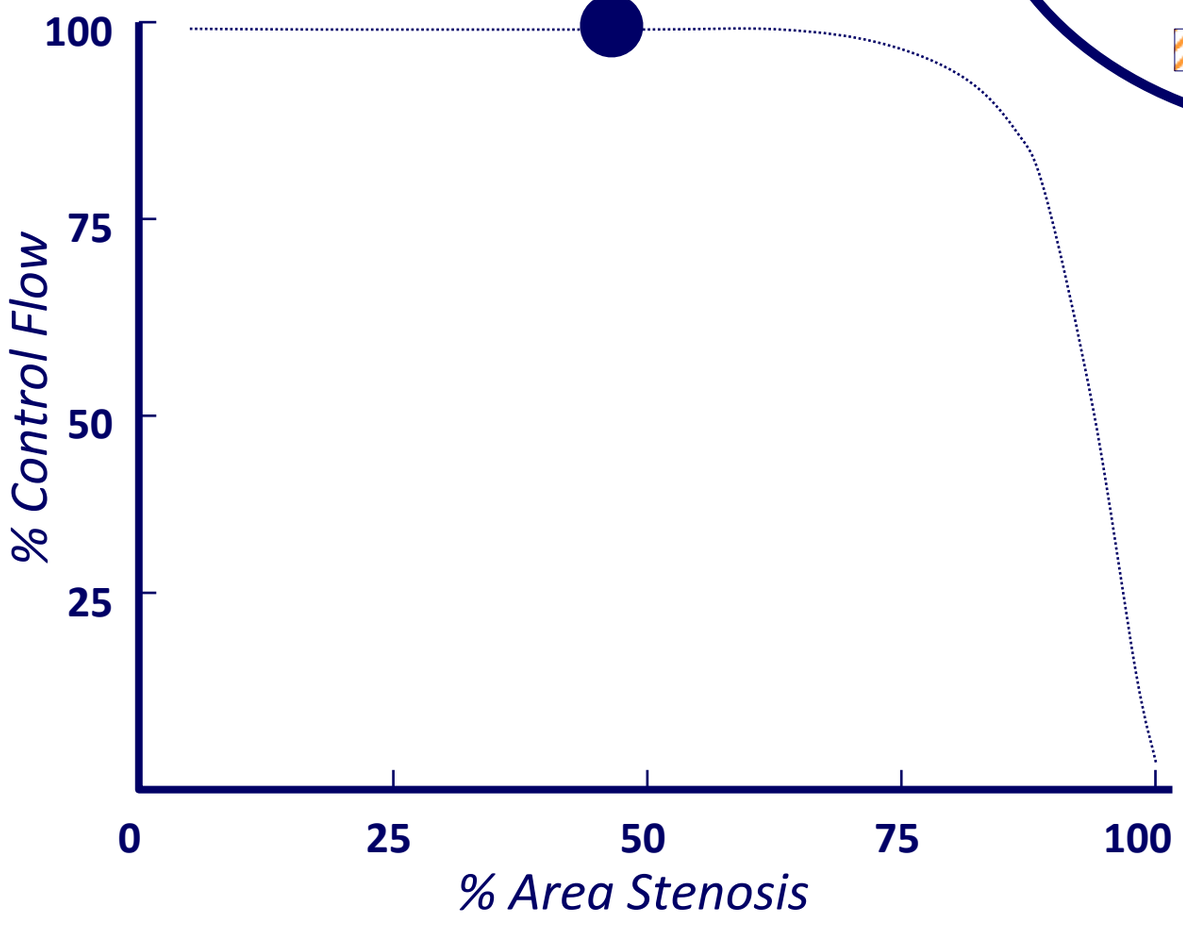




$$F = \frac{\otimes P}{R_{epi}\uparrow + R_{myo}\downarrow}$$

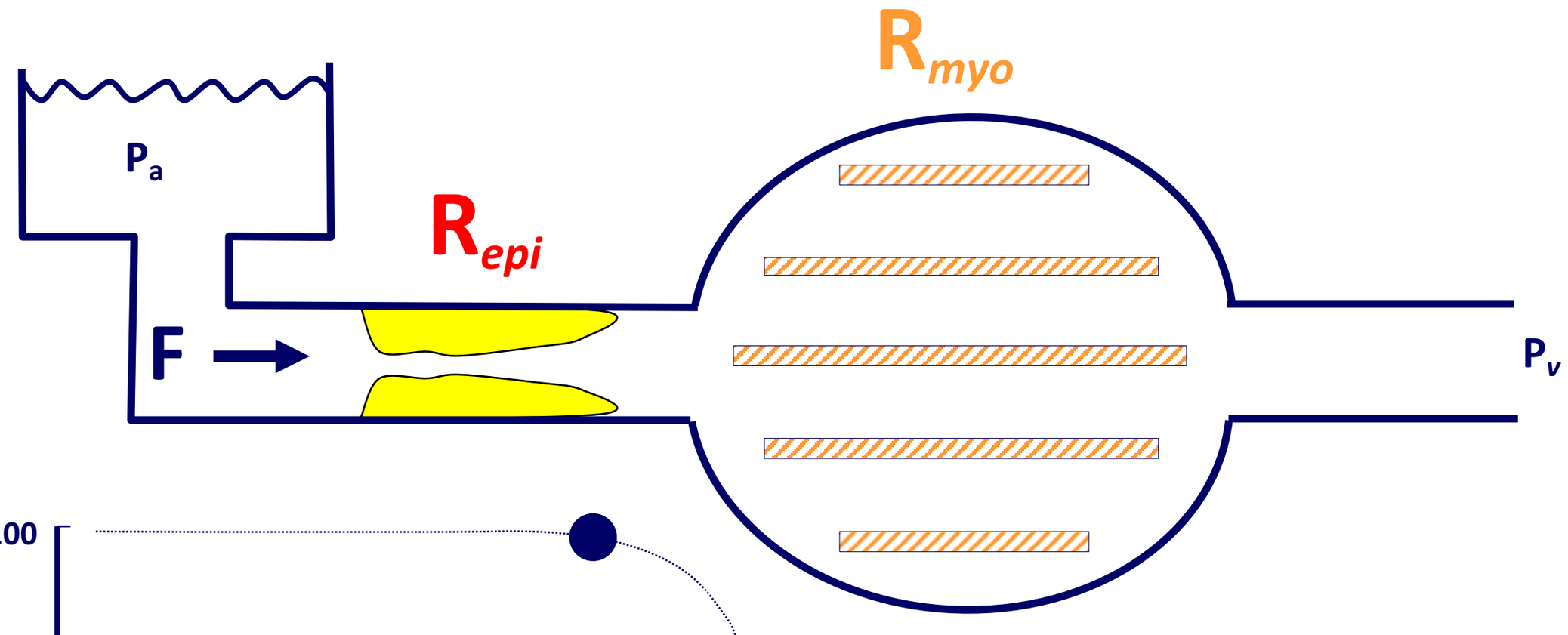
K. Lance Gould, 1974

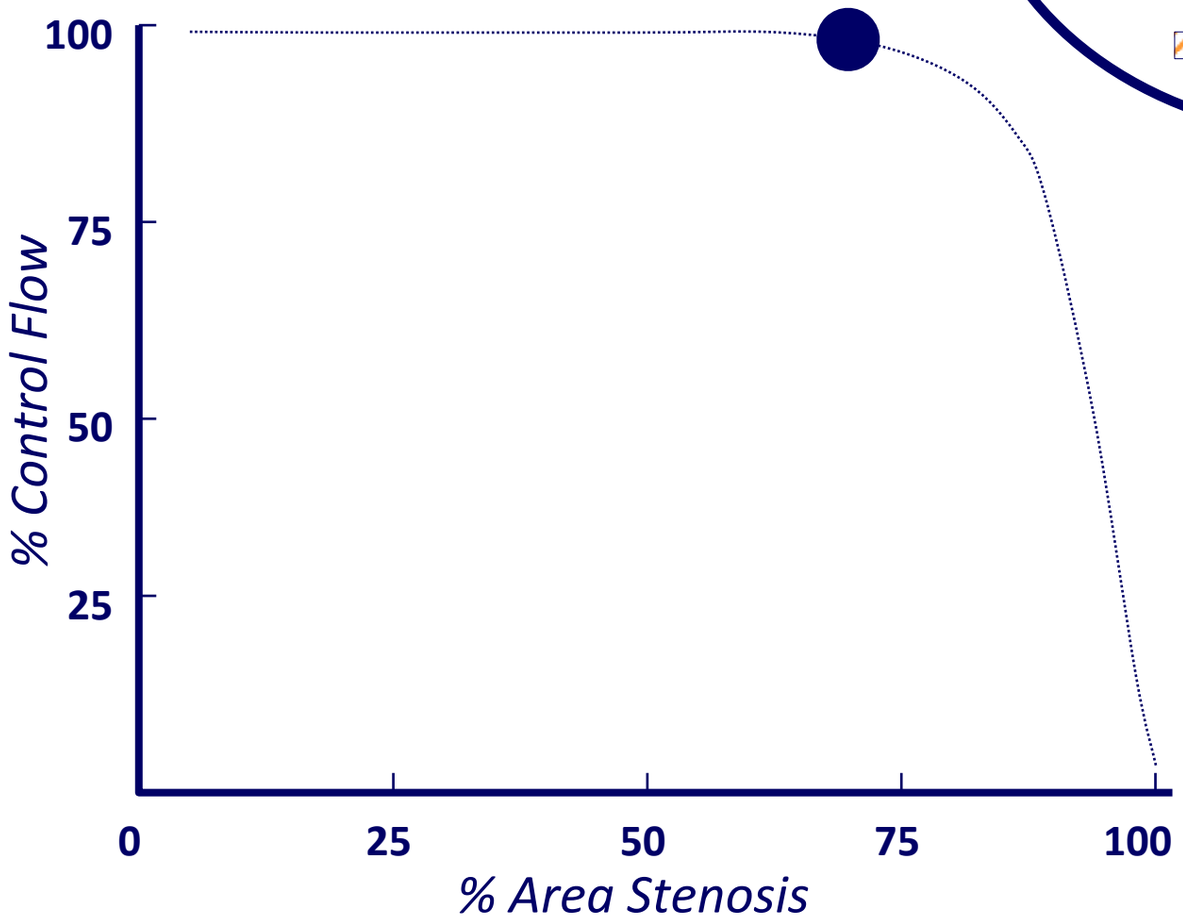




$$F = \frac{\otimes P}{R_{epi}\uparrow + R_{myo}\downarrow}$$

K. Lance Gould, 1974





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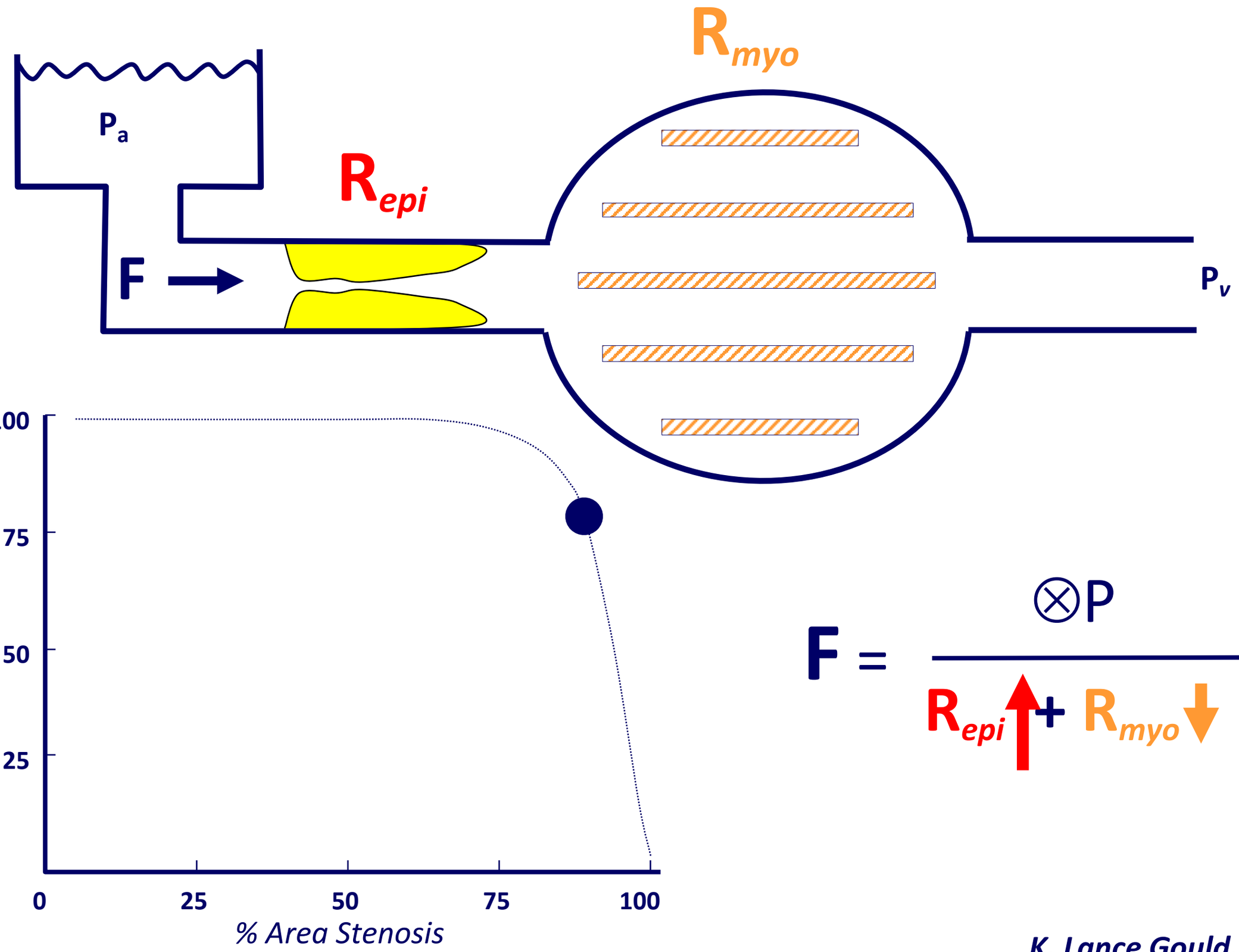
K. Lance Gould, 1974



$$F = \frac{\otimes P}{R_{epi}\uparrow + R_{myo}\downarrow}$$

K. Lance Gould, 1974

The Microcirculation and Maximal Hyperaemia?

