Index of Microcirculatory Resistance: *The Basics*

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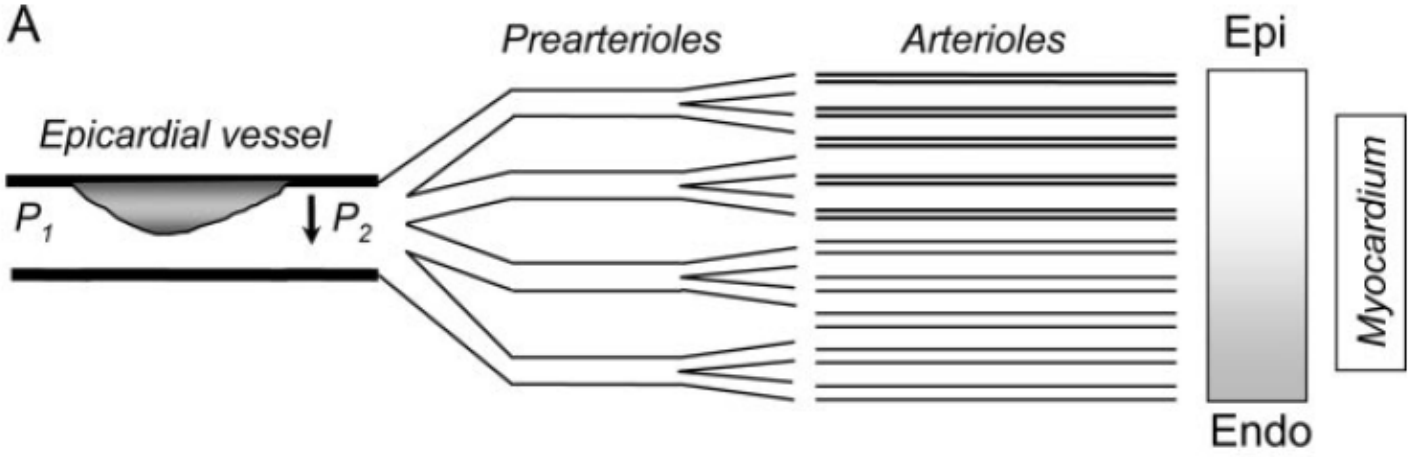
Disclosure Statement of Financial Interest

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, NHLBI
Consulting Fees/Honoraria	Medtronic
Major Stock Shareholder/Equity	
Royalty Income	
Ownership/Founder	
Intellectual Property Rights	
Other Financial Benefit	Minor stock options: HeartFlow

Assessment of the Microvasculature

Diagnostic Challenge

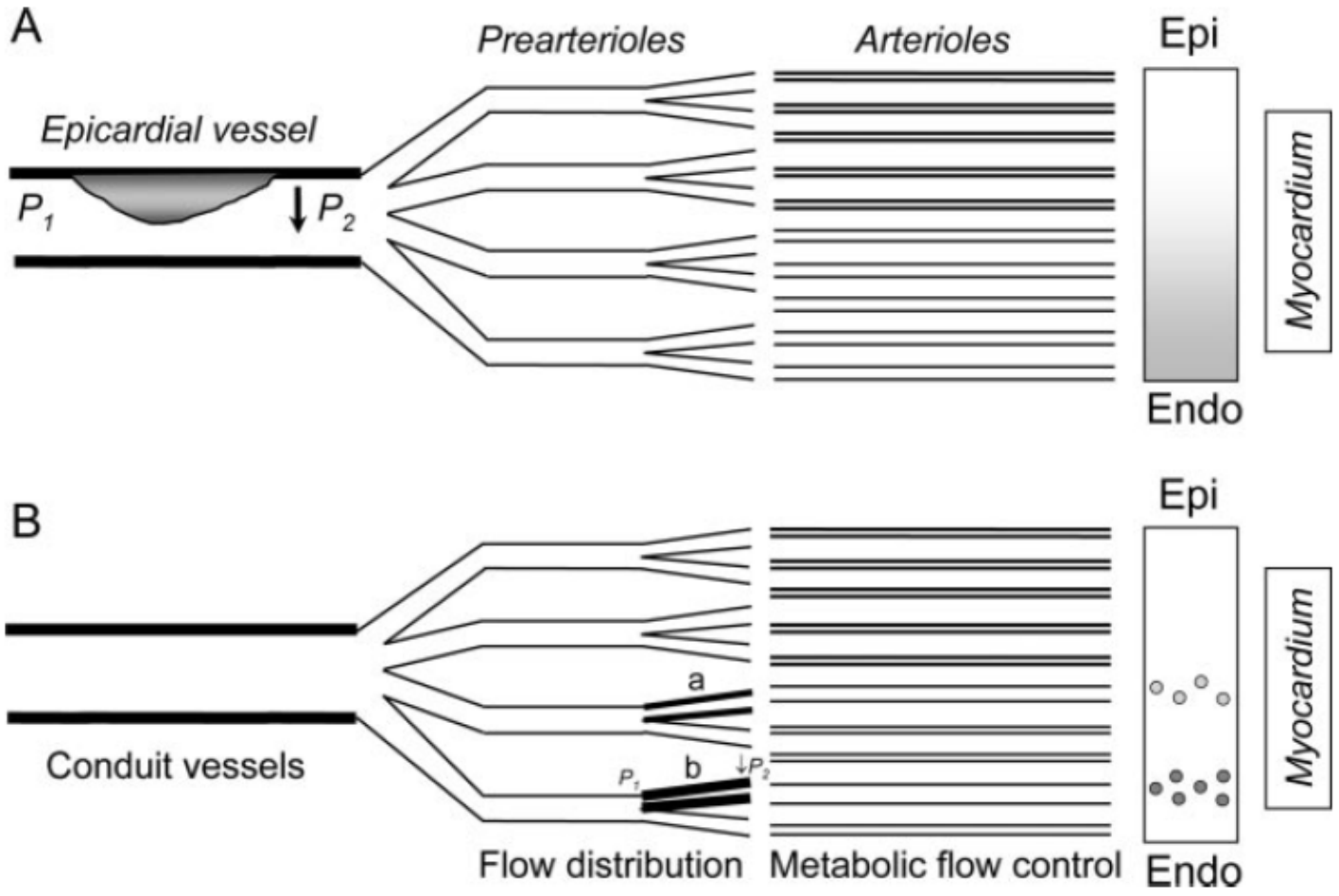


Epicardial CAD

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

Assessment of the Microvasculature

Diagnostic Challenge



Epicardial CAD

Microvascular Dysfunction

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

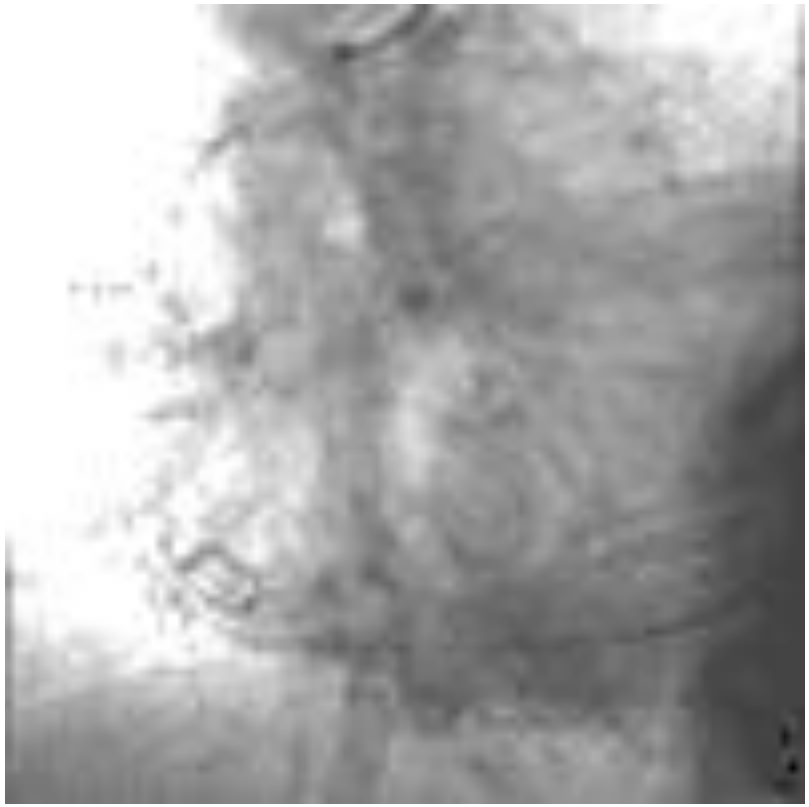
Assessment of the Microvasculature

- Extremely challenging diagnosis
  - Heterogeneous patient population
  - Variety of pathogenetic mechanisms
  - Poor anatomic resolution
  - Potentially patchy nature of the disease

- Therefore, assessment of the microvasculature is primarily *functional* and not *anatomic*

Evaluating the Microcirculation…
…in the Cath Lab

TIMI Myocardial Perfusion Grade:



Evaluating the Microcirculation…
…in the Cath Lab

TIMI Myocardial Perfusion Grade:

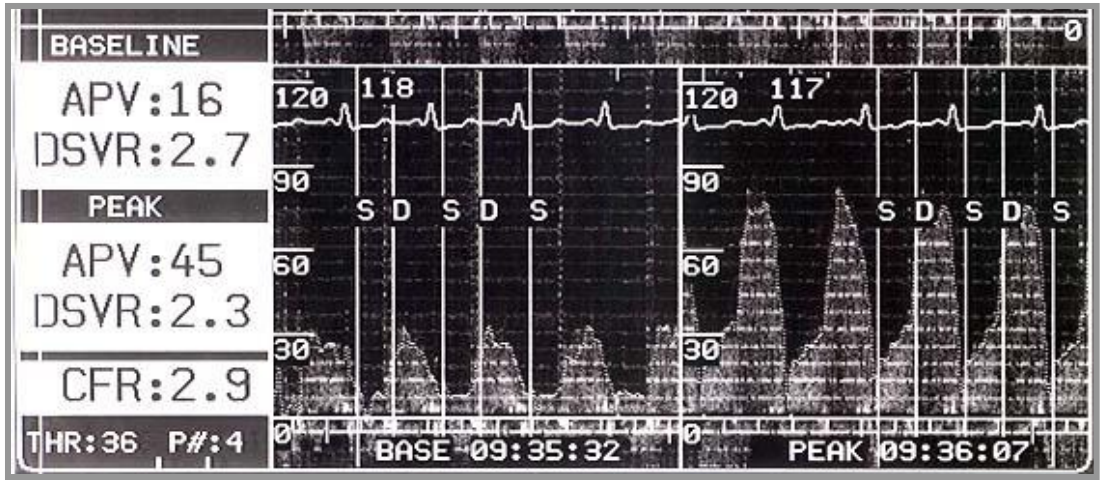
- Easy to obtain
- Specific for microvasculature
- Predictive of outcomes in large studies

Drawbacks:

- Qualitative
- Interobserver variability
- Not as useful in smaller studies

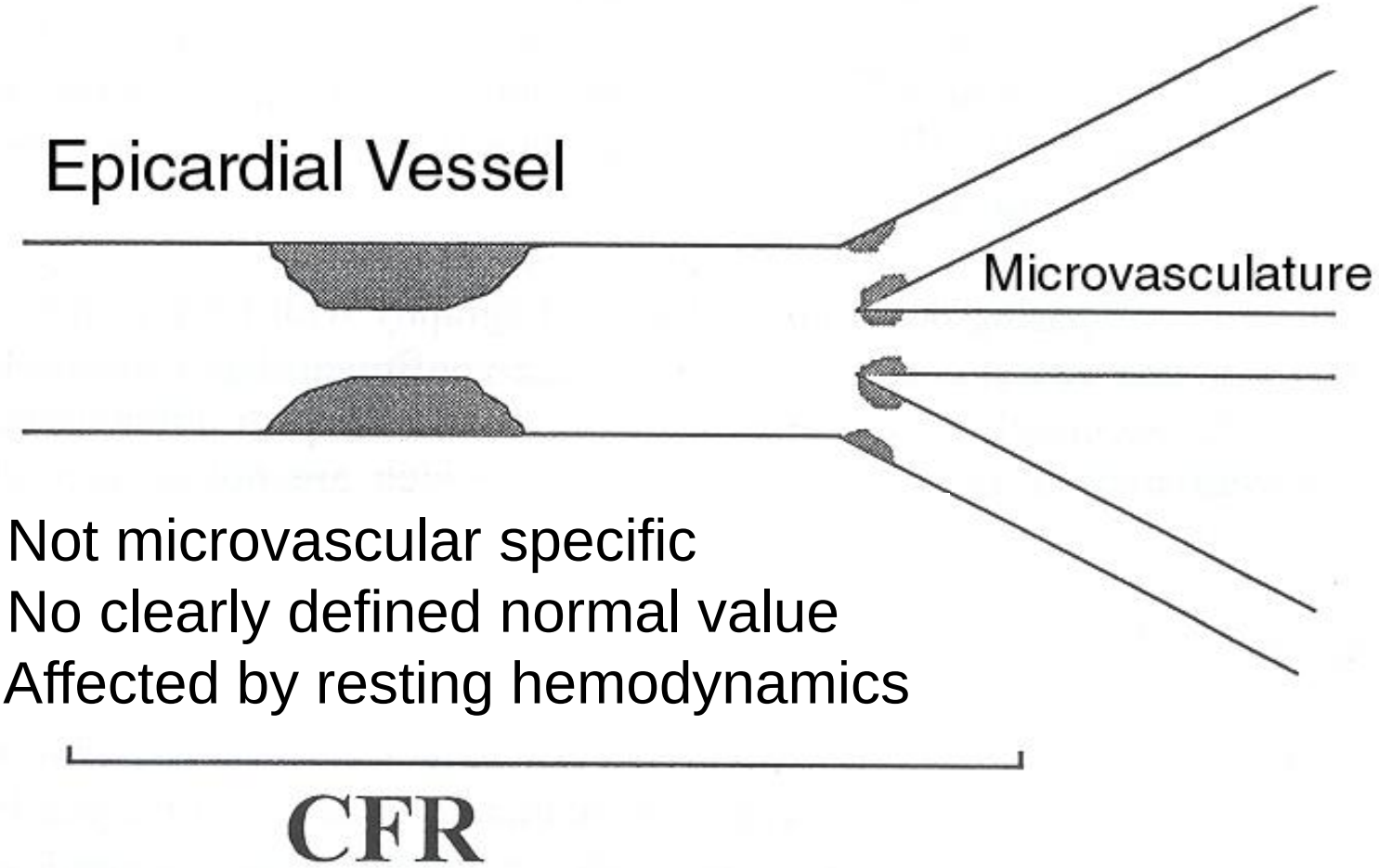
Doppler Wire Coronary Flow Reserve

$$CFR = \frac{Hyperemic\ Flow}{Resting\ Flow}$$



Coronary Wire-Based Assessment

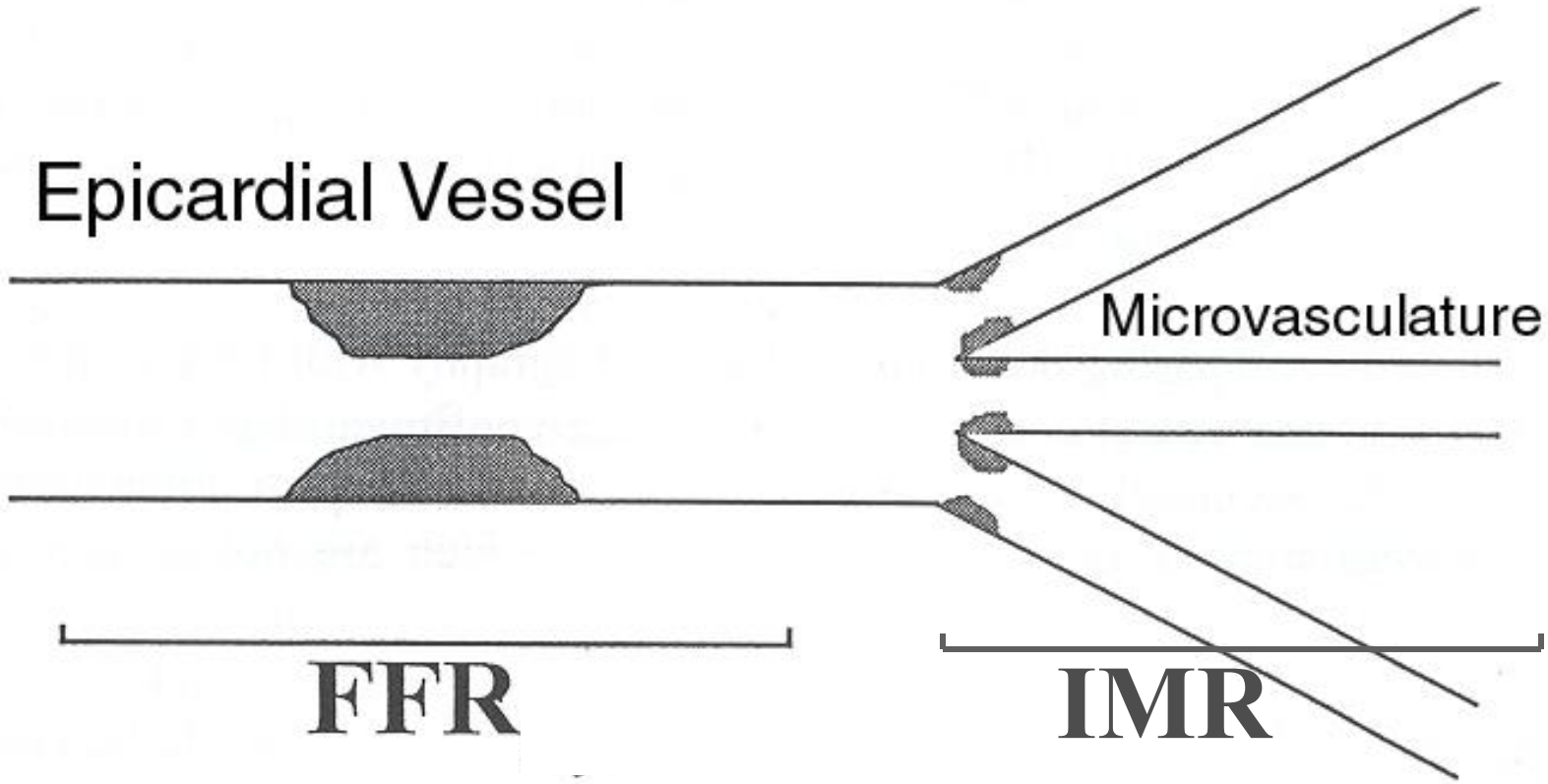
Coronary Flow Reserve



- Not microvascular specific
- No clearly defined normal value
- Affected by resting hemodynamics

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

Index of Microcirculatory Resistance

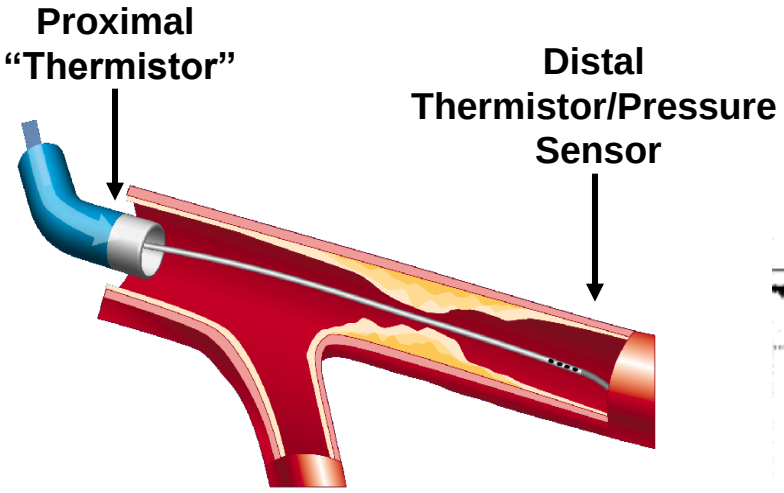


Index of Microcirculatory Resistance

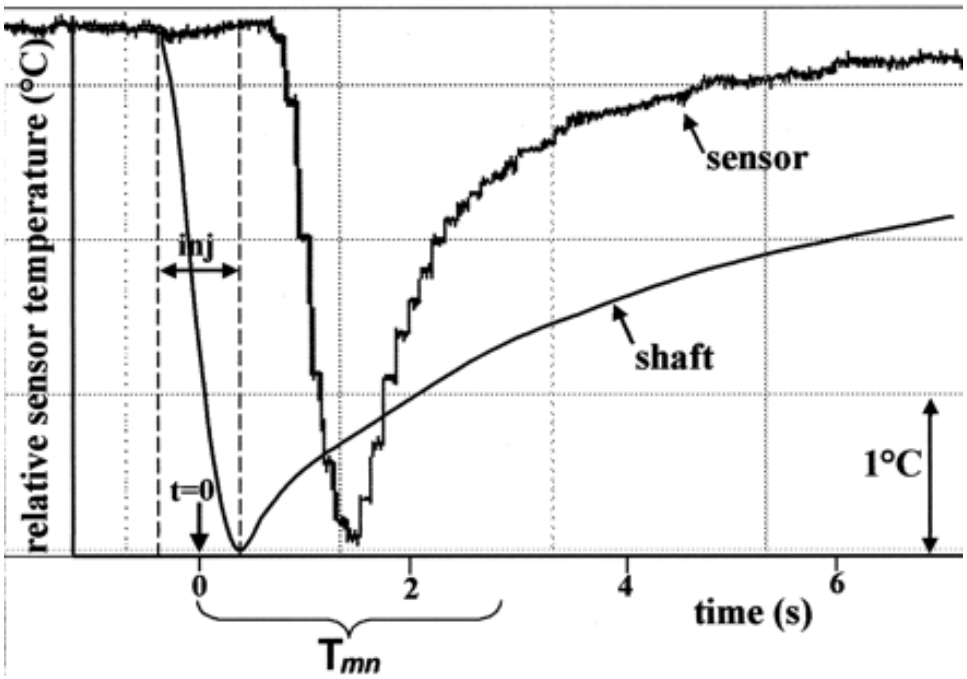
Potential Advantages:

- Readily available in the cath lab
- Specific for the microvasculature
- Quantitative and reproducible
- Predictive of outcomes

Estimation of Coronary Flow



Calculation of mean transit time



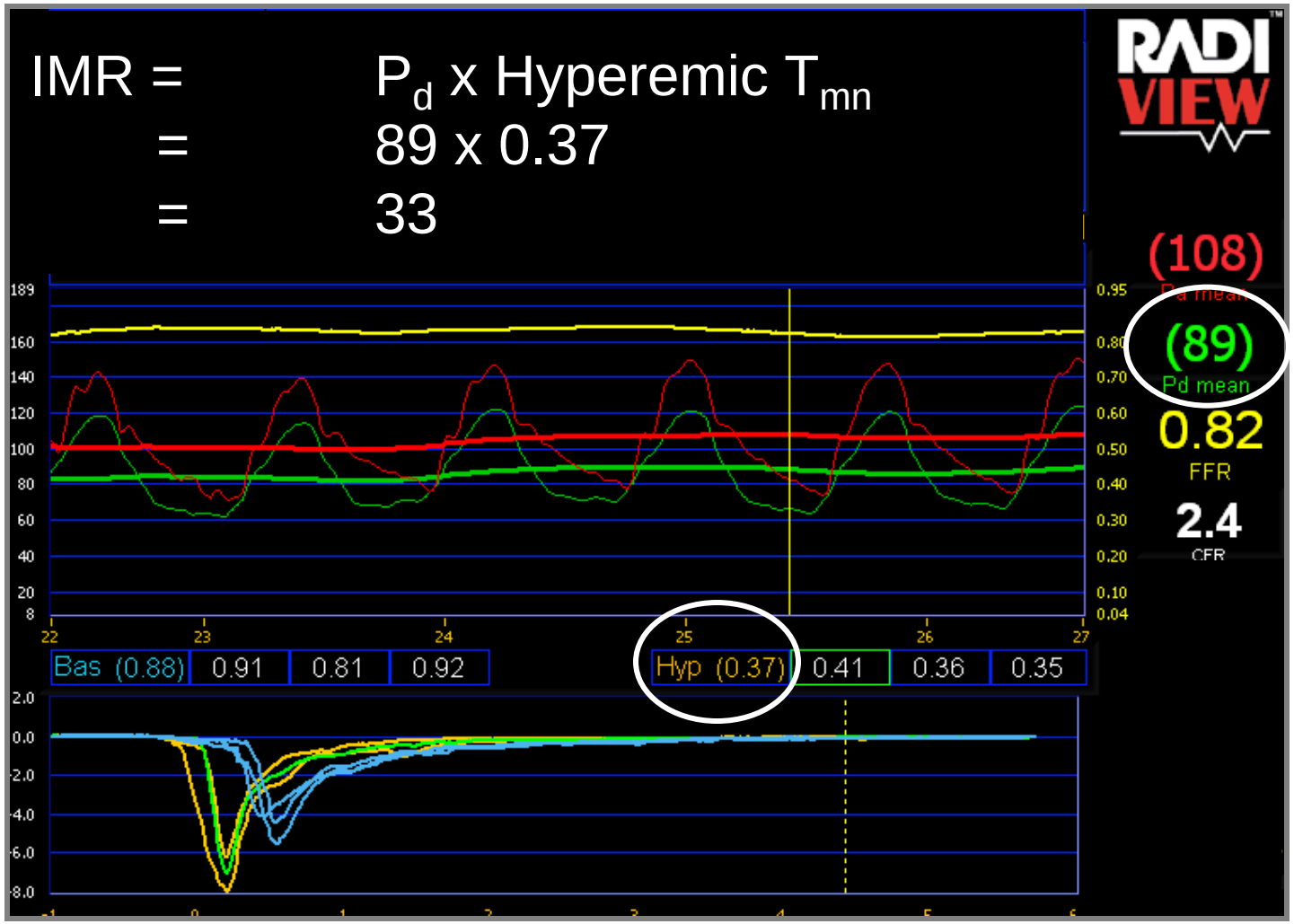
De Bruyne, et al. Circulation 2002;104:2003

Derivation of IMR:

- Resistance = Δ Pressure / Flow
- Δ Pressure = P_d-P_v Flow $\cong$ 1 / T_{mn}
- IMR = P_d-P_v / (1 / T_{mn})
- IMR = P_d x T_{mn} ***at maximal hyperemia…***

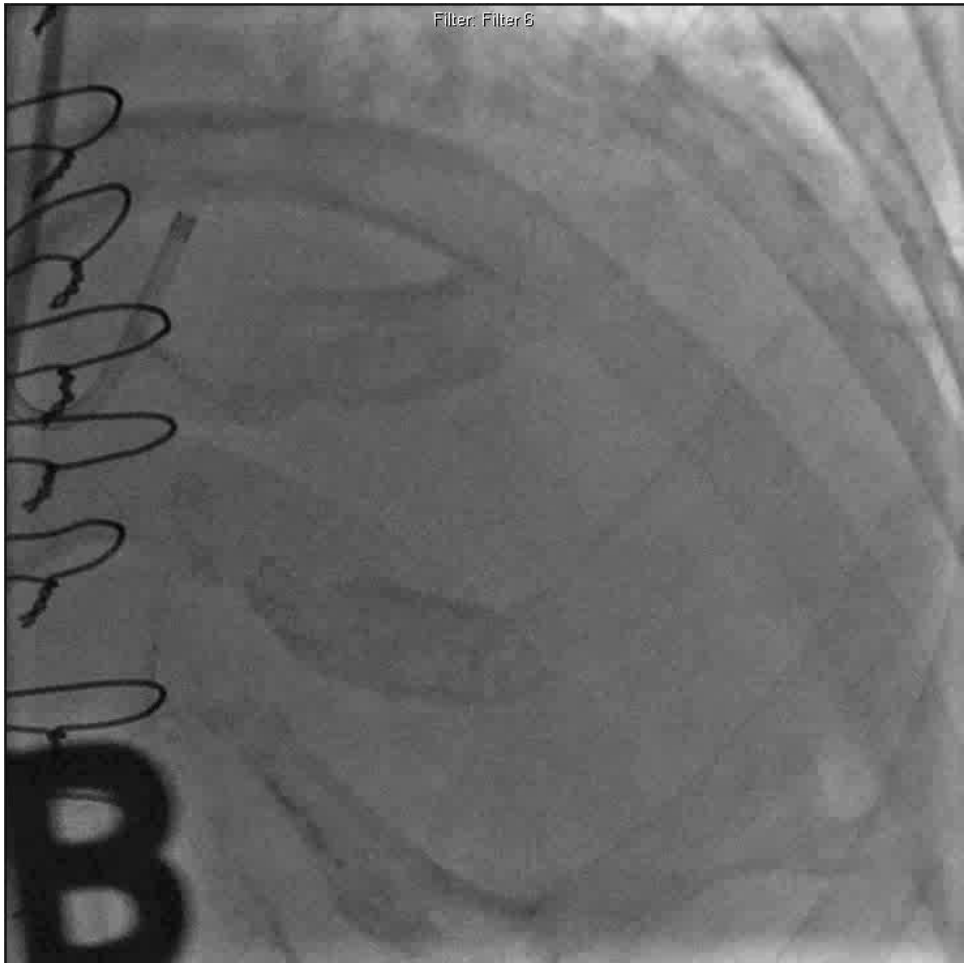
Circulation 2003;107:3129-3132.

Practical Measurement of IMR



IMR Case Example

Cardiac transplant recipient enrolled in study evaluating ACE inhibition



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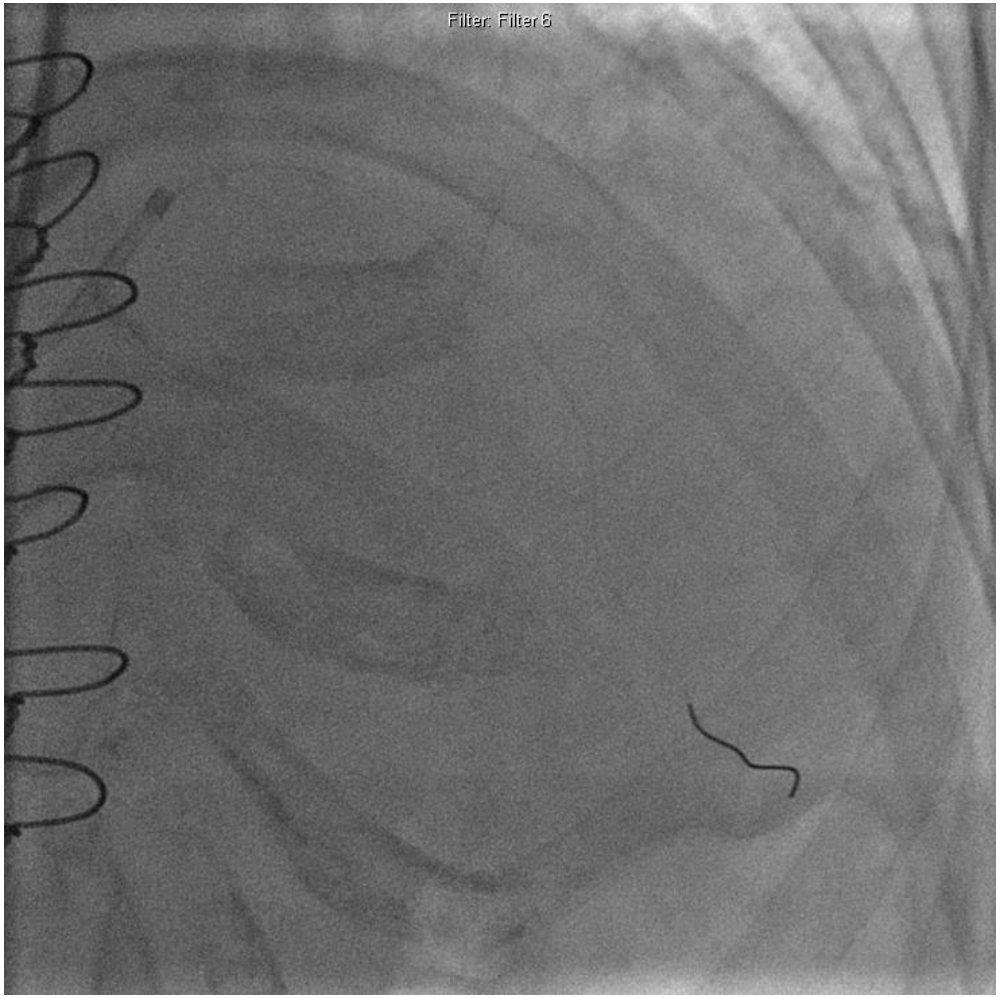