- FFR requires that myocardial microvascular resistance be rendered constant and minimal. This allows the impact of any epicardial stenosis on myocardial blood flow to be interrogated.

- When we measure FFR we are testing the ability of the microcirculation subtended by the artery being studied to maximally dilate by administering a potent vasodilator combination of GTN/adenosine.

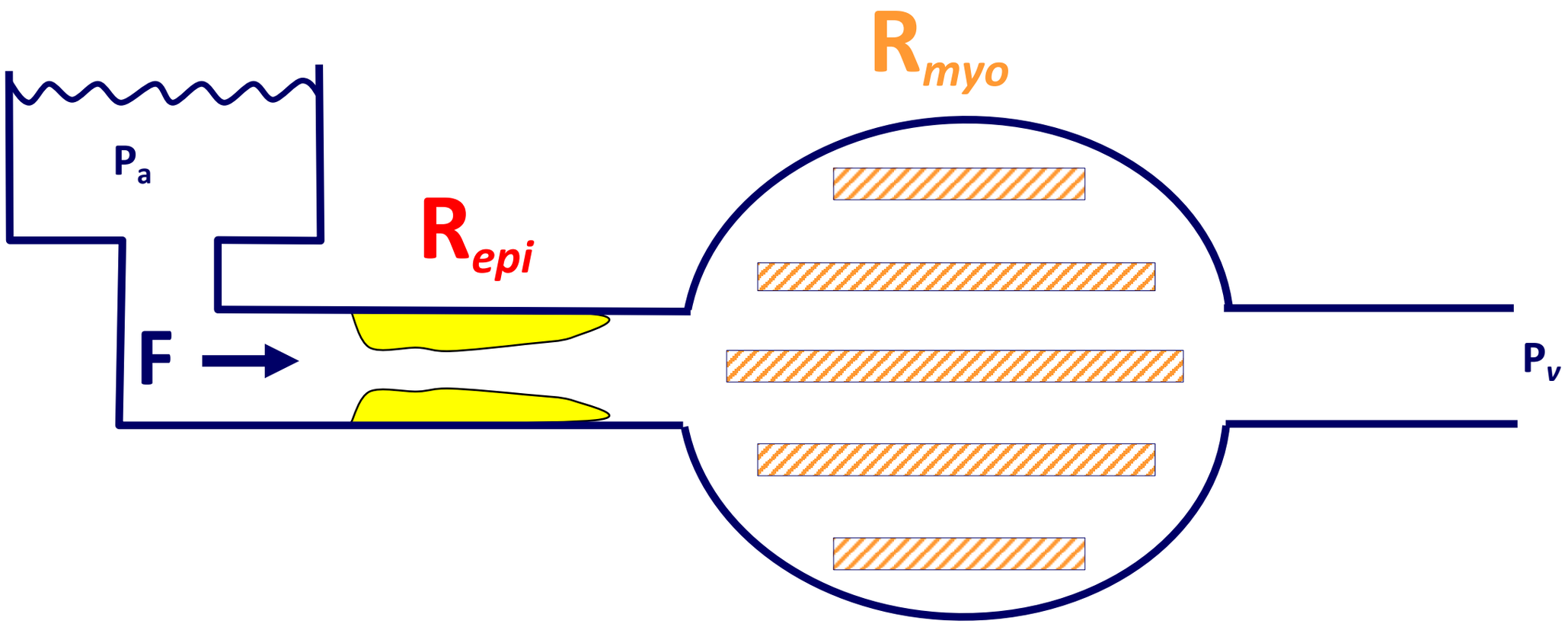
- A common question about and criticism of FFR is: “How Do I Know if Minimal Resistance (maximal hyperaemia) Has Been Attained?

The Microcirculation and Maximal Hyperaemia?

- The degree of hyperaemia obtained with pharmacological vasodilatation is more feasible, predictable and repeatable than that achieved during exercise testing.

- Dose response studies have confirmed that in the majority of patients, maximal hyperaemia is achieved with:
  intravenous adenosine: 140mcg/kg/min
  intracoronary adenosine: 100mcg

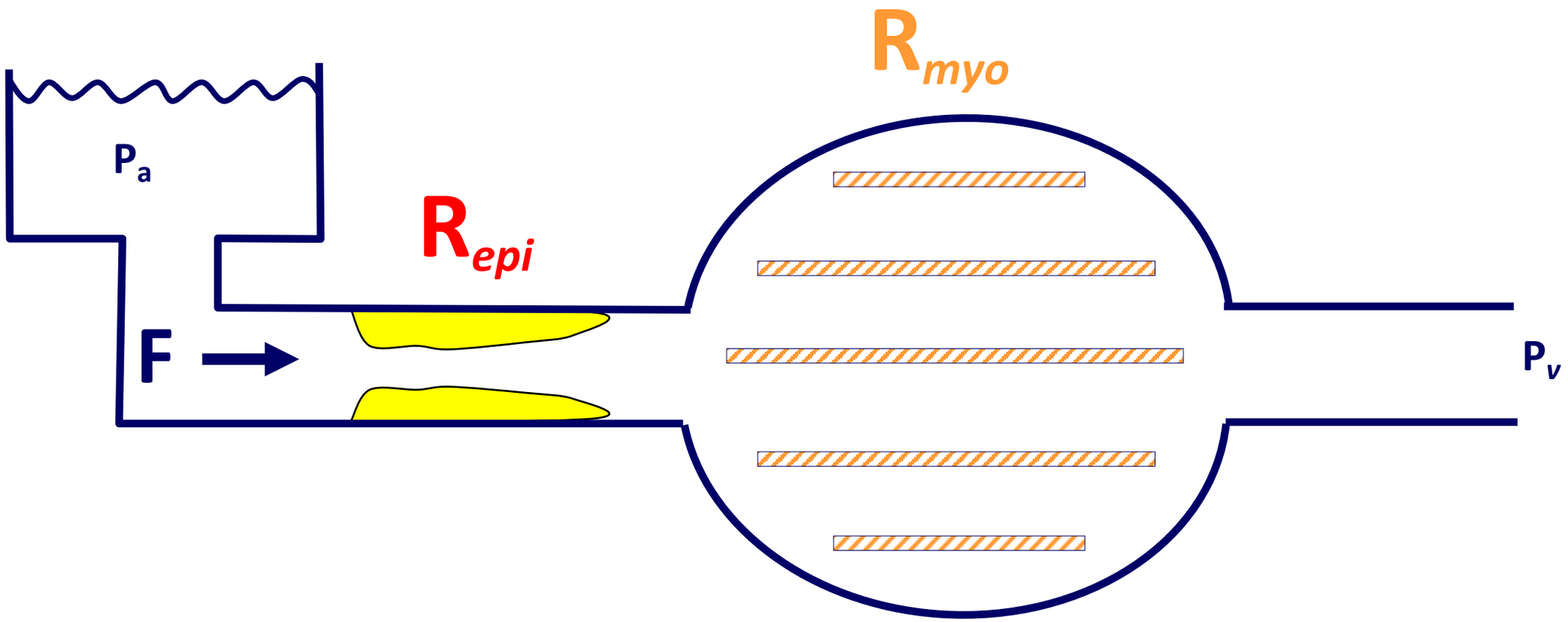
- Variation in the absolute level of minimal resistance (maximal hyperaemia) obtained is a strength of FFR:
  reflects myocardial perfusion
  describes unique vessel-level coronary physiology



50% area stenosis

$$F = \frac{\otimes P}{R_{epi}\uparrow + R_{myo}\downarrow}$$

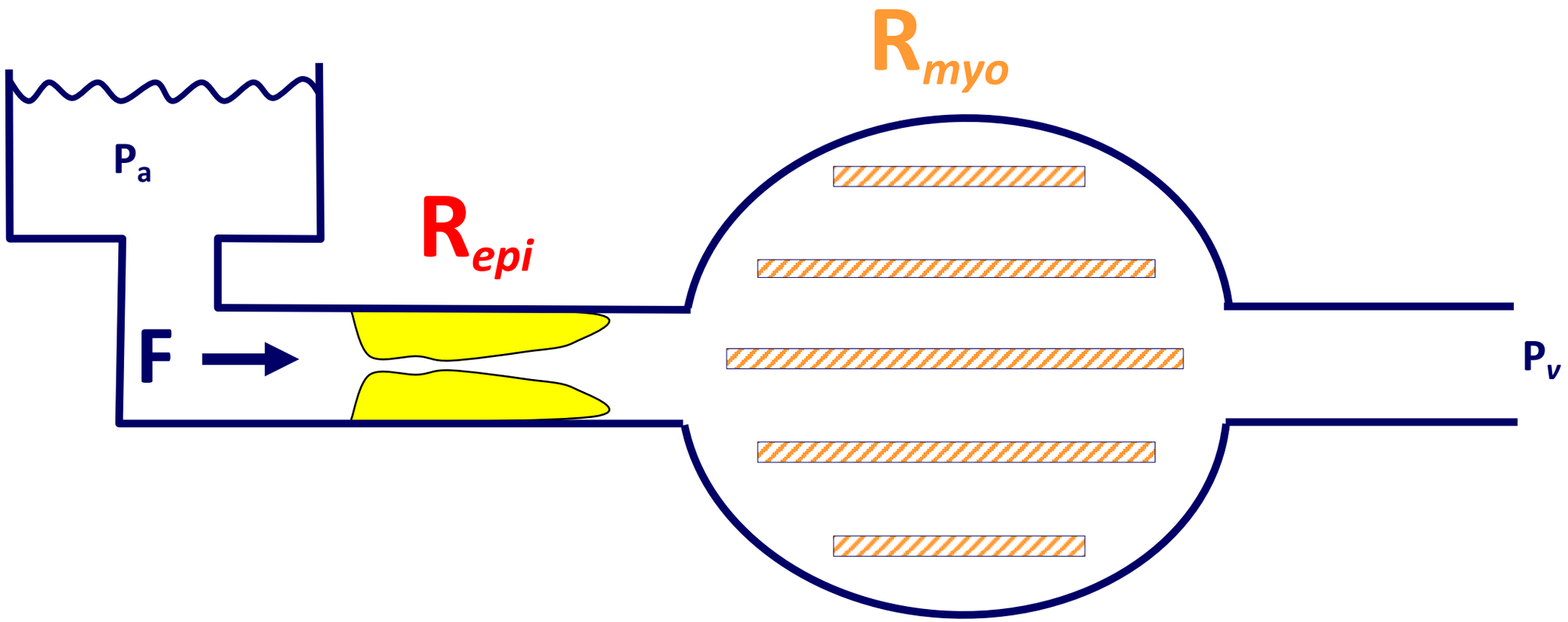
FFR = 0.85



50% area stenosis

$$F = \frac{\otimes P}{R_{epi}\uparrow + R_{myo}\downarrow\downarrow}$$

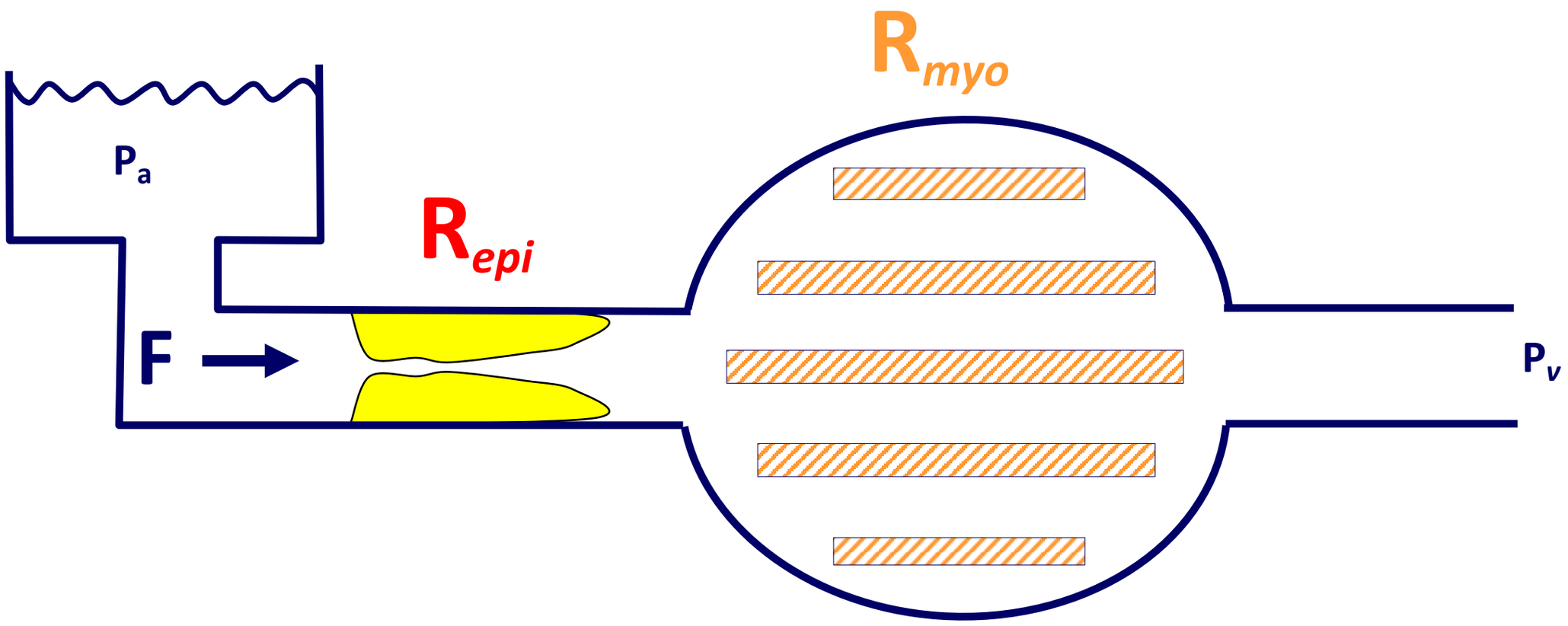
FFR = 0.70



90% area stenosis

$$F = \frac{\otimes P}{R_{epi}\uparrow + R_{myo}\downarrow}$$

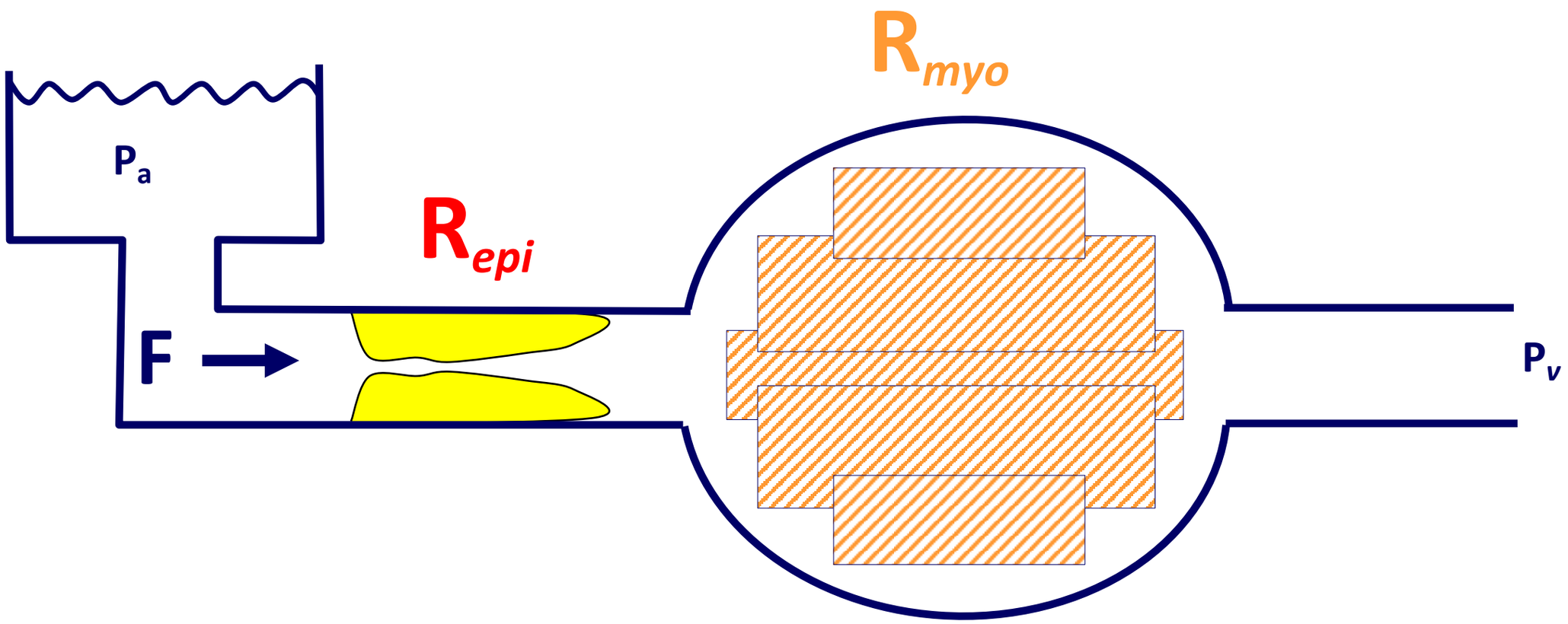
FFR = 0.70



90% area stenosis

$$F = \frac{\otimes P}{R_{epi}\uparrow + R_{myo}\downarrow}$$

FFR = 0.85



90% area stenosis
with severe MVO

$$F = \frac{\otimes P}{R_{epi} + R_{myo}}$$

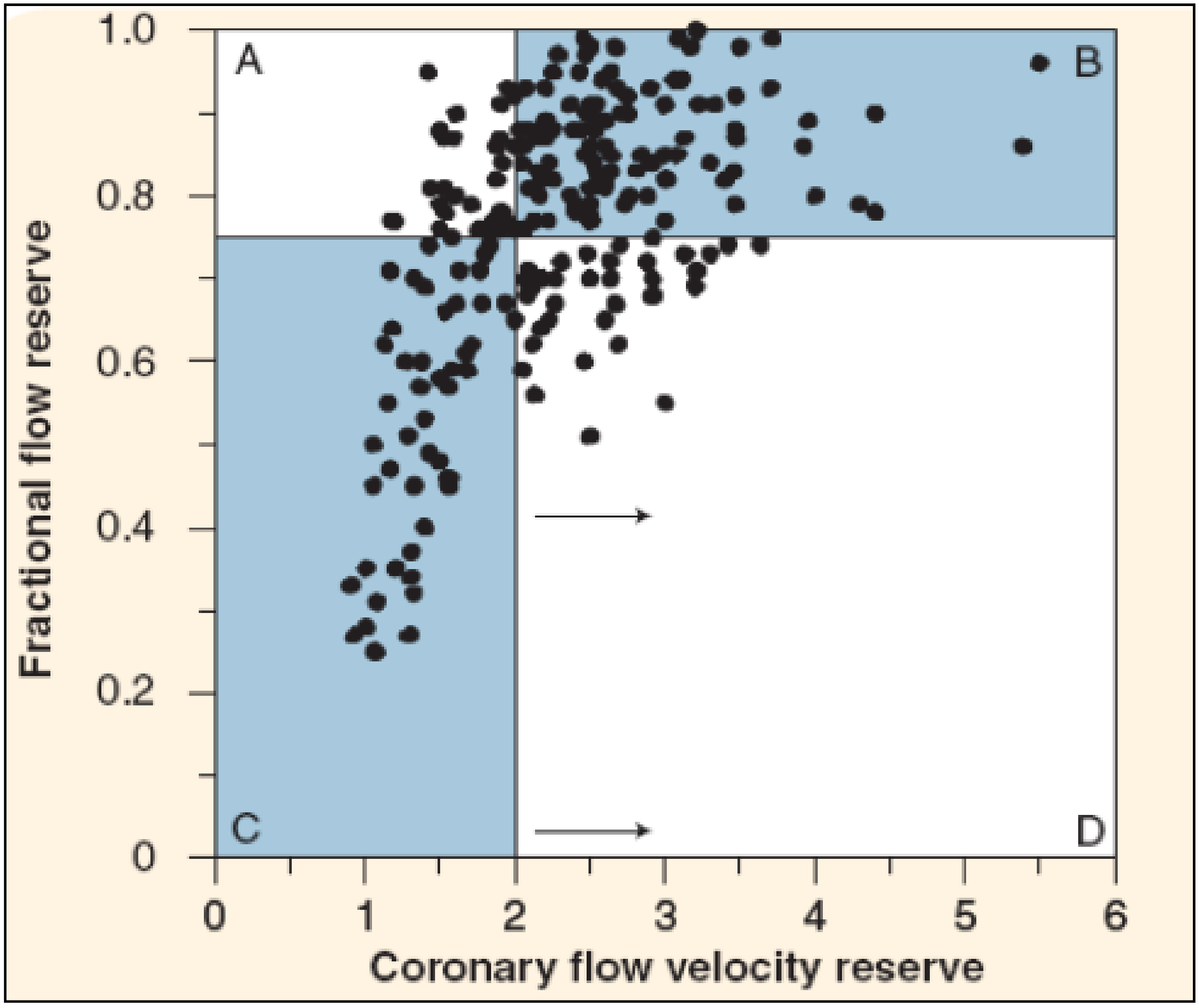
FFR = 1.00!!!!!
(No Reflow)

The Clinical Importance of the Microcirculation

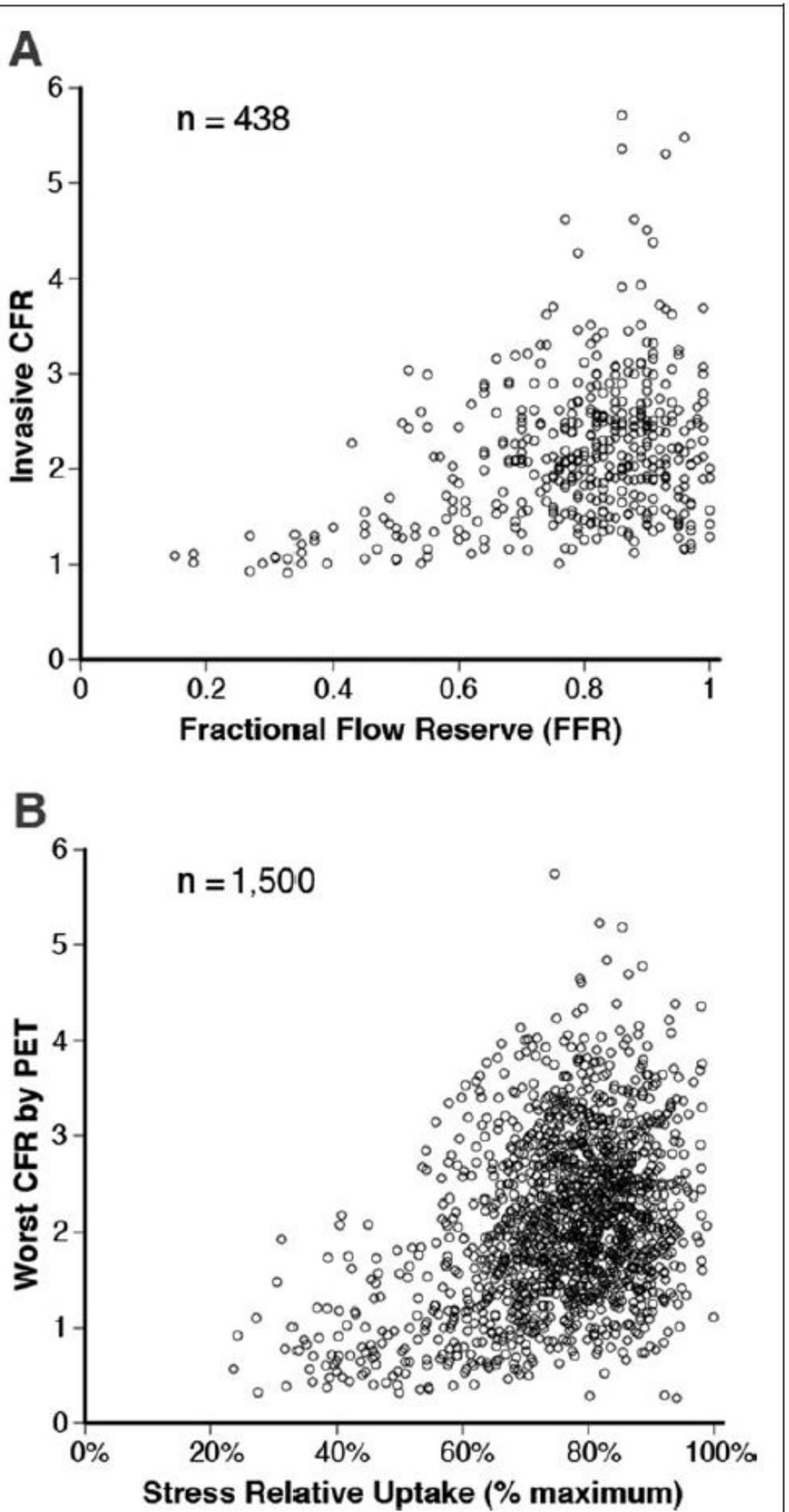
- Major determinant of myocardial blood flow and therefore maximal hyperaemia

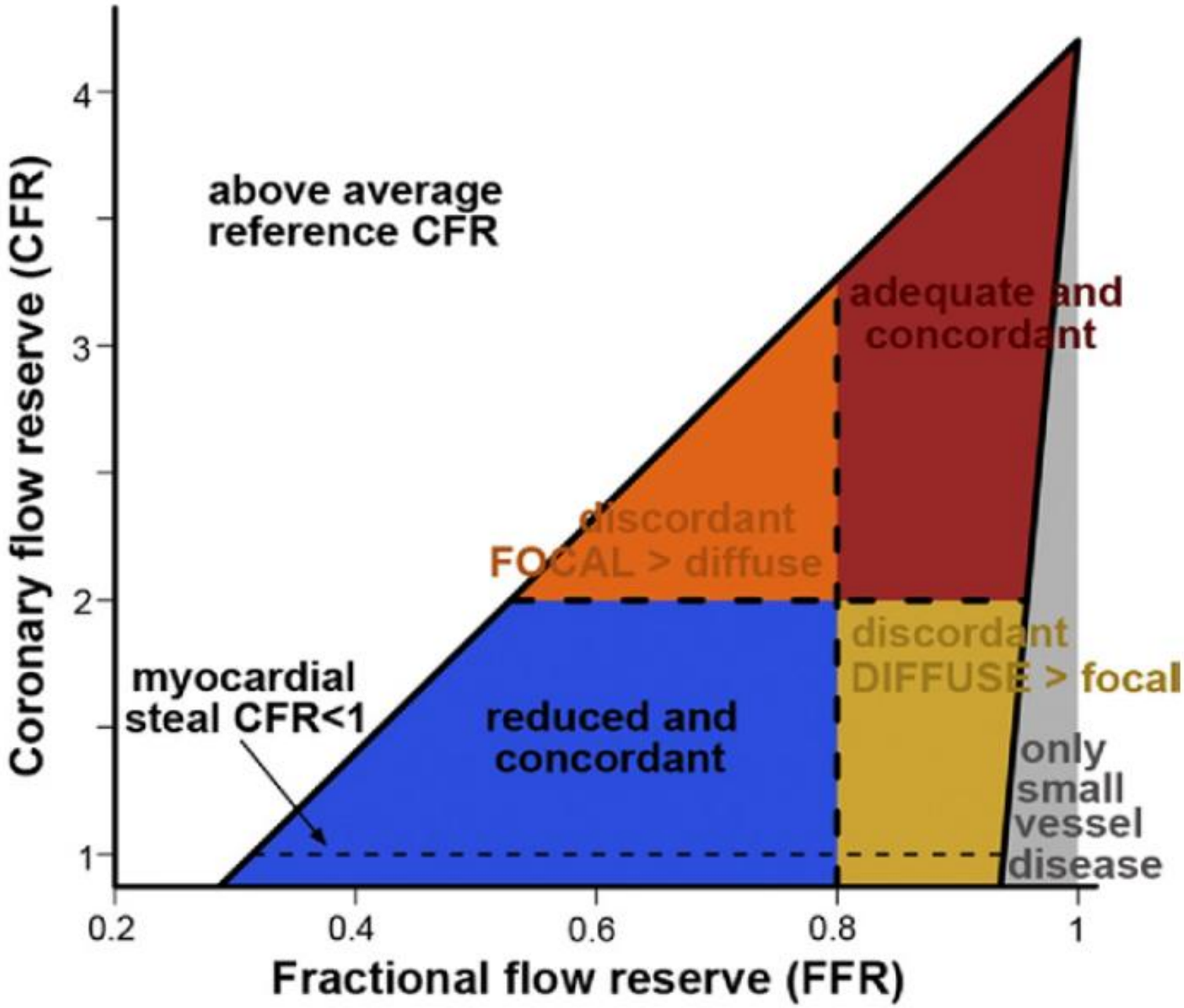
- **Significant impact on prognosis - FFR/CFR discordance**