Accessing IMR

System

↓

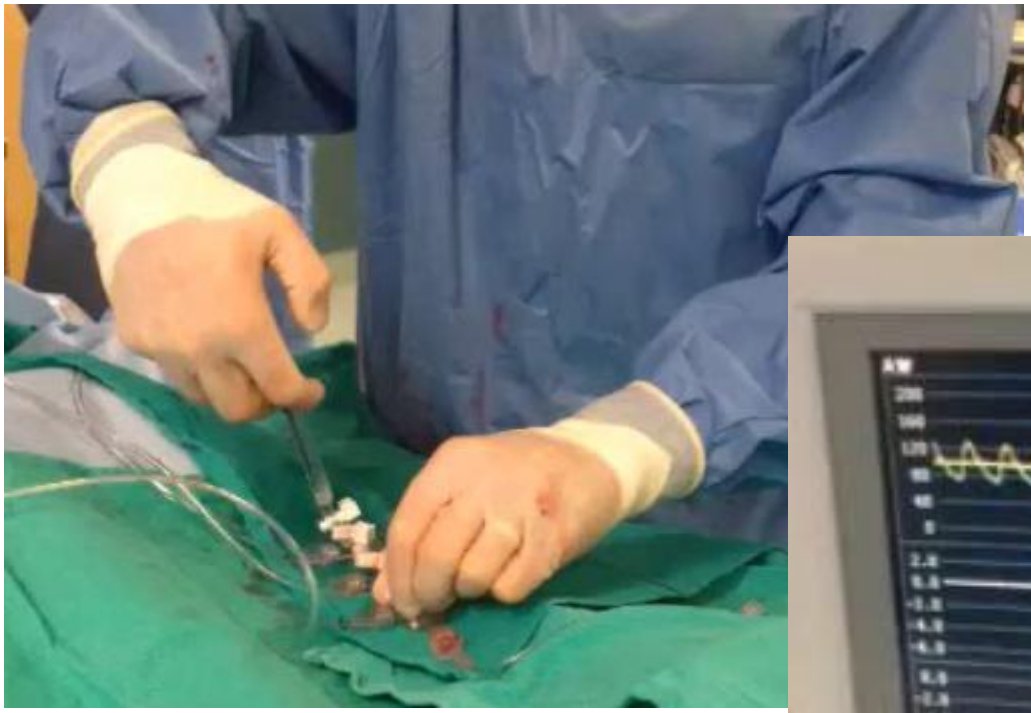
Options

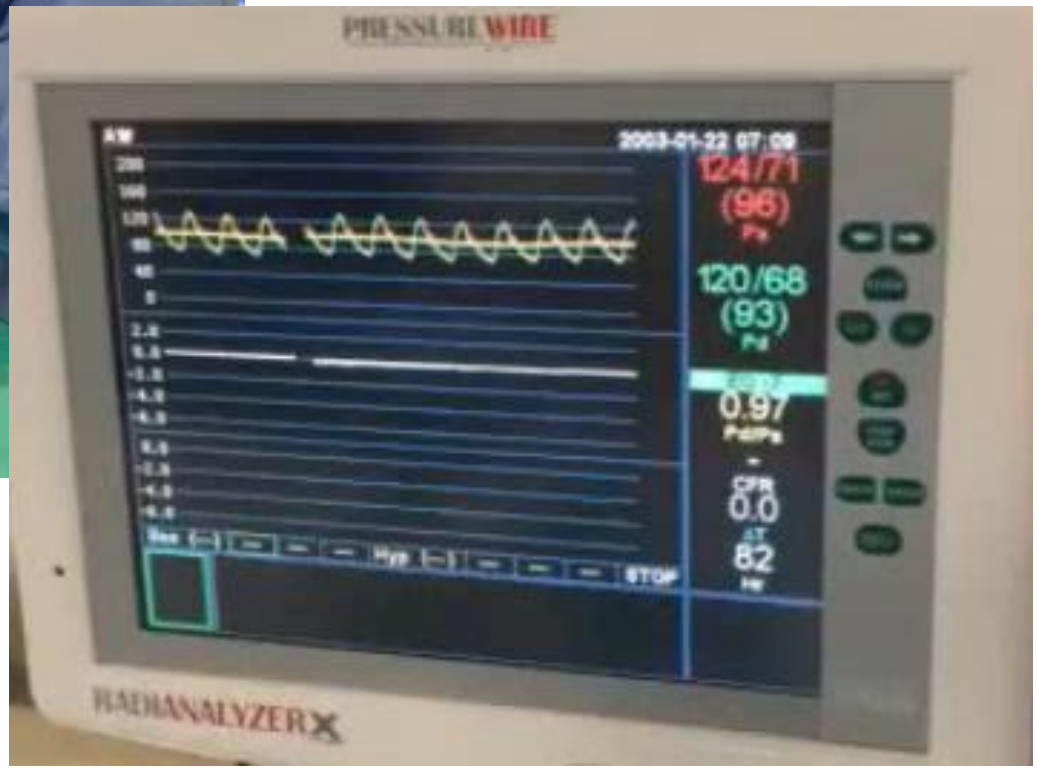
↓

CFR

Flushing the System

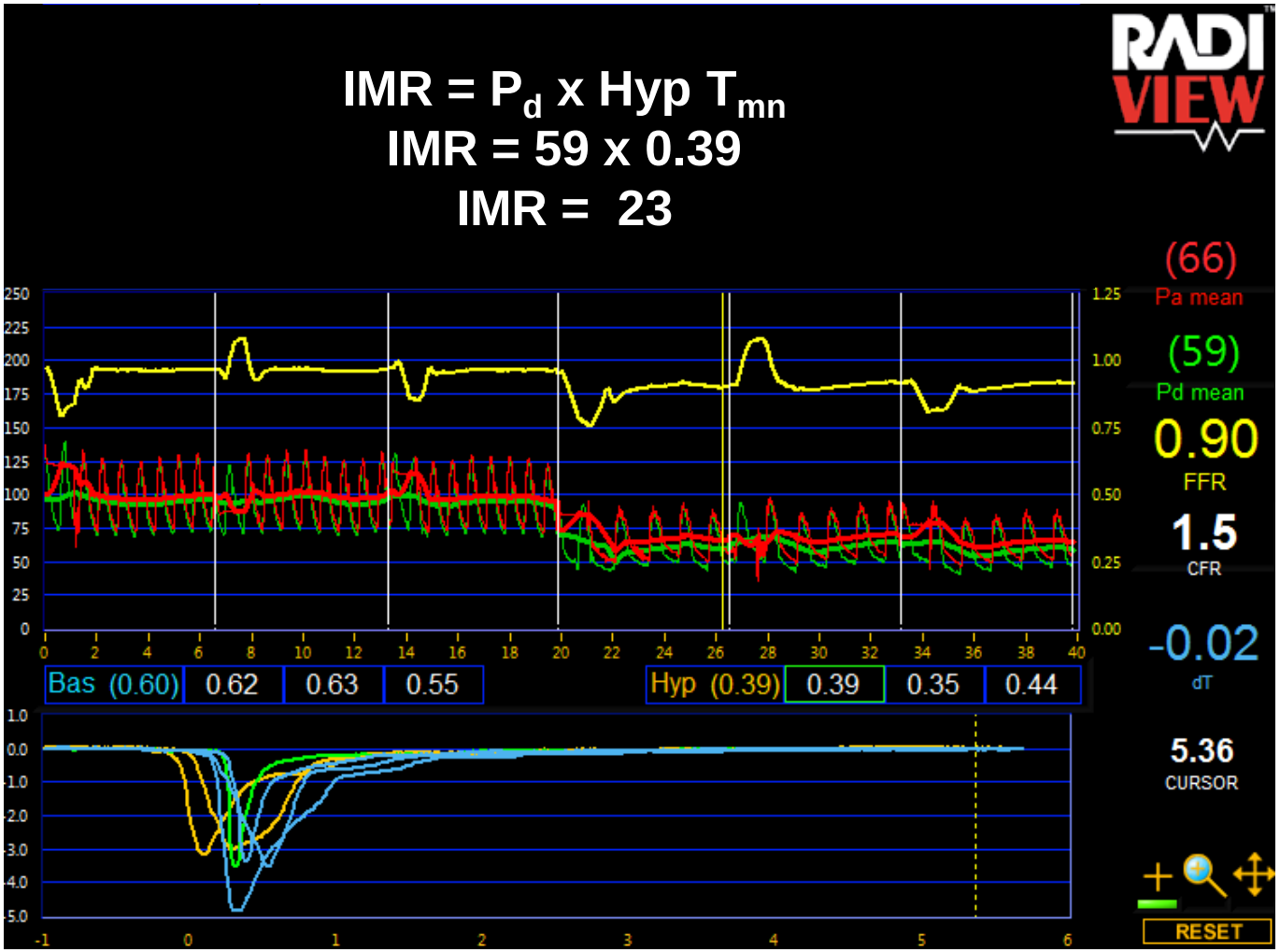
Resting T_{mn} Measurements



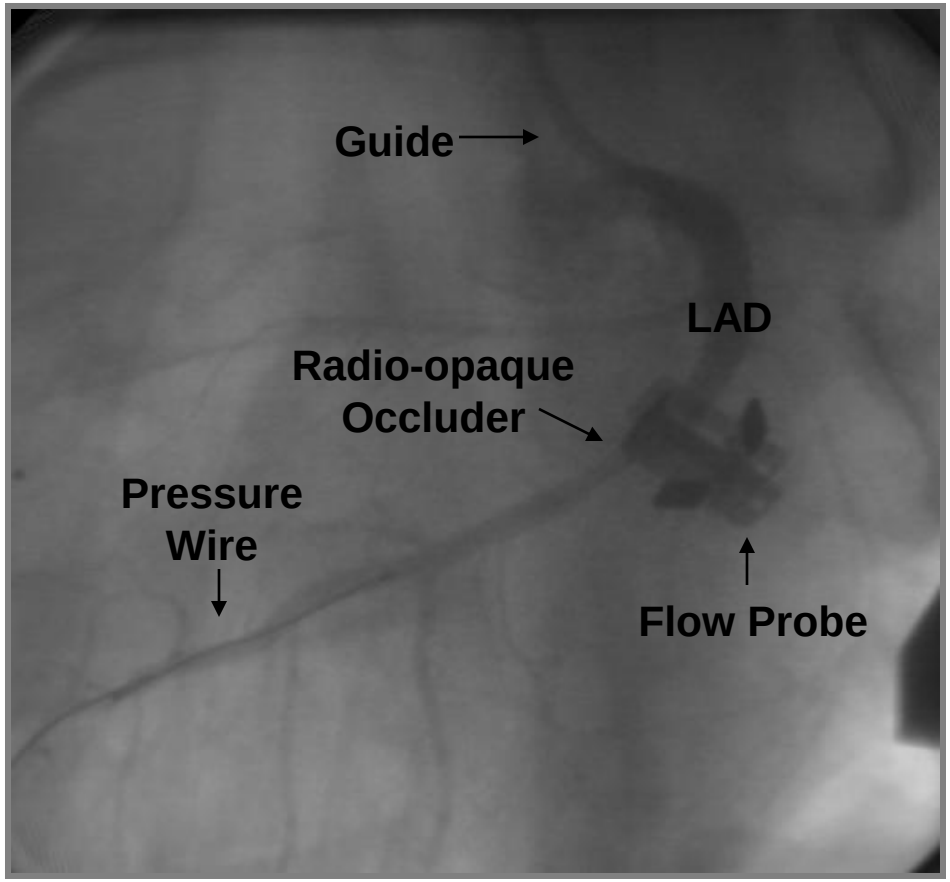


Hyperemic T_{mn} Measurements

Calculating IMR



Animal Validation of IMR



Circulation 2003;107:3129-3132.