- Critically important in shock states

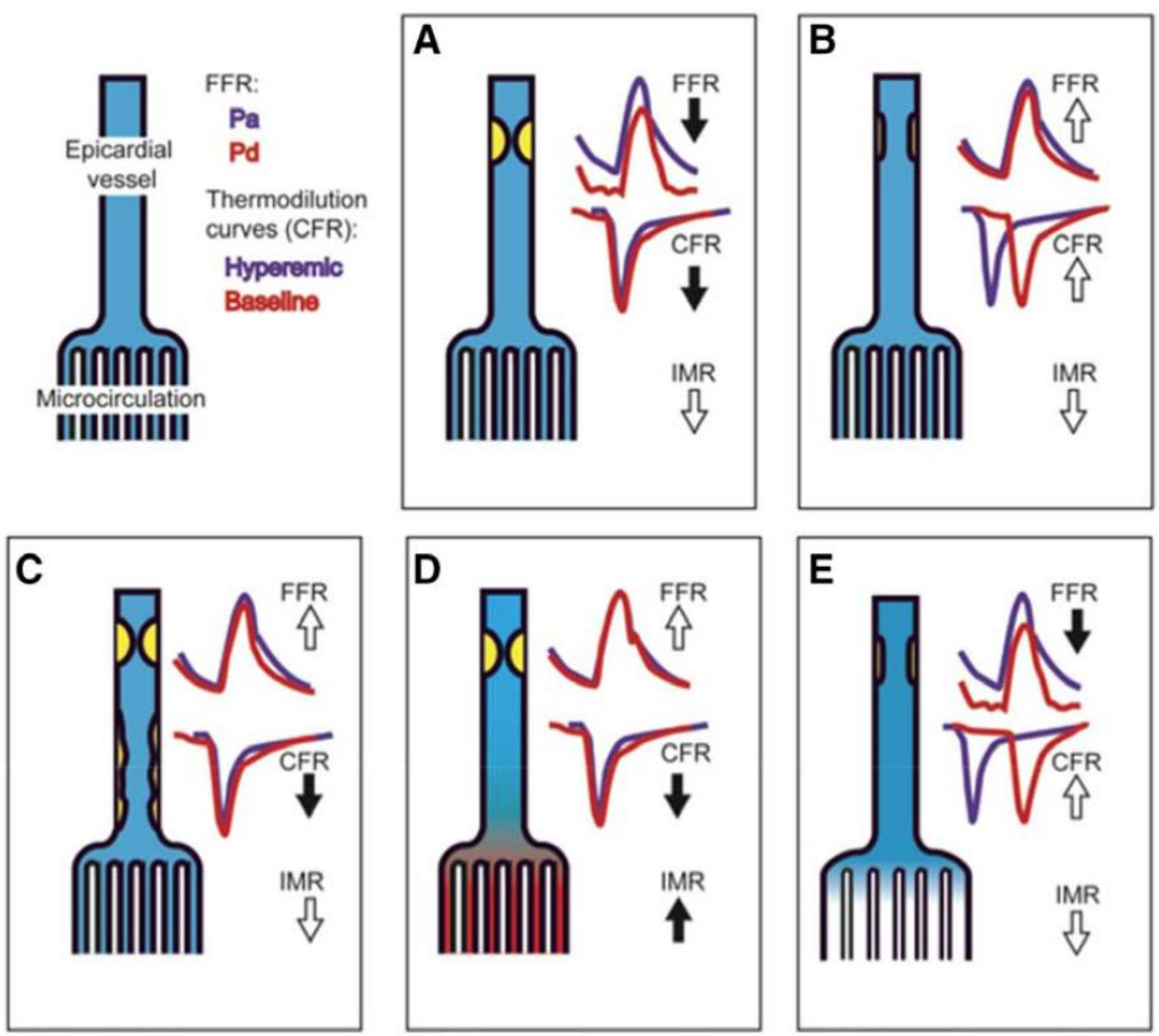


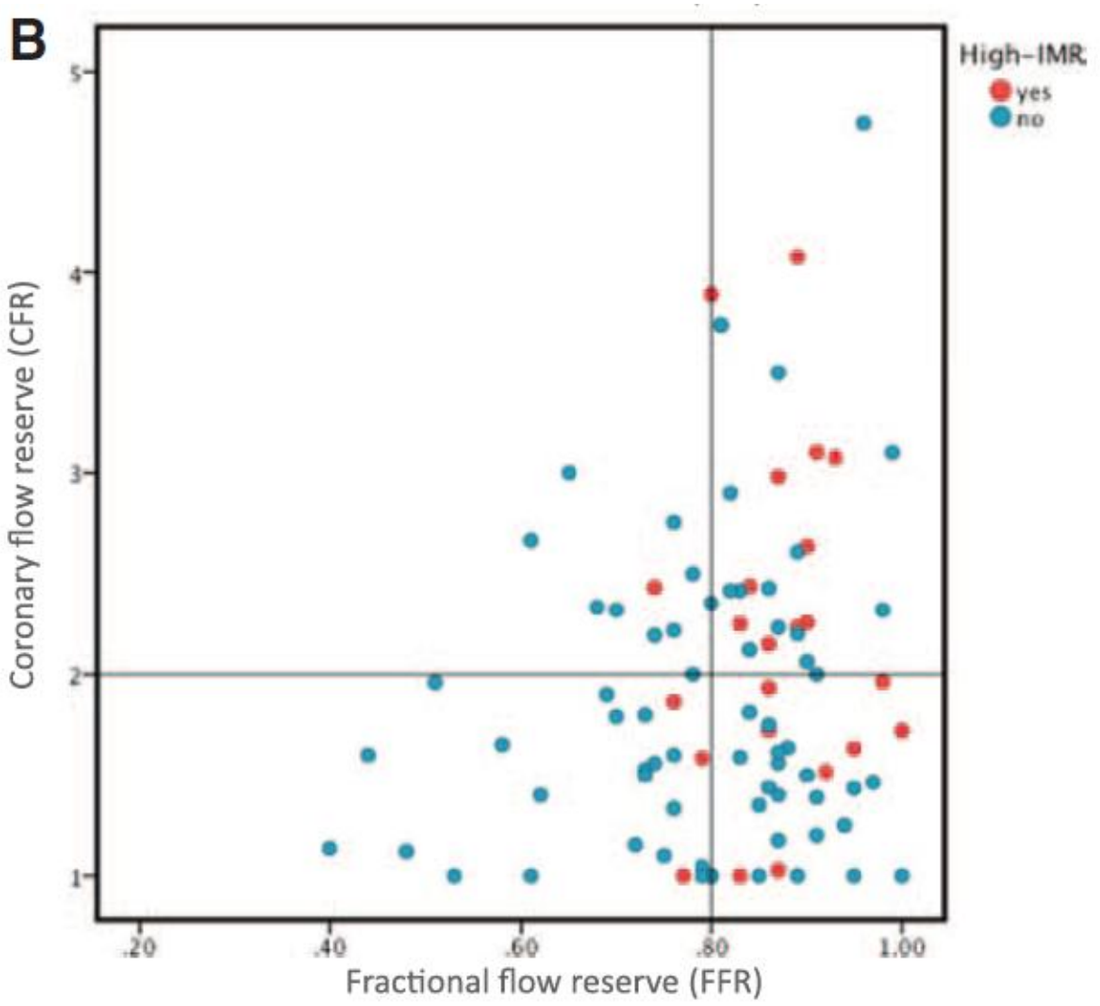
Meuwissen et al. Circulation 2001



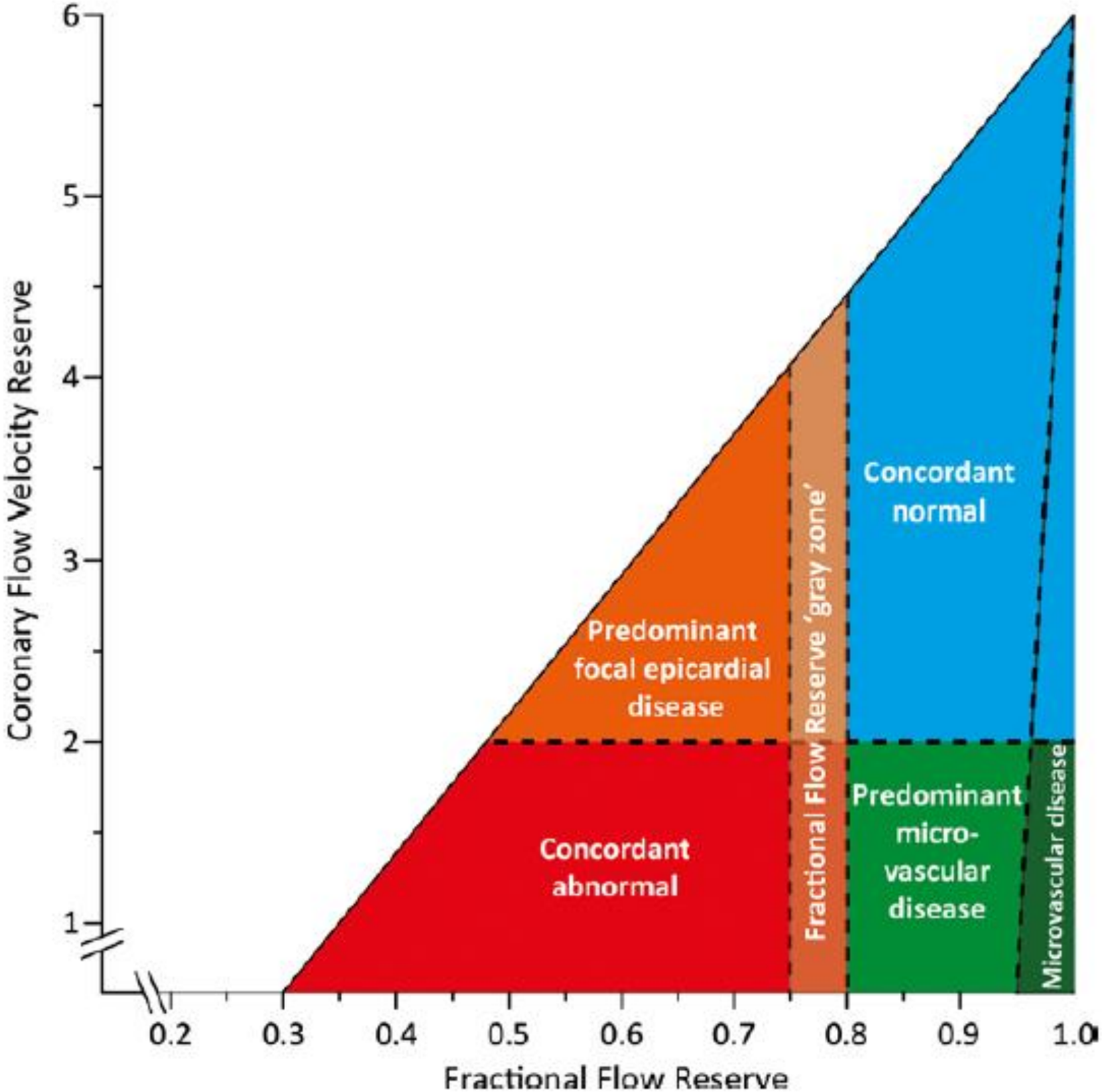


Johnson et al. J Am Coll Cardiol Img 2012;5:193–202

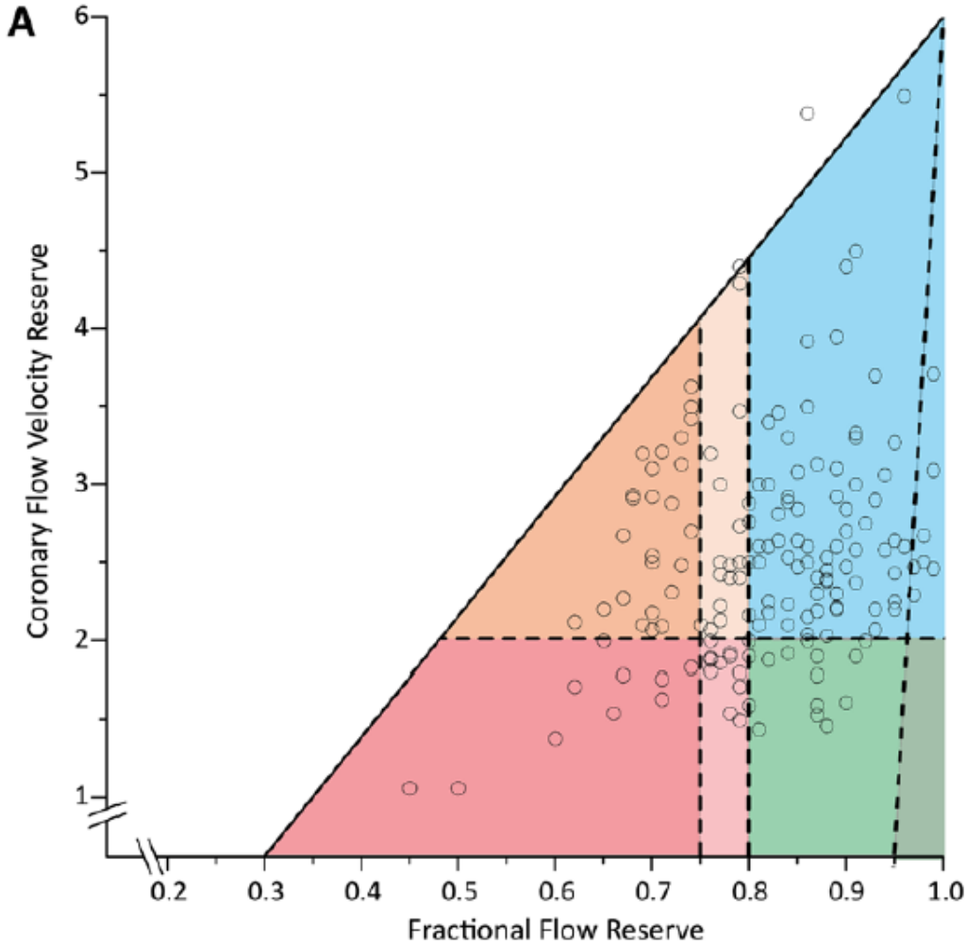


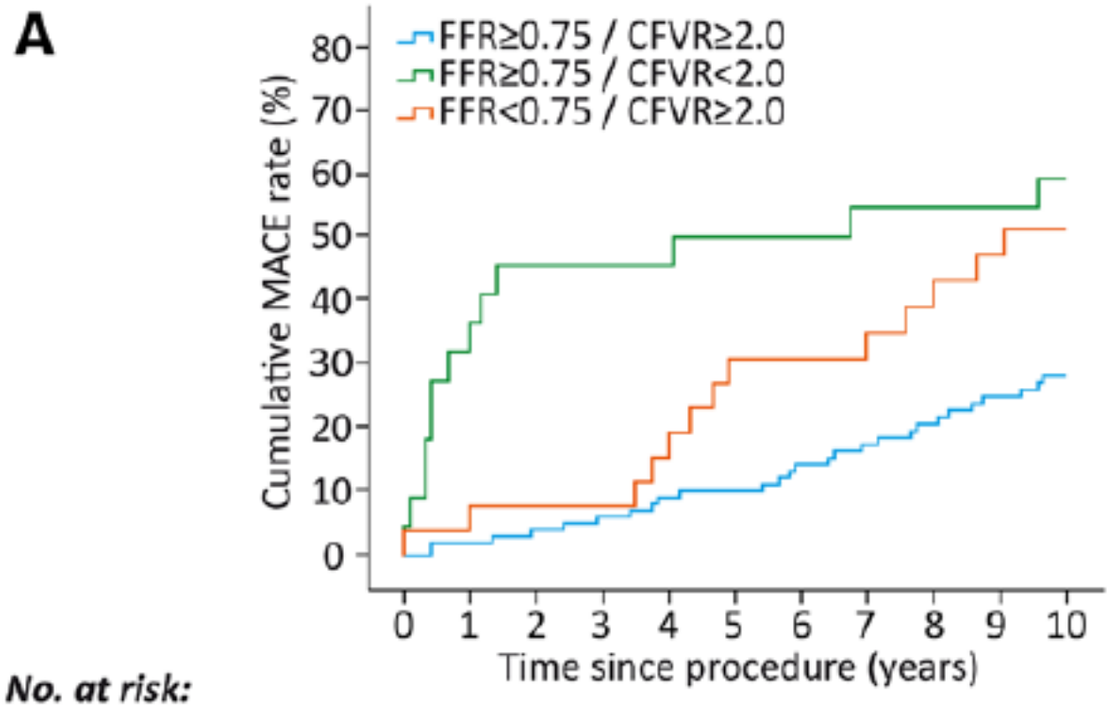


Echavarria-Pinto et al. Circ 2013



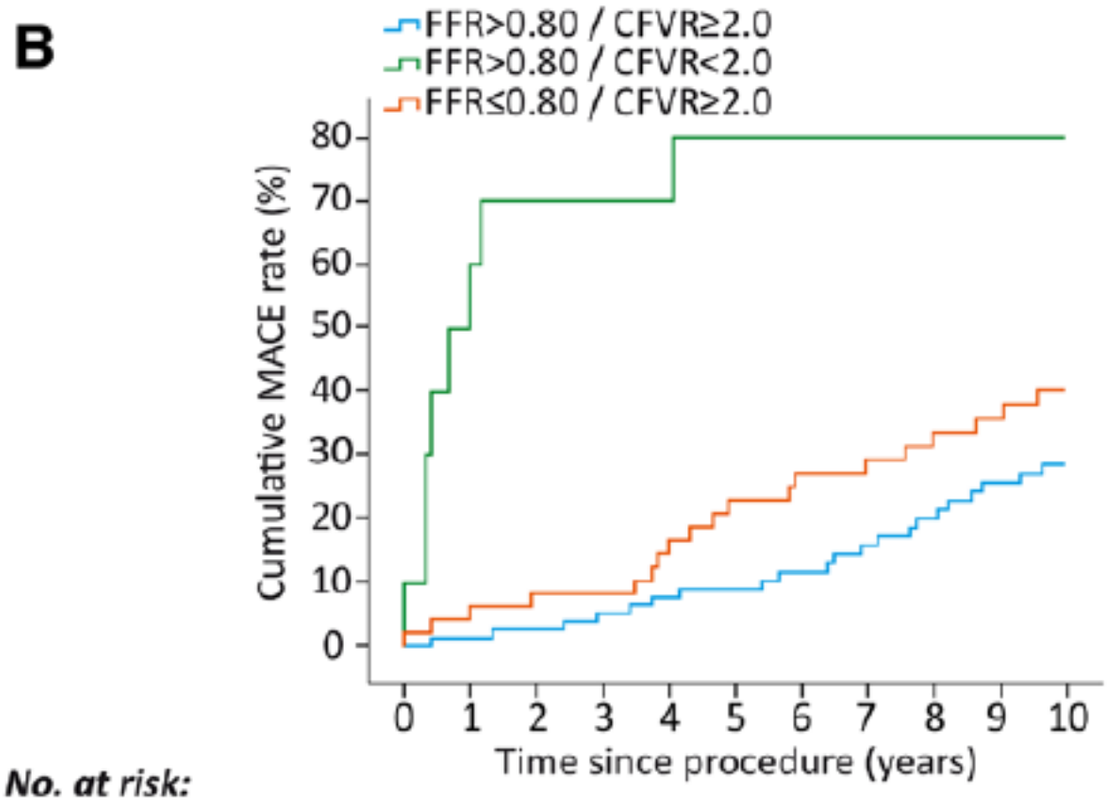
van de Hoef et al. Circ Cardiovasc Int 2014





No. at risk:

FFR≥0.75 / CFVR≥2.0	100	95	90	83	74	61
FFR≥0.75 / CFVR<2.0	22	12	12	11	10	8
FFR<0.75 / CFVR≥2.0	26	24	21	18	14	11



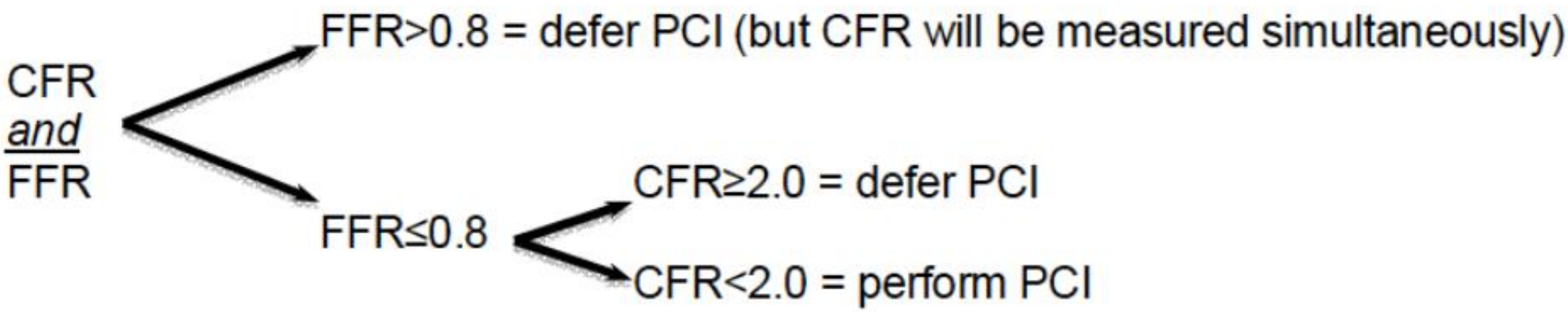
No. at risk:

FFR>0.80 / CFVR≥2.0	78	75	71	66	57	48
FFR>0.80 / CFVR<2.0	10	3	3	2	2	2
FFR≤0.80 / CFVR≥2.0	48	44	40	35	31	24

van de Hoef et al. Circ Cardiovasc Int 2014

Protocol update

Treatment plan



The Clinical Importance of the Microcirculation

- Major determinant of myocardial blood flow and therefore maximal hyperaemia
- Significant impact on prognosis - FFR/CFR discordance
- **Critically important in shock states**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guitton, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien Du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D. for the SEPSISPAM Investigators*

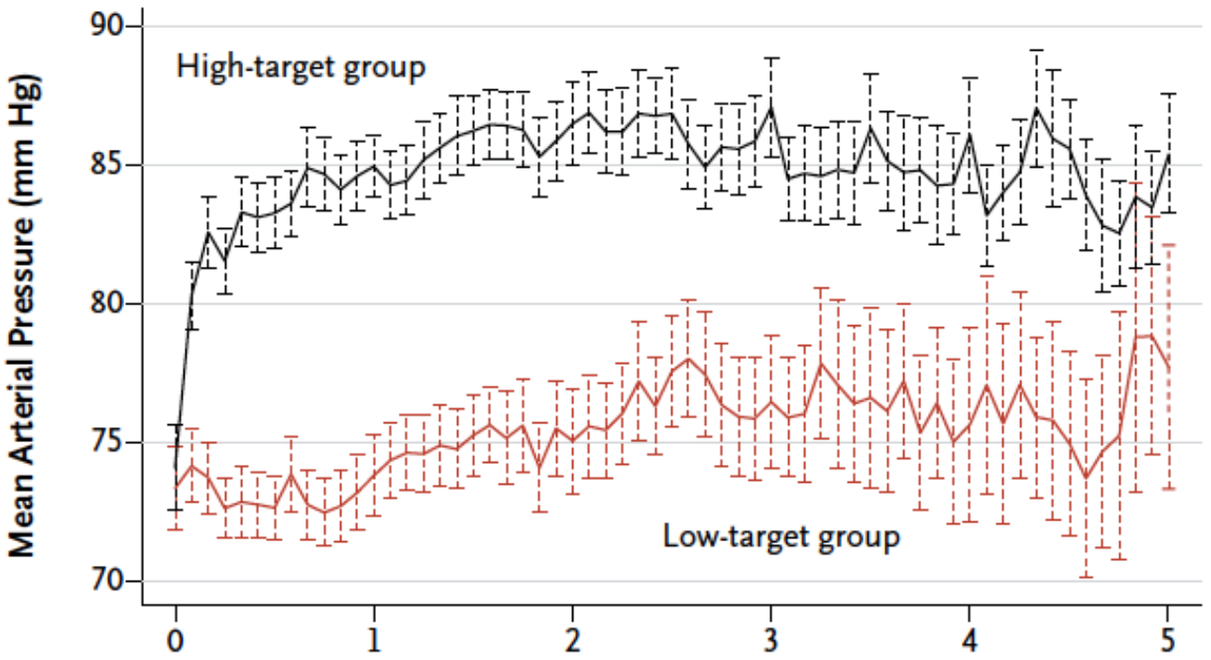
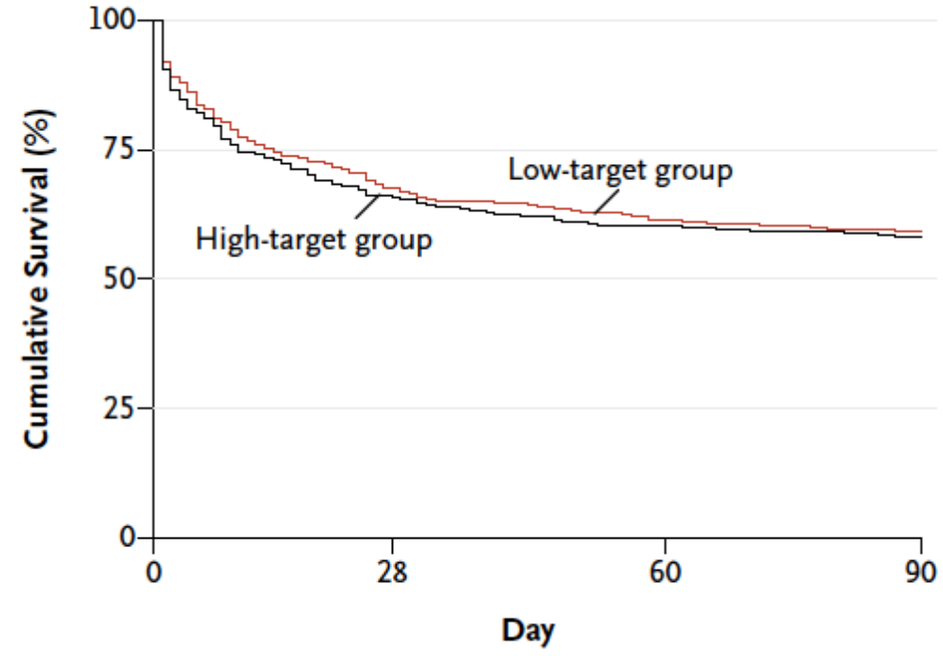


Figure 2. Mean Arterial Pressure during the 5-Day Study Period.