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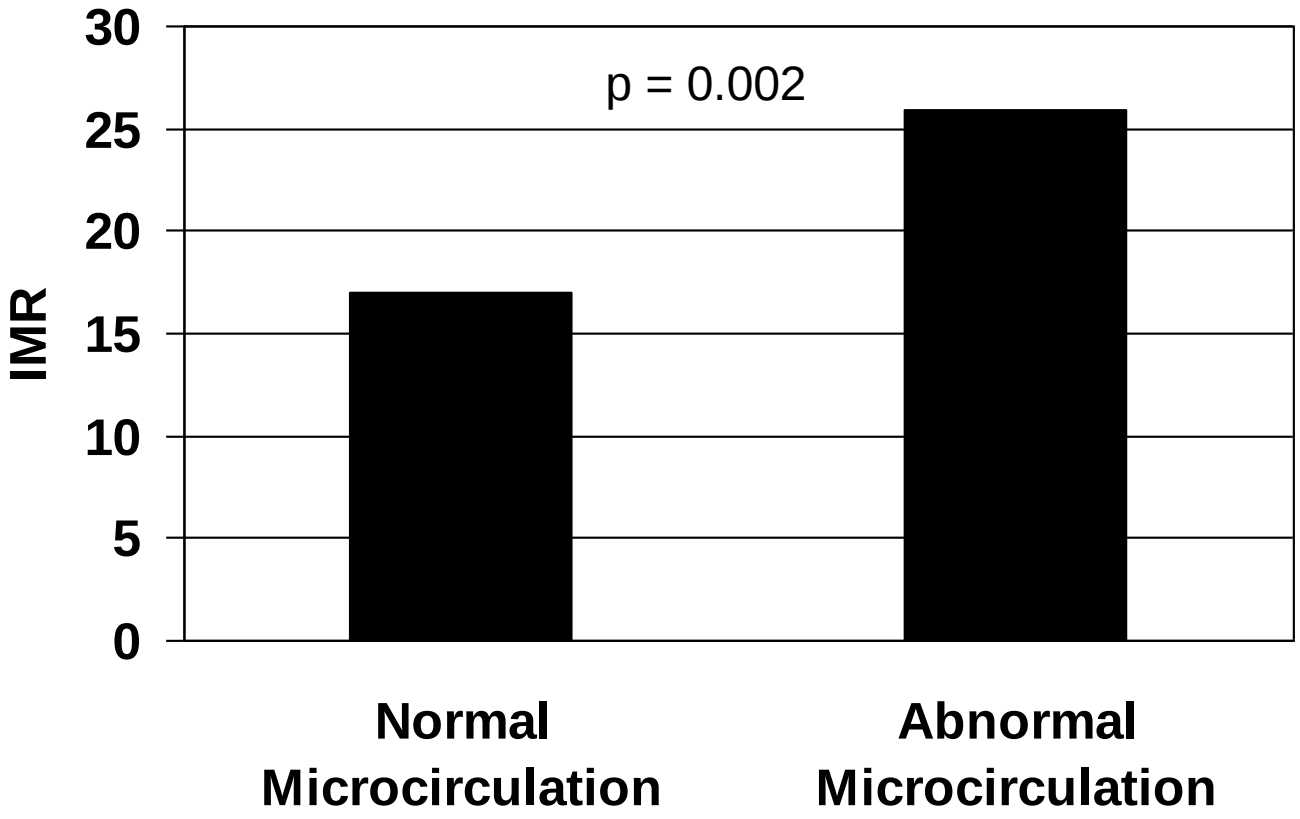

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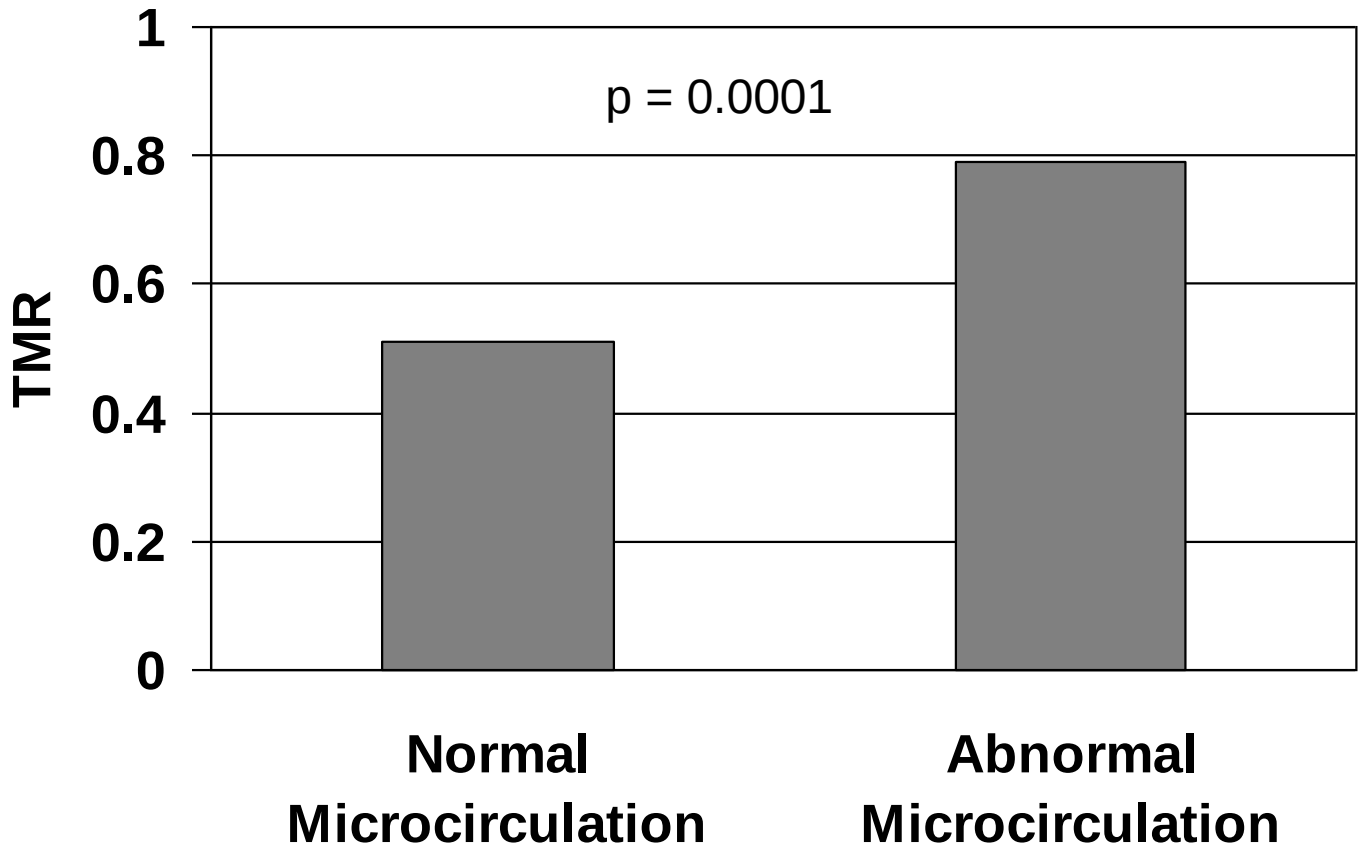

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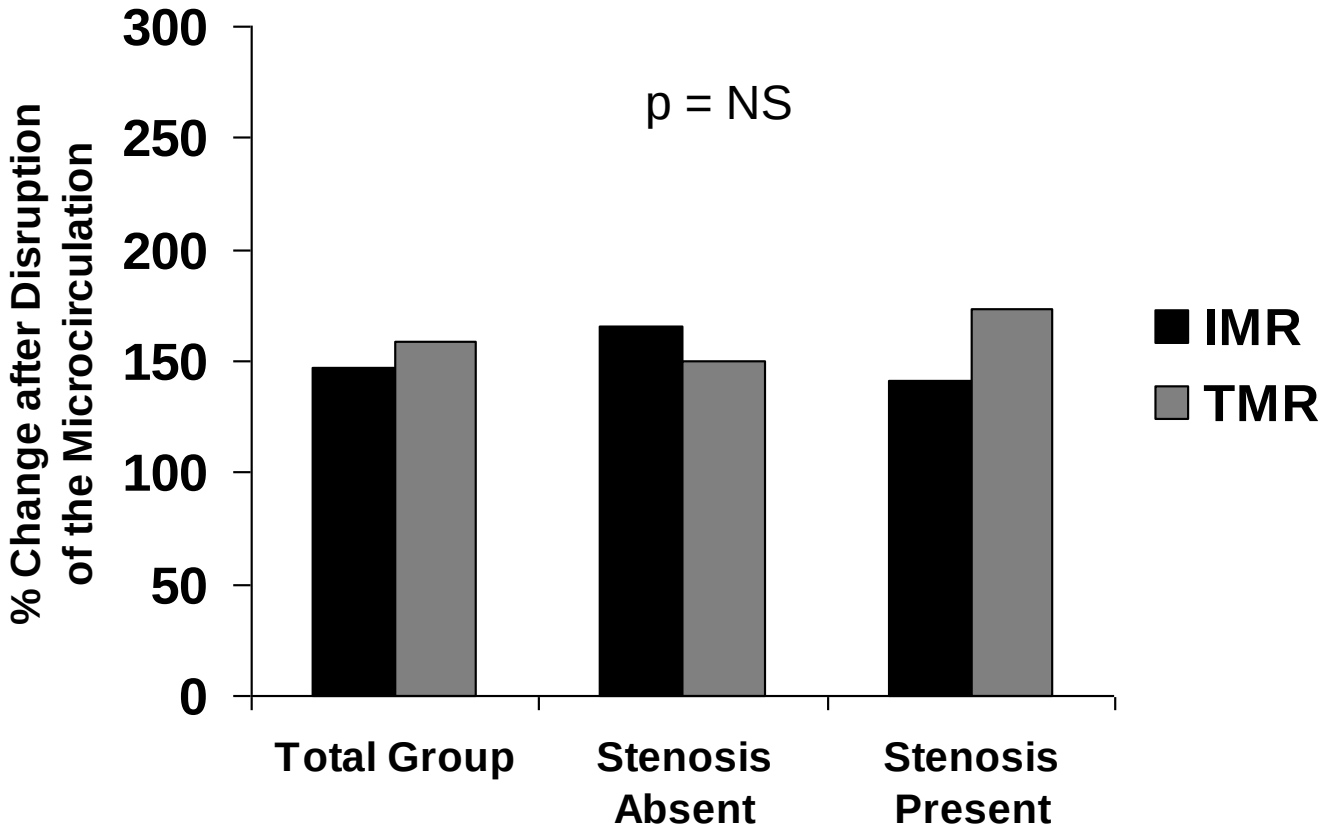


Circulation 2003;107:3129-3132.