Mean arterial pressures were significantly lower in the low-target group than in the high-target group during the 5 protocol-specified days (P=0.02 by repeated-measures regression analysis), although the values exceeded the target values of 80 to 85 mm Hg in the high-target group and 65 to 70 mm Hg in the low-target group. The I bars represent 95% confidence intervals.



No. at Risk				
Low target	379	256	233	225
High target	375	249	227	219

Figure 3. Kaplan–Meier Curves for Cumulative Survival.

Data for the survival analysis, which was performed in the intention-to treat population, were censored at 90 days. There was no significant difference in survival between the high-target group and the low-target group (P=0.57 at 28 days; P=0.74 at 90 days).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

ABSTRACT

ProCESS

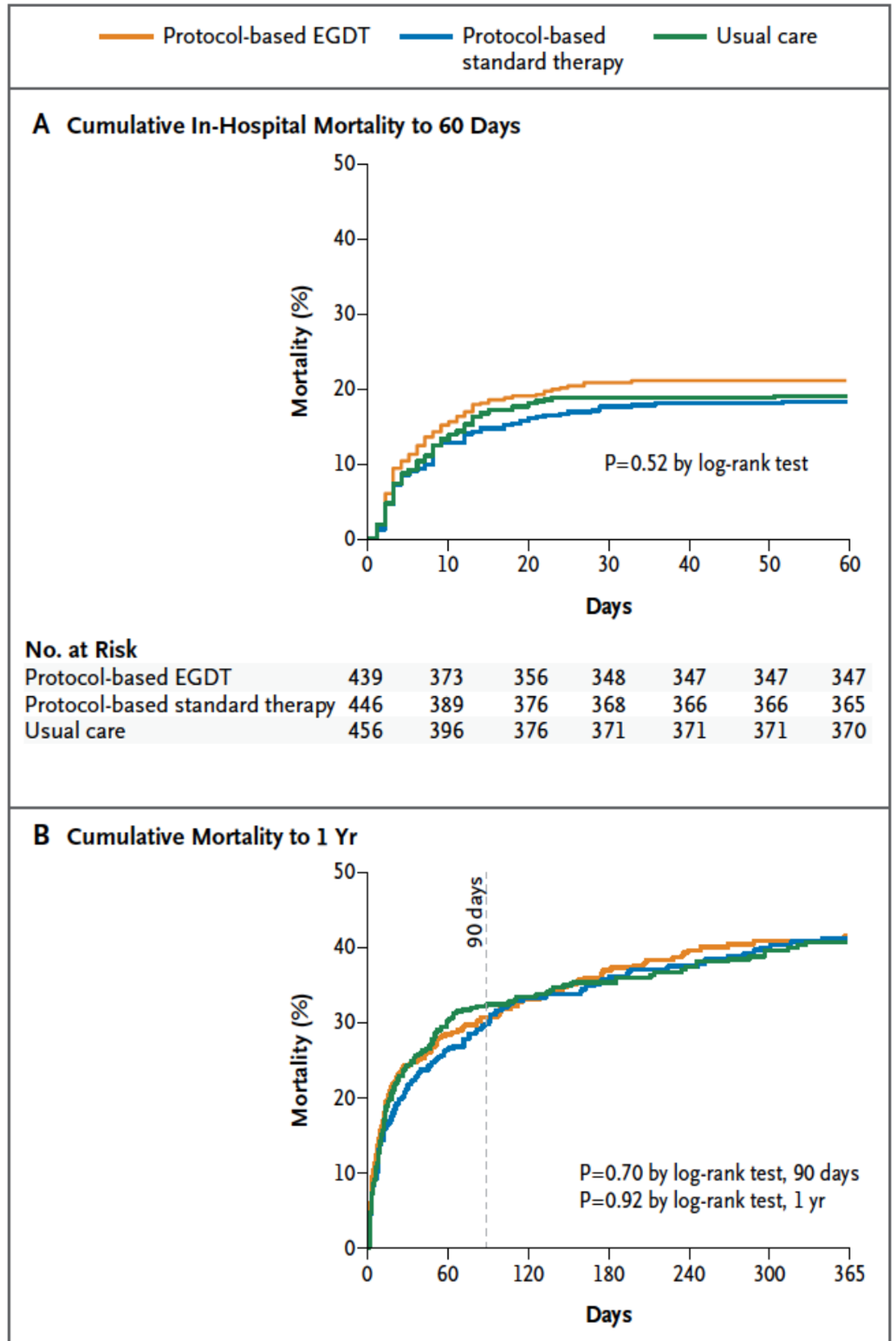


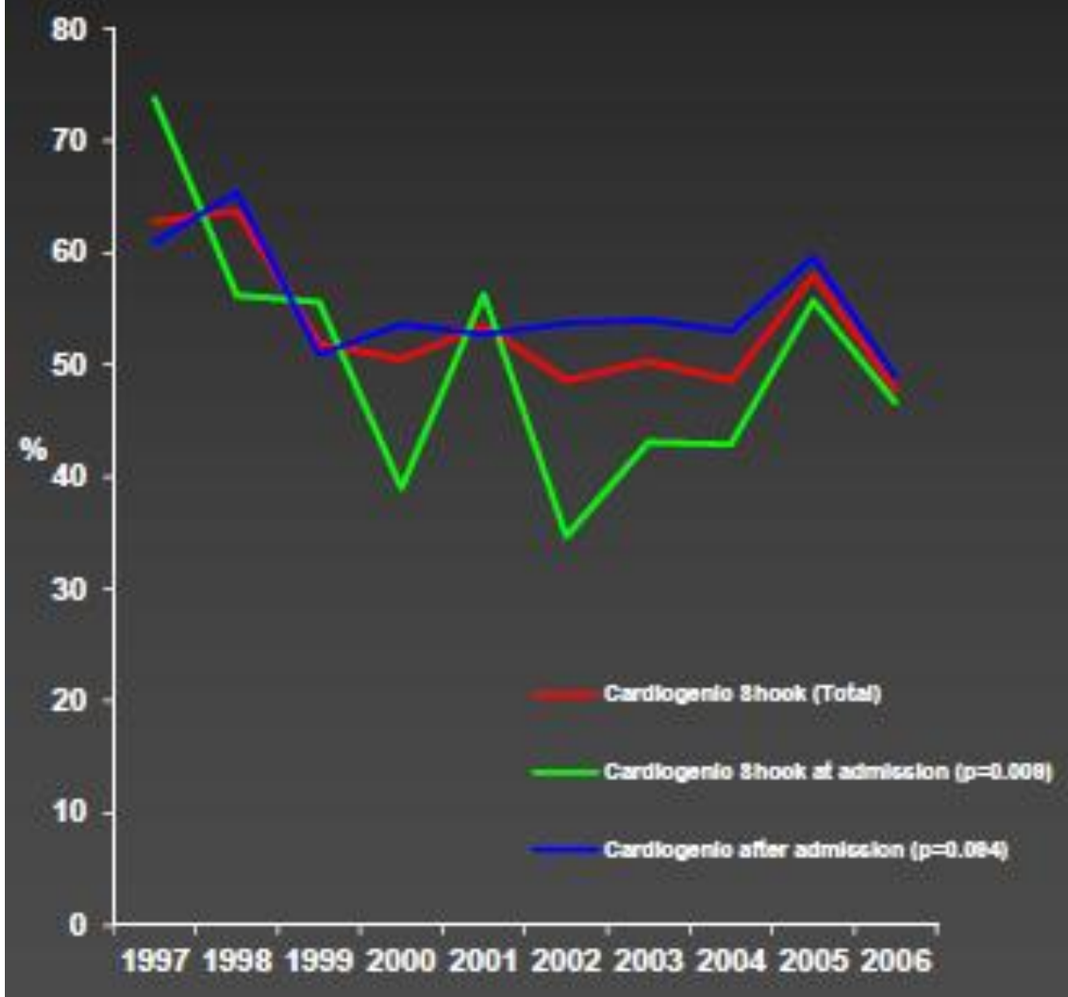
Figure 2. Cumulative Mortality.

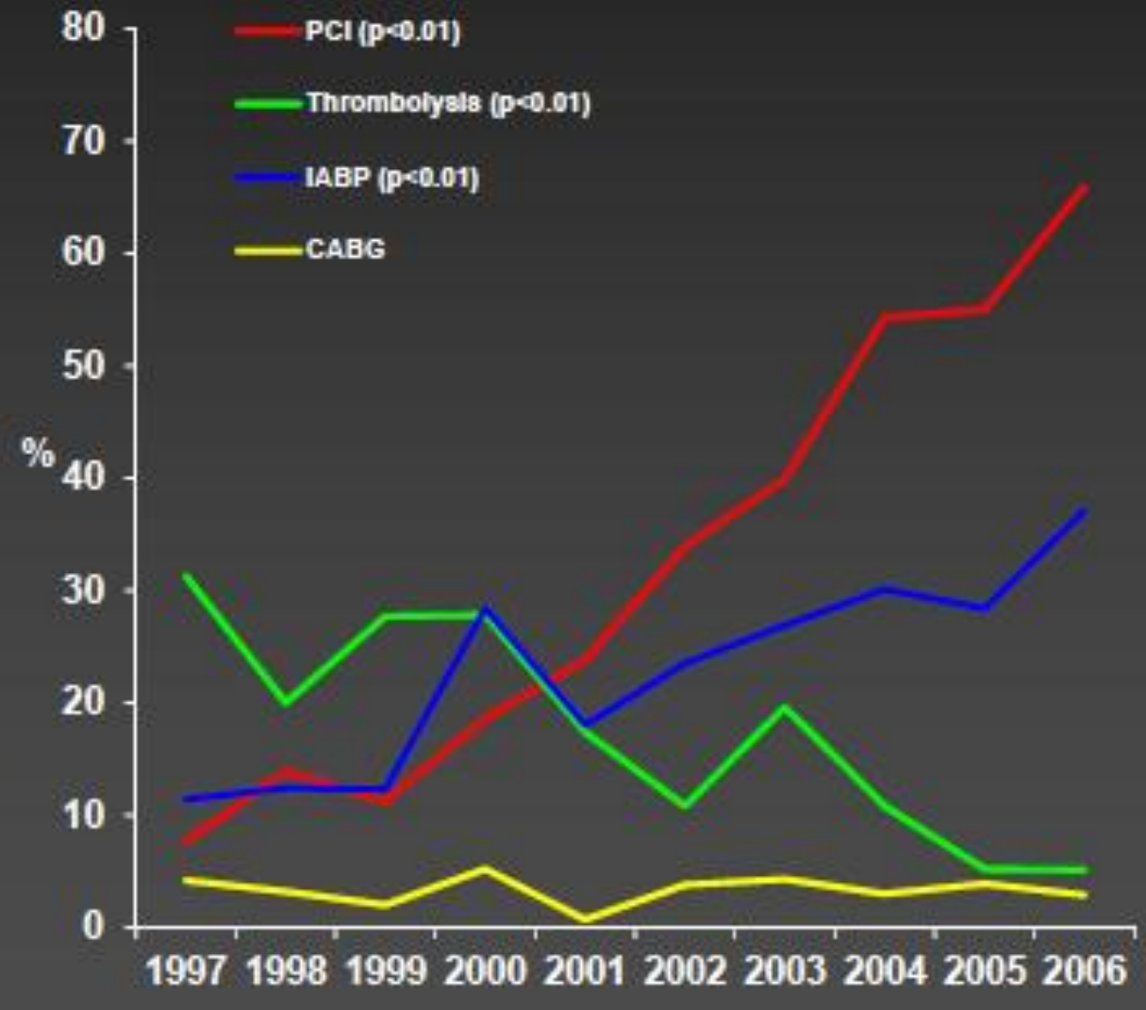
Panel A shows cumulative in-hospital mortality, truncated at 60 days, and Panel B cumulative mortality up to 1 year after randomization.

Cardiogenic Shock: In-hospital Mortality

Registry: 70 of 106 Hospitals in Switzerland

23696 ACS patients -> 1977 with cardiogenic shock (564 at admission; 1413 after admission)





UNIVERSITÄT LEIPZIG
HERZZENTRUM

Jeger et al. Ann Int Med 2008;149:618-626

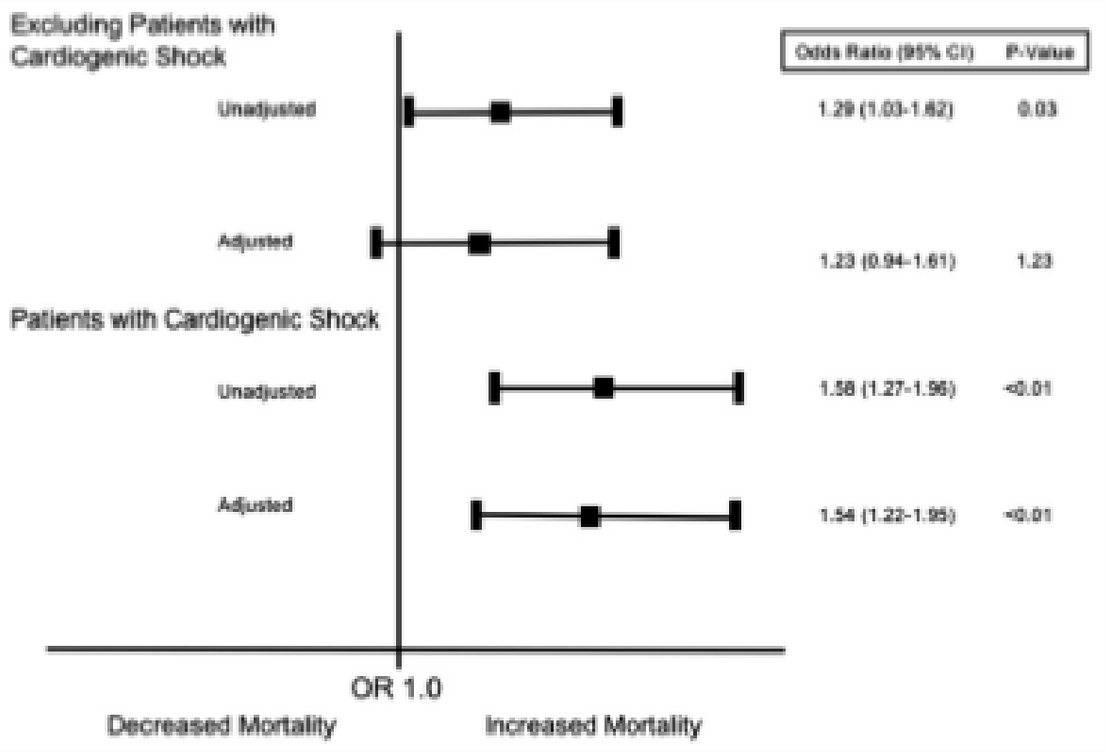
STEMI with cardiogenic shock: single or. multivessel PCI?