Reproducibility of IMR

Effect of Pacing on FFR/CFR/IMR

	Baseline	RV Pacing at 110 bpm
CFR	3.1±1.1	2.3±1.2†
IMR, U	21.8±6.5	22.9±6.9
FFR	0.88±0.07	0.87±0.07

Effect of Blood Pressure on FFR/CFR/IMR

	Baseline	Nitroprusside
CFR	2.9±0.9	2.5±1.2
IMR, U	23.85±6.1	24.00±7.9
FFR	0.88±0.04	0.87±0.05

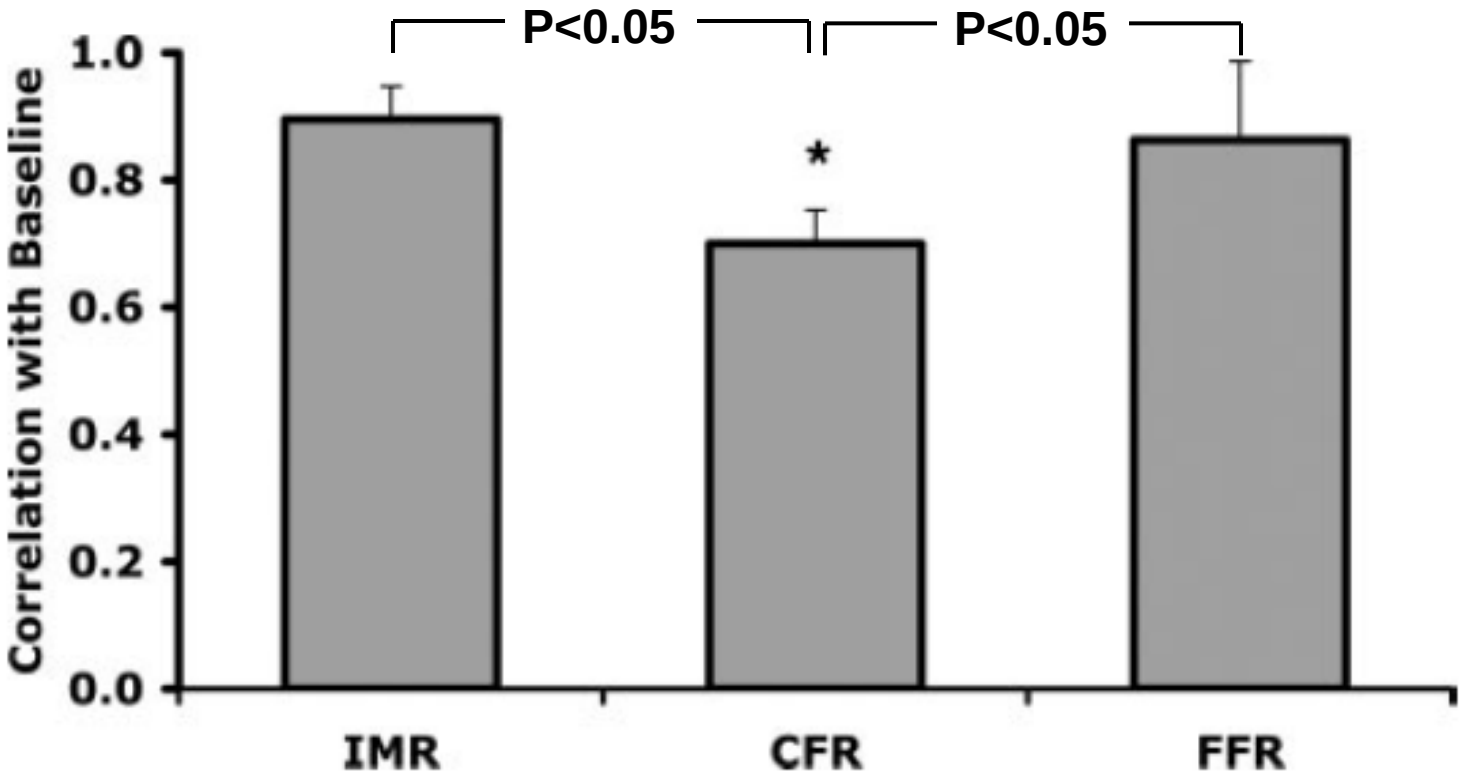
Change in LV Contractility and FFR/CFR/IMR

	Baseline	Dobutamine
CFR	3.0±1.0	1.7±0.6†
IMR, U	22.2±6.0	23.6±8.2
FFR	0.88±0.06	0.87±0.06

Ng, et al. Circulation 2006;113:2054-61.

Reproducibility of IMR

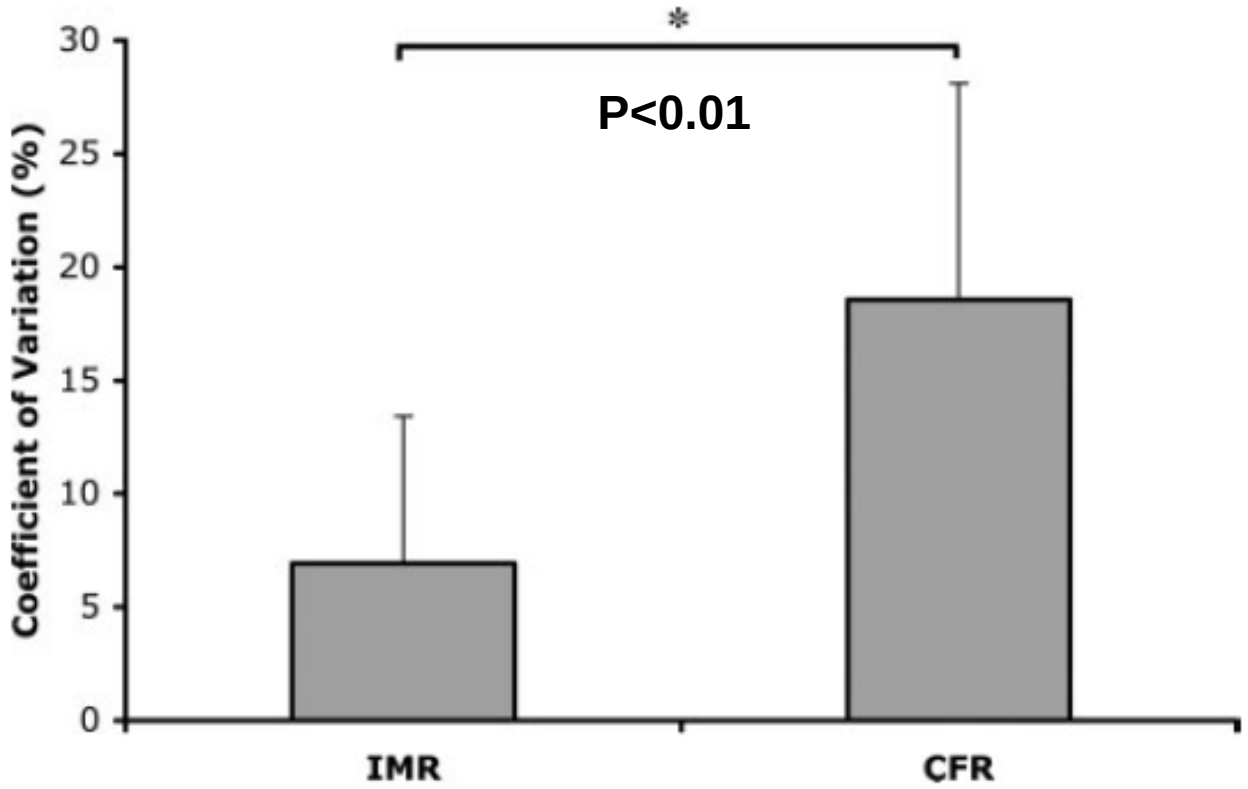
Mean correlation coefficients of IMR, CFR and FFR values comparing baseline measurement with each hemodynamic intervention



Ng, et al. Circulation 2006;113:2054-61.

Reproducibility of IMR

Coefficient of variation between pairs of baseline values of IMR and CFR



Ng, et al. Circulation 2006;113:2054-61.

Reproducibility of IMR

Correlation between IMR and cardiac MR assessment of microvascular obstruction in 108 patients after STEMI

- Repeated IMR measurements obtained by 4 different operators in 12 STEMI patients were highly correlated (r=0.99, P<0.001), with a mean difference between IMR measurements of 0.01 (mean standard error 1.59 [95% CI −3.52 to 3.54], P=0.48).

Payne, et al. J Am Heart Assoc 2012;1:e002246.

IMR: *Normal Value*

An IMR ≤ 25 is considered normal

- The mean IMR measured in 15 subjects (22 arteries) without any evidence of atherosclerosis and no/minimal risk factors was 19±5.

- The mean IMR measured in 18 subjects with normal stress tests and normal coronary angiography was 18.9±5.6.