National Cardiovascular Data Registry

In hospital outcomes shock pts.

	1 vessel PCI	Multi-vessel PCI	p value
Patients	2654	433	
Death	27.8%	36.5%	<0.01
Death in lab	2.7%	5.8%	0.25
Stroke	1.5%	2.6%	0.18
Bleeding	12.5%	13.8%	0.44
Renal failure	7.1%	9.7%	0.03

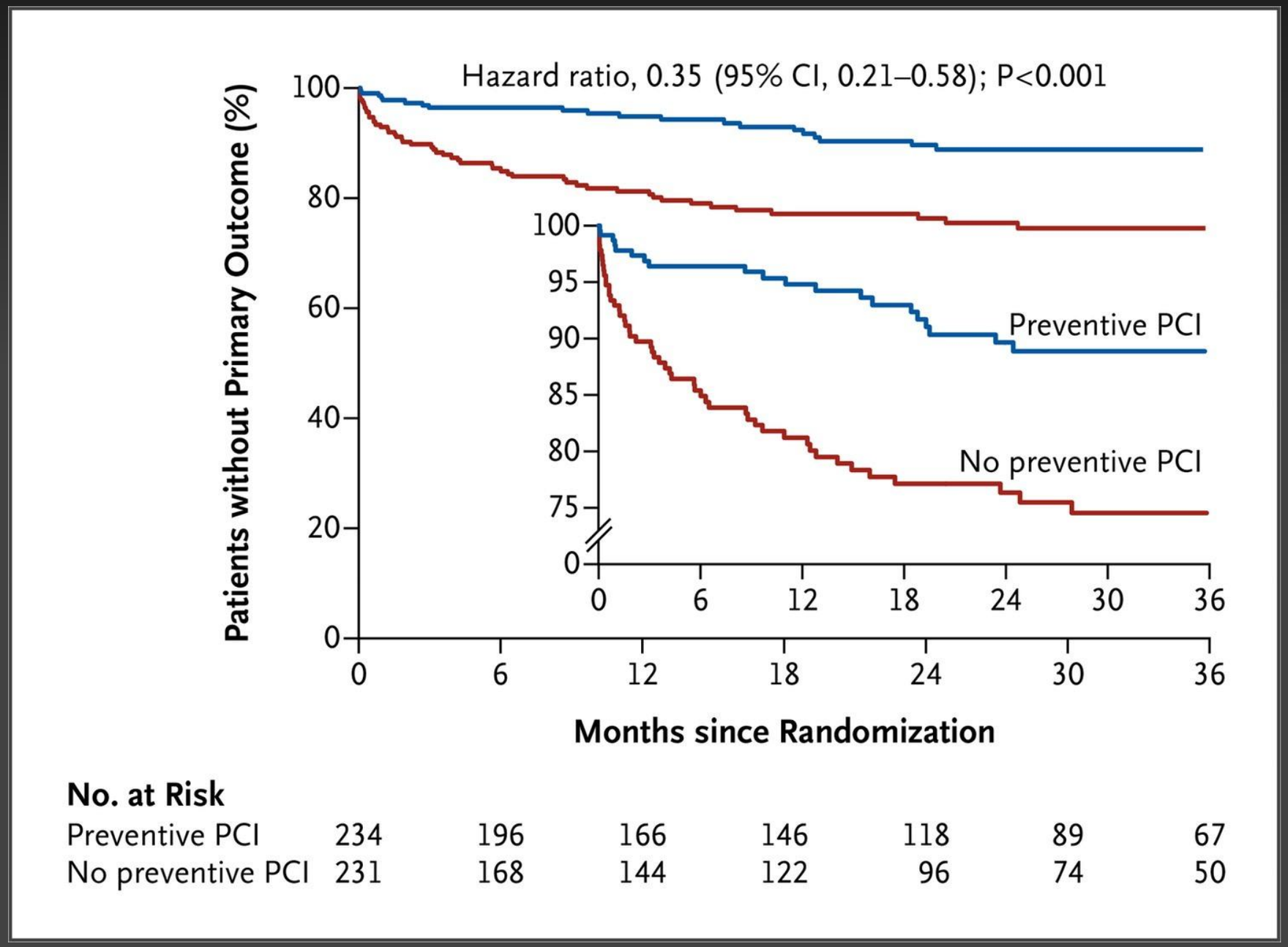
Odds ratios mortality



Multi- vs. 1-vessel PCI

MA Cavender et al.
Am J Cardiol 2009;104: 507-513

Multivessel PCI or Culprit Lesion Only PCI



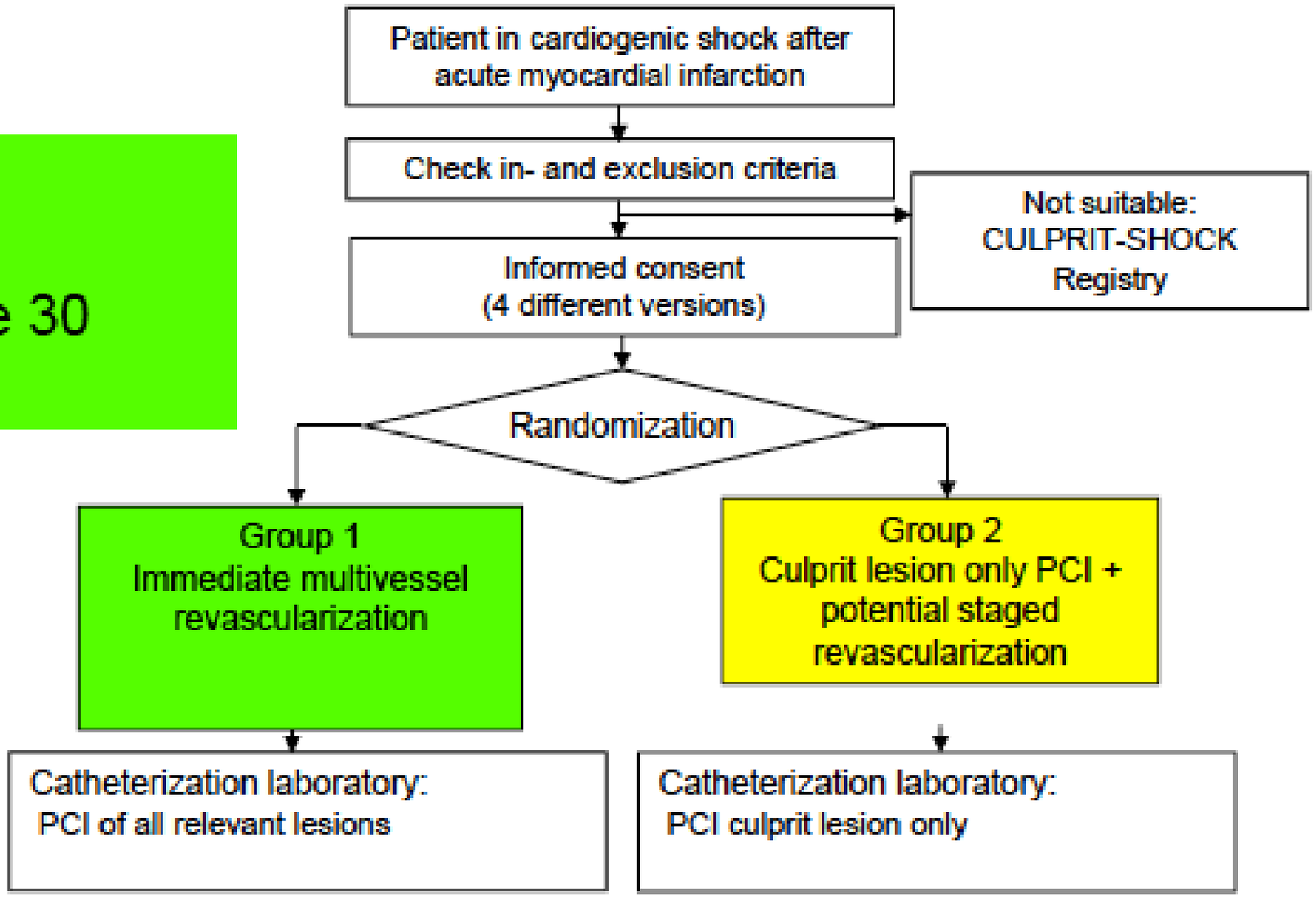
No. at Risk

Preventive PCI	234	196	166	146	118	89	67
No preventive PCI	231	168	144	122	96	74	50

Wald DS et al. N Engl J Med 2013;369:1115-1123.

CULPRIT-SHOCK Trial – Study Flow

Primary Endpoint:
Mortality and/or severe renal failure 30 days



Systemic microcirculation

Sidestream Dark Field imaging

14 Megapixel sensor, pixelsize 1,4 µm

Light weight (150 grams)