Melikian, et al. Eurointervention 2010;5:939-945
Luo, et al. Circ Cardiovasc Interv 2014;7:

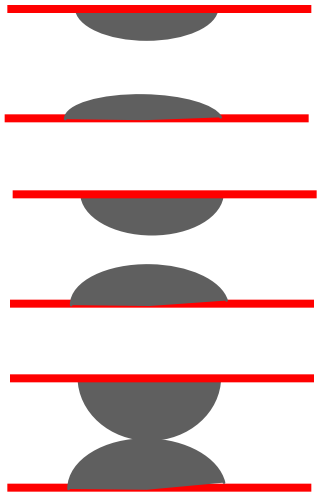
IMR and Epicardial Stenosis

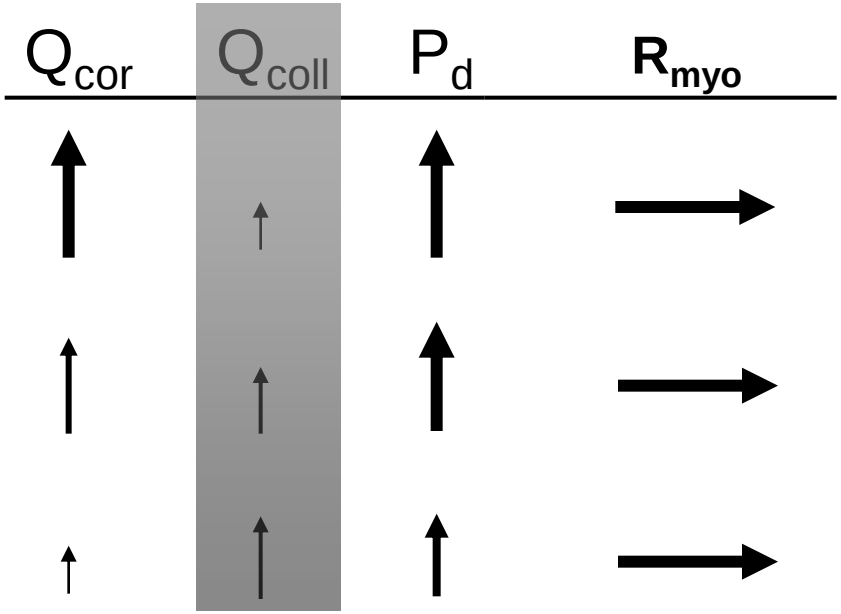
Role of collaterals when measuring IMR in patients with significant epicardial stenosis

- Resistance = Pressure / Q_{myo}
- $Q_{myo} = Q_{cor} + Q_{coll}$
- Simplified IMR = P_d x T_{mn}
- But T_{mn} is inversely proportional to *coronary flow*

Catheter Cardiovasc Interv 2004;62:56-63.

Importance of Collaterals when Measuring IMR





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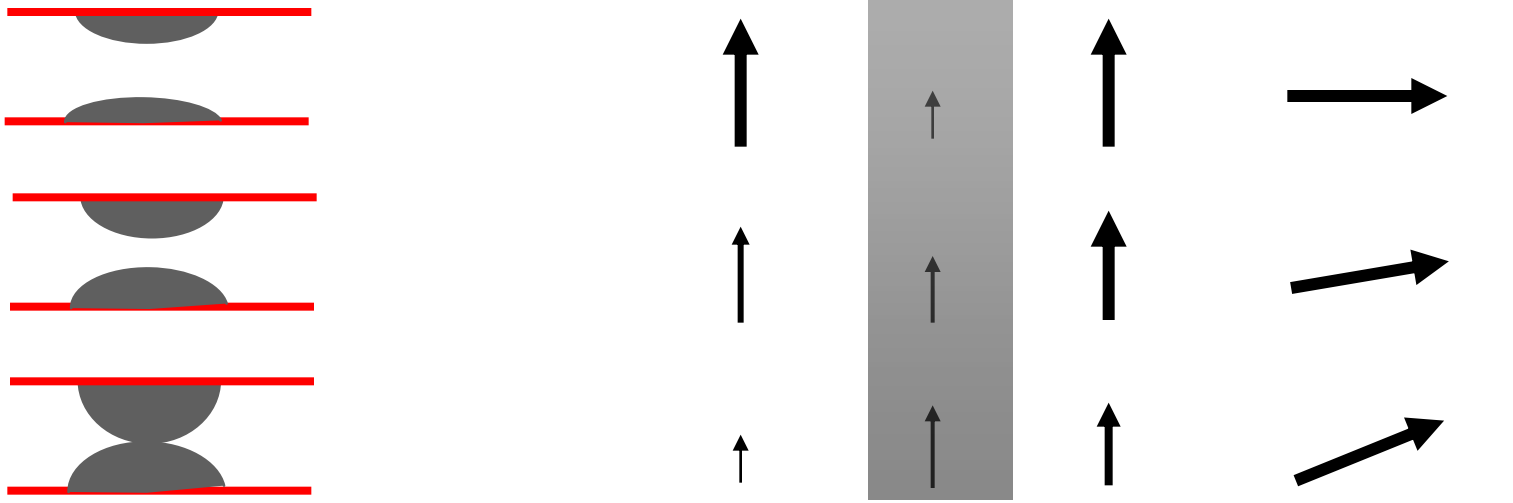


Flow ↓'s more than it should, T_{mn} ↑'s and $IMR_{app} = P_d \times T_{mn}$ ↑'s

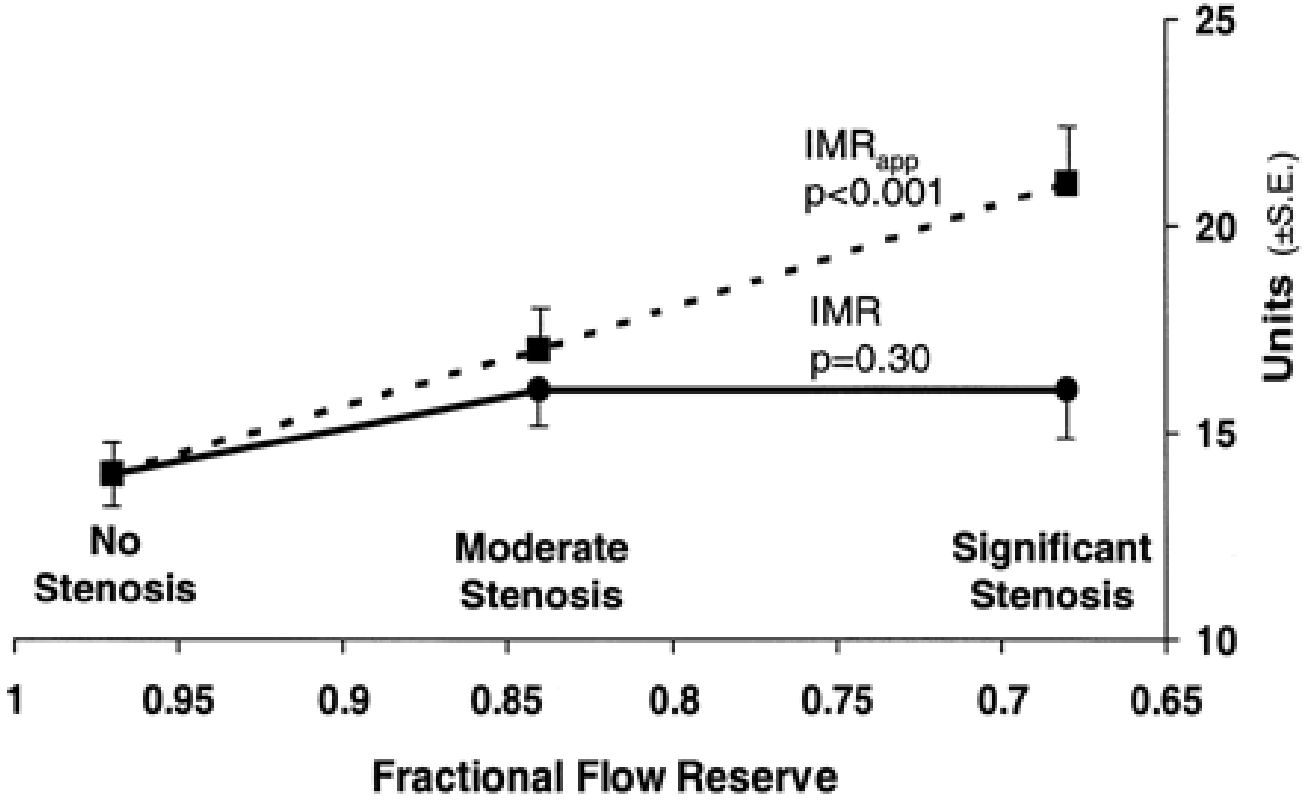
To measure true IMR, must measure coronary wedge pressure to incorporate collateral flow

$$\mathbf{IMR = P_d \times T_{mn} \times (FFR_{cor} / FFR_{myo})}$$

Catheter Cardiovasc Interv 2004;62:56-63.

IMR is not affected by epicardial stenosis severity:

Animal Validation

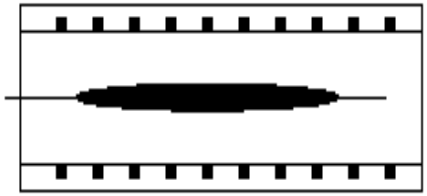


Circulation 2004;109:2269-2272

IMR is not affected by epicardial stenosis severity:

Human Validation

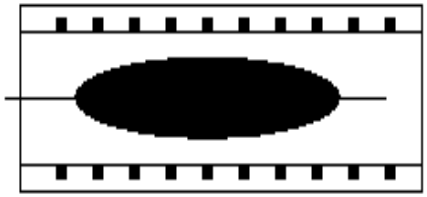
10% AS



FFR = 0.84 ± 0.08

IMR = 22 ± 15

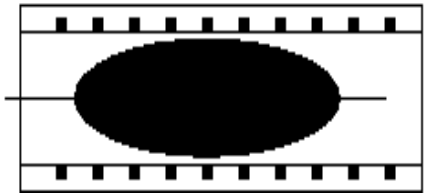
50% AS



FFR = 0.69 ± 0.09

IMR = 23 ± 14

75% AS



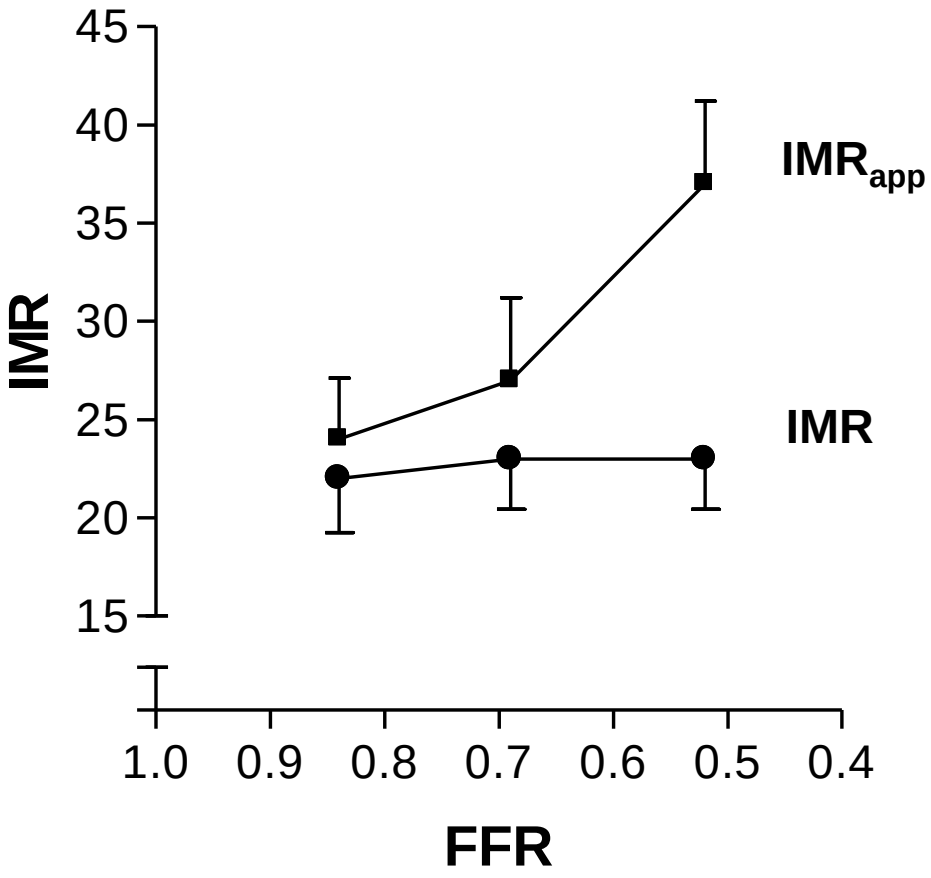
FFR = 0.52 ± 0.11

IMR = 23 ± 14

Aarnoudse, et al. Circulation 2004;110:2137-42

IMR is not affected by epicardial stenosis severity:

Human Validation



Aarnoudse, et al. Circulation 2004;110:2137-42

Estimating True IMR without Wedge

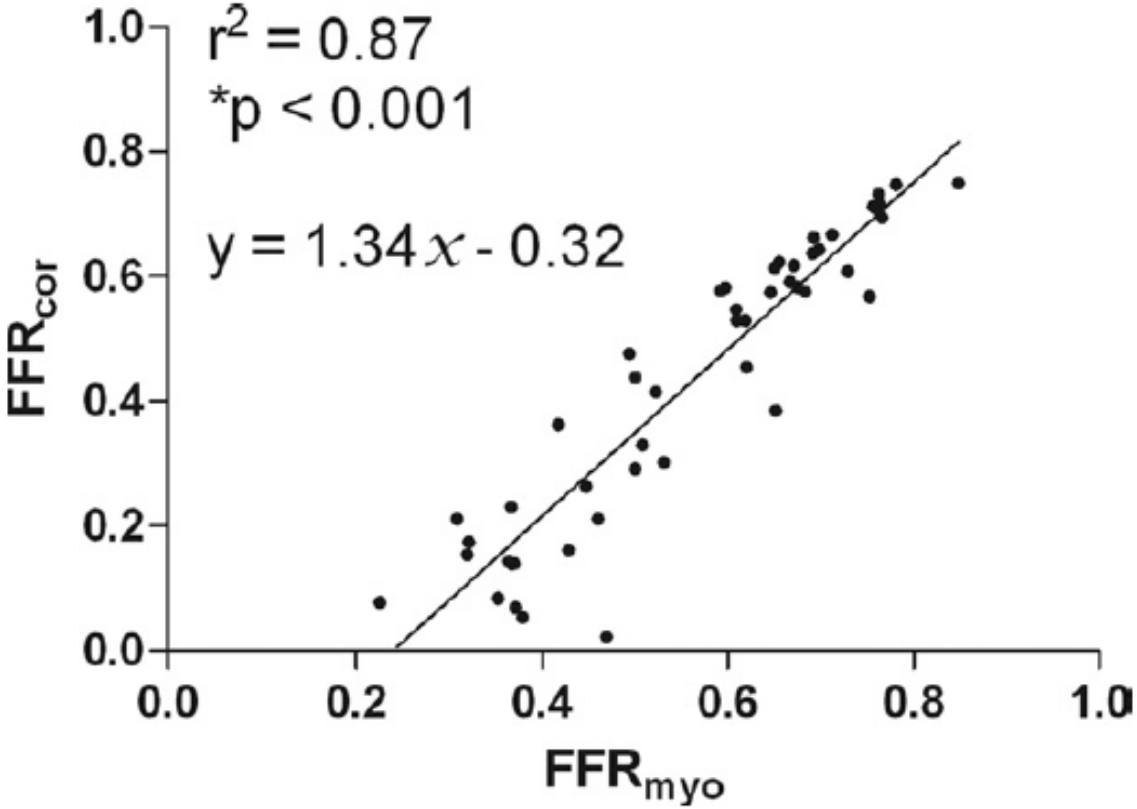
- $IMR = P_d \times T_{mn} \times (FFR_{cor} / FFR_{myo})$
- $IMR = P_d \times T_{mn} \times ((P_d-P_w)/(P_a-P_w) / (P_d/P_a))$

- **If there is a relationship between FFR_{cor} and FFR_{myo}, perhaps we can estimate FFR_{cor} without having to measure the coronary wedge pressure.**

Yong, et al. J Am Coll Cardiol Intv 2013;6:53-8.

Estimating True IMR without Wedge

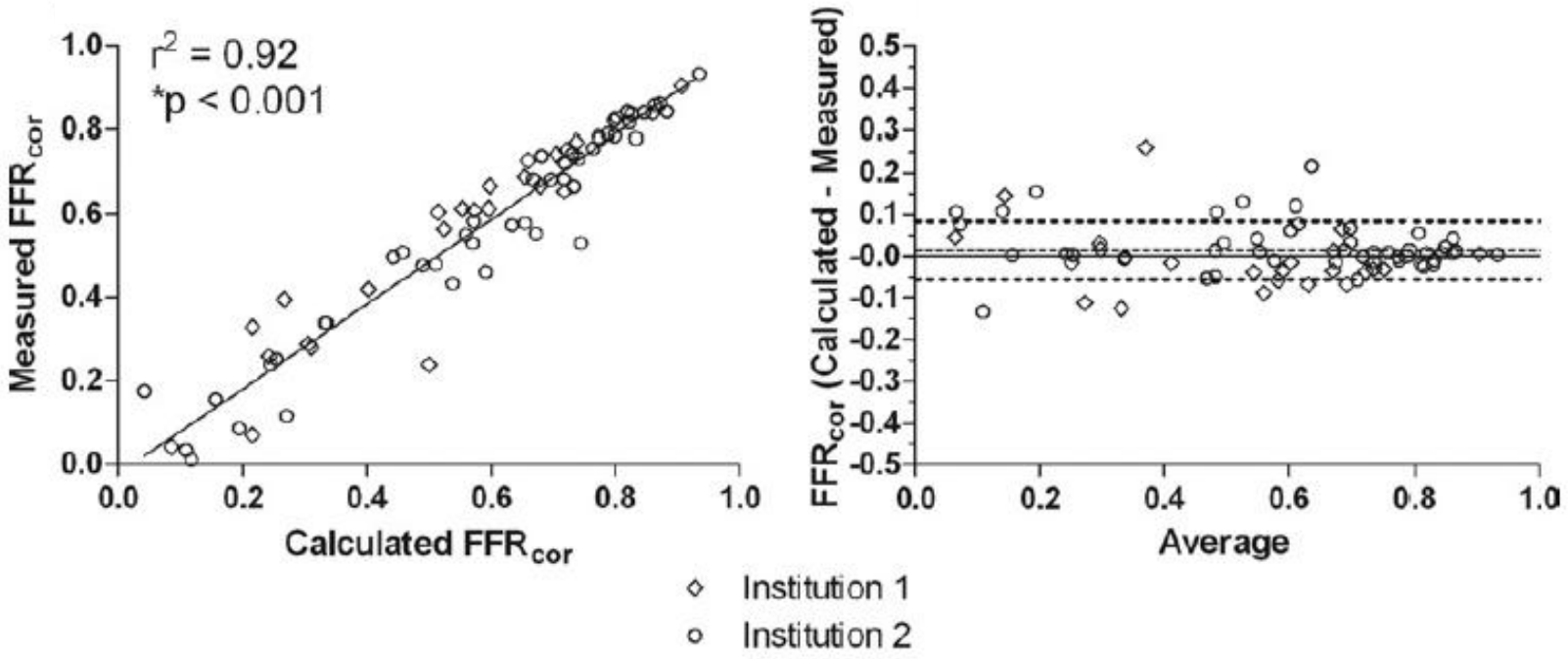
In a derivation cohort of 50 patients, a strong linear relationship was found between FFR_{cor} and FFR_{myo}.



Yong, et al. J Am Coll Cardiol Intv 2013;6:53-8.

Estimating True IMR without Wedge

In a validation cohort of 72 patients, there was no significant difference in IMR with estimate FFR_{cor} or measured $FFR_{cor.}$



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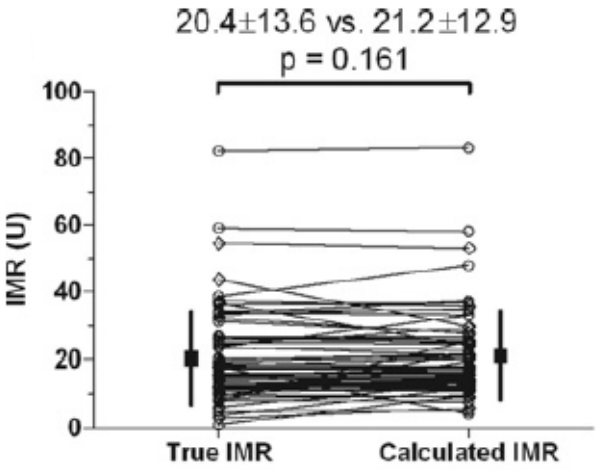
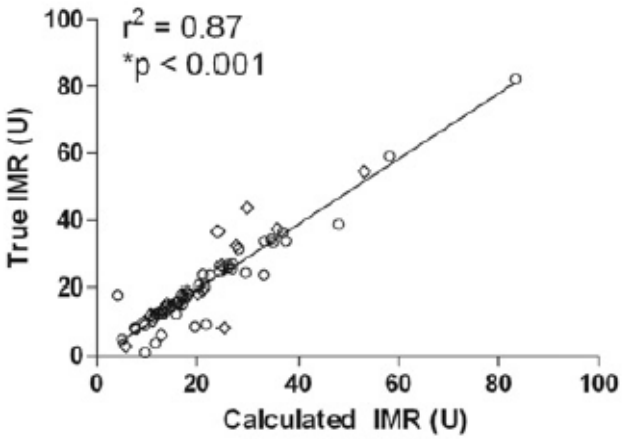
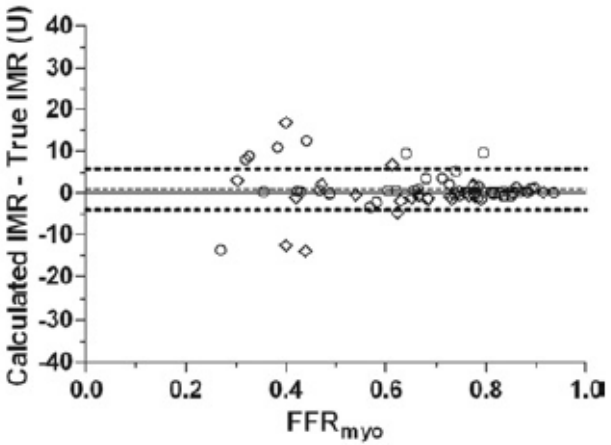