Optics /sensor resolution optimized

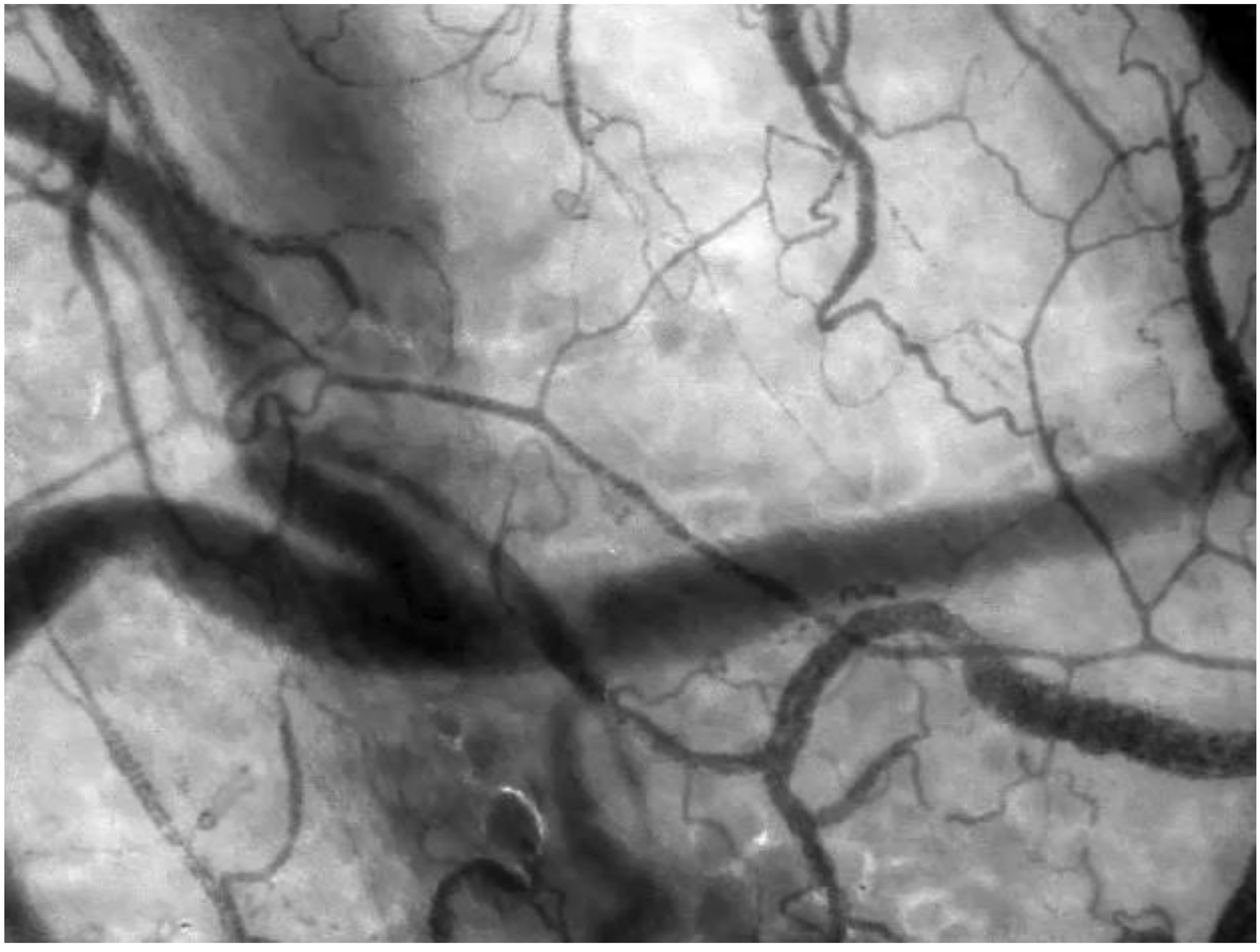
Camera and illumination PC control

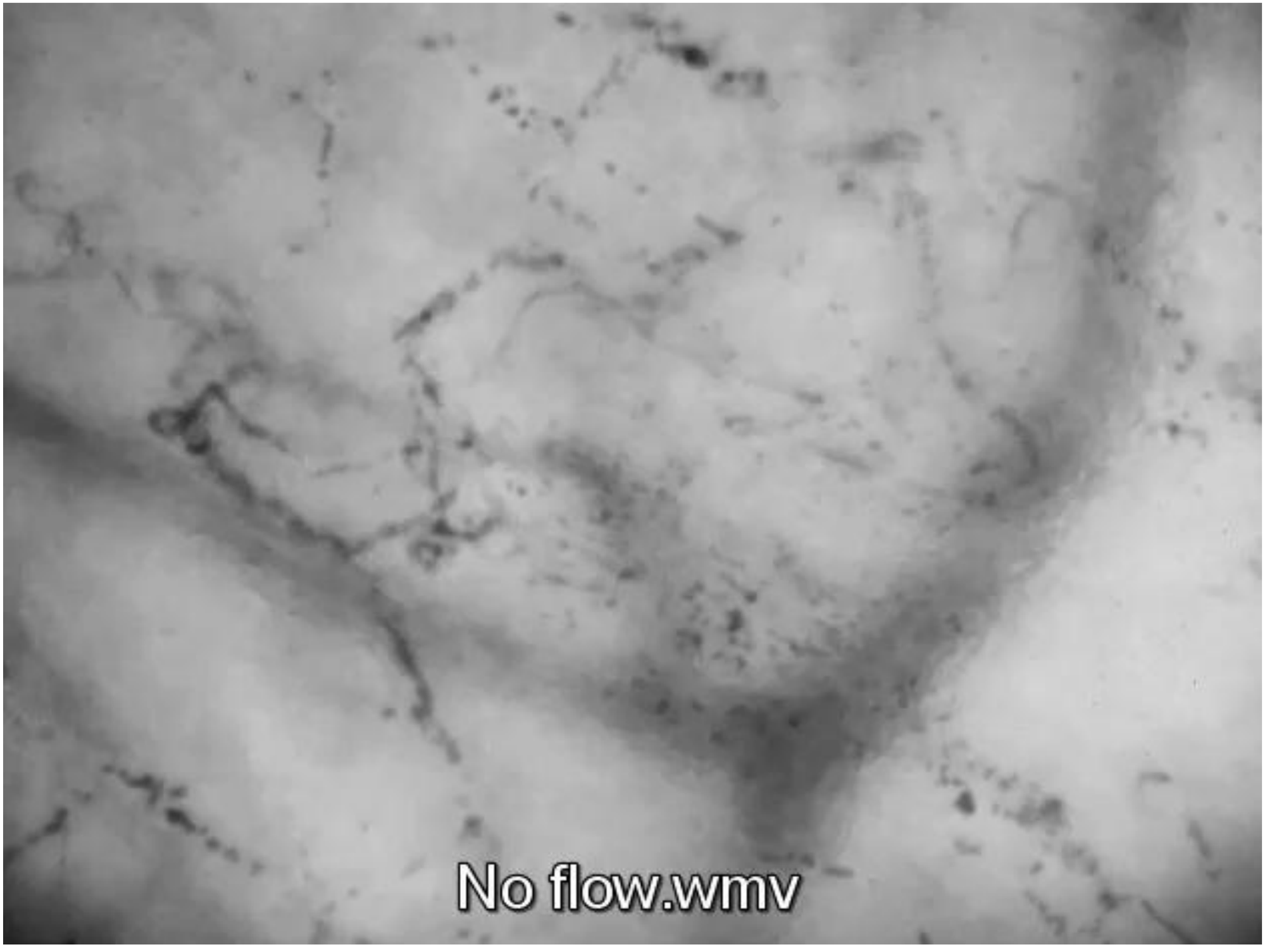
Stepping motor focus control

Quality control of image acquisition

Automatic image quantification

Adapted from C Ince




No flow.wmv

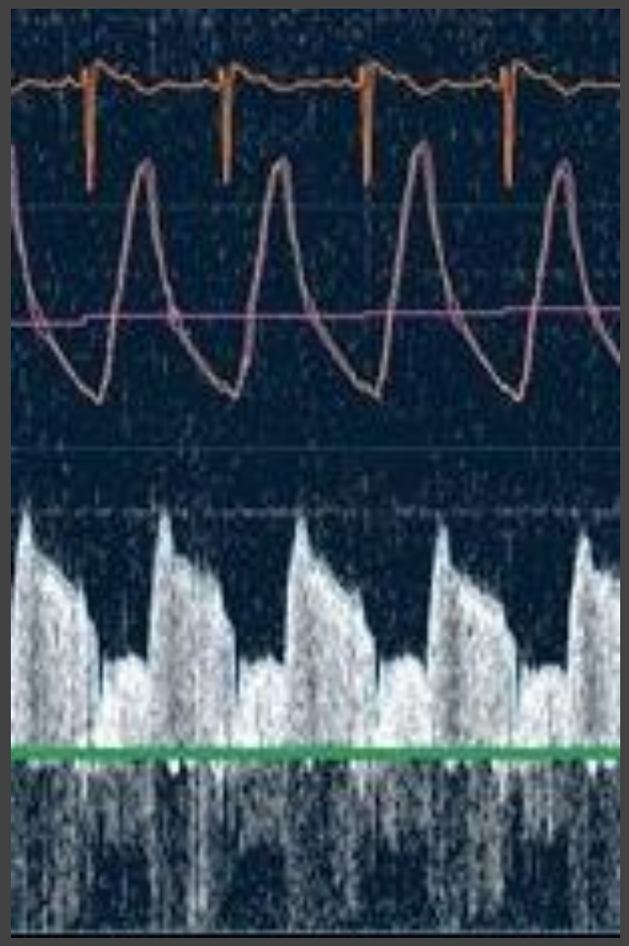

Cardiogenic shock.wmv

Microcirculation substudy

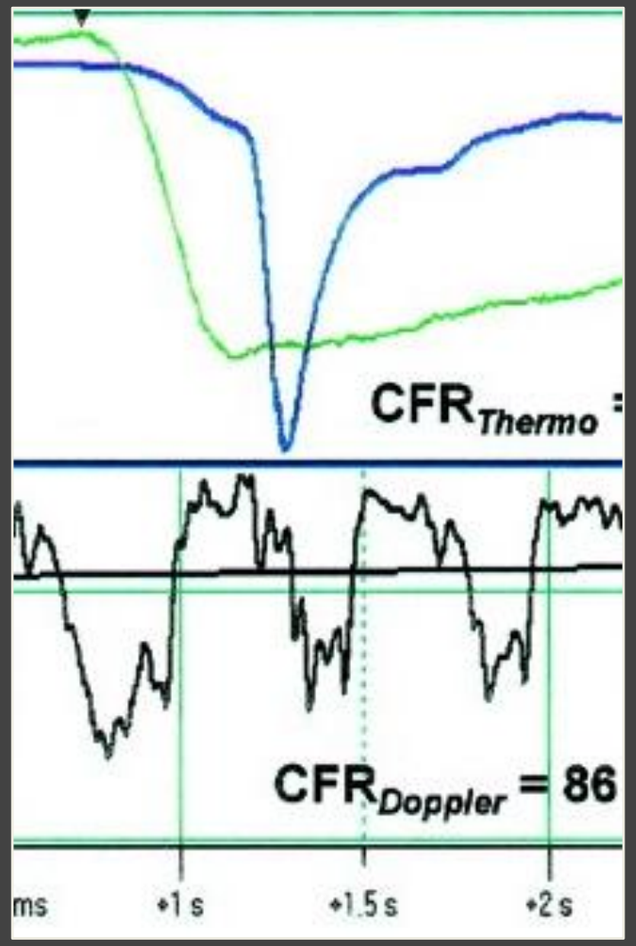
- Recent technological advances allow intravascular and noninvasive assessment of microvascular function

Myocardial

Doppler

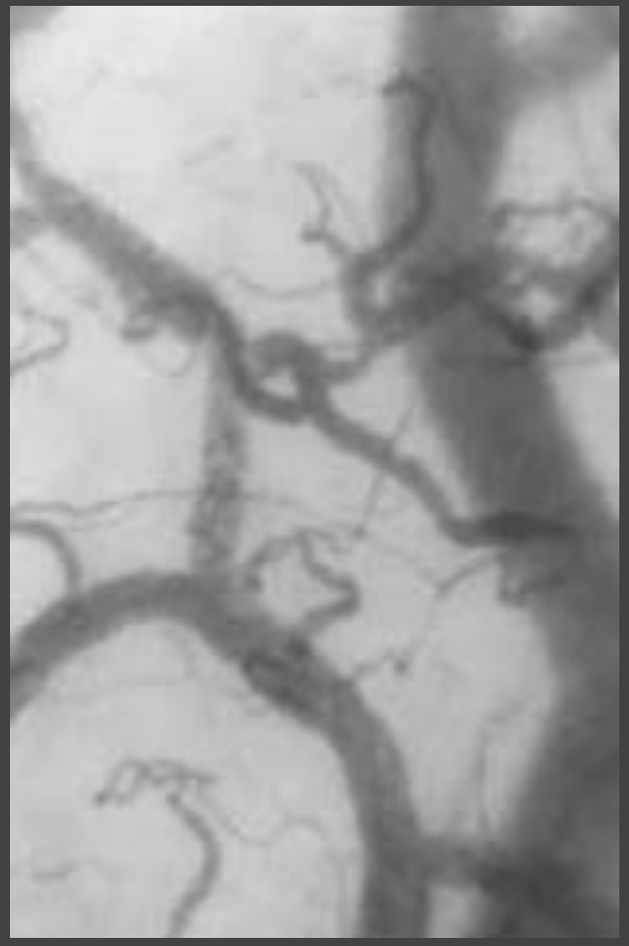


Thermodilution



Systemic

Sidestream Darkfield



- **Coronary microvascular dysfunction due to essential thrombocythemia and polycythemia vera: the missing piece in the puzzle of their increased cardiovascular risk?**

- LAD - CFR by TTDE at rest, and during adenosine infusion
- The mutation of JAK2 gene was associated with abnormal CFR.

	ET	PV	CONTROLS
CFR	2.9+/-0.94	2.2+/-0.7	3.8+/-0.7
CFR <2.5	38.5%	68.2%	4.1%
CFR < 2.0	15.4%	40.9%	0

- Am J Hematol. 2015 Feb;90(2):109-13.

The Clinical Importance of the Microcirculation

- Major determinant of myocardial blood flow
- Explains why anatomy cannot predict FFR
- Explains why non-hyperaemic indices cannot predict FFR
- Significant impact on prognosis
- Critically important in shock states - ongoing trials
- Possible target for new therapeutic agents and strategies especially in STEMI

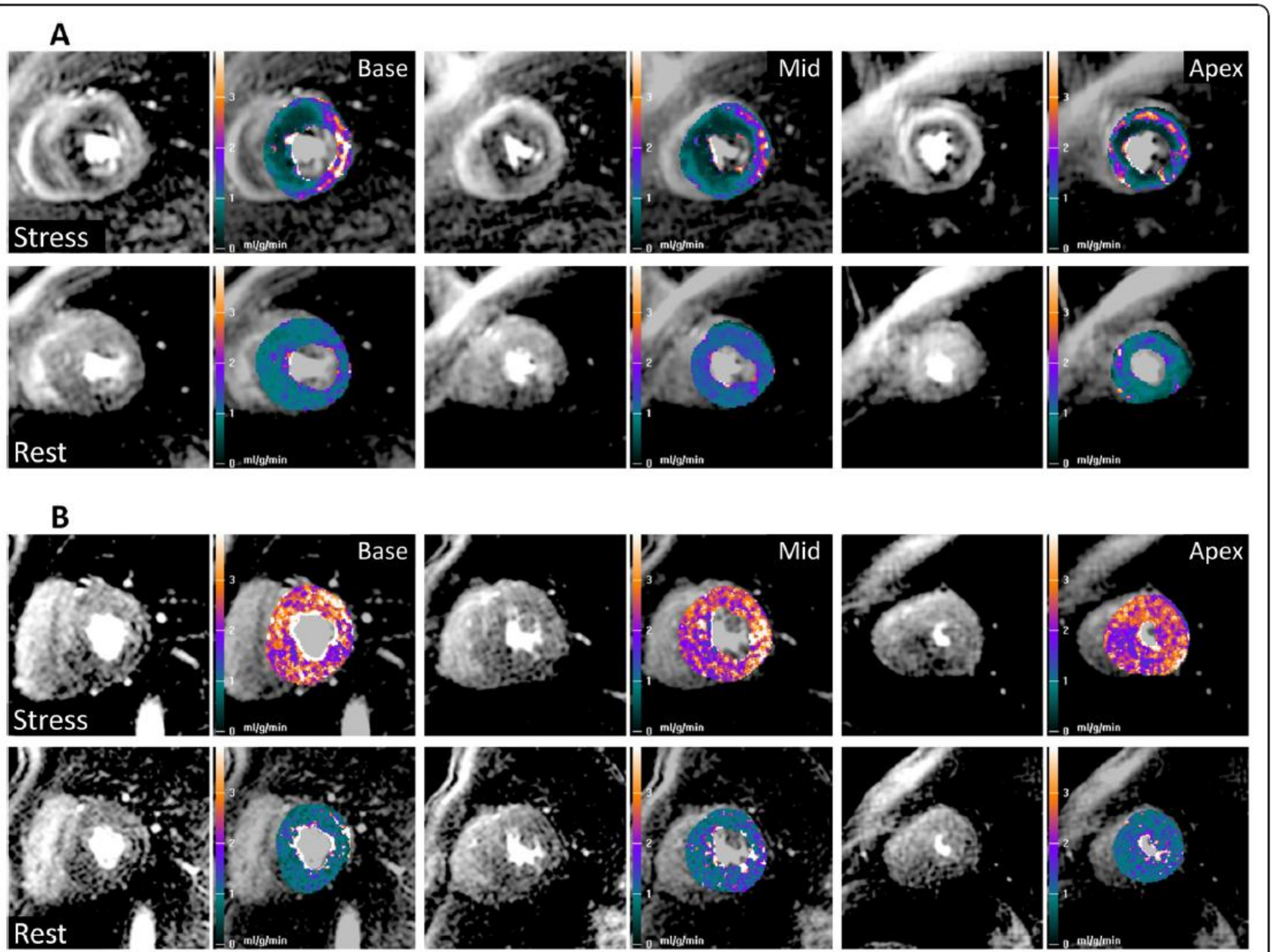


Figure 2 Examples of results of pixel-wise quantitative first-pass cardiovascular magnetic resonance perfusion imaging (ml/g/min) for (A) severe microvascular dysfunction and (B) non-severe patients. Stress images are shown on the top row and rest images on the bottom row for identical basal, mid-ventricular and apical slices together with their corresponding pixel maps.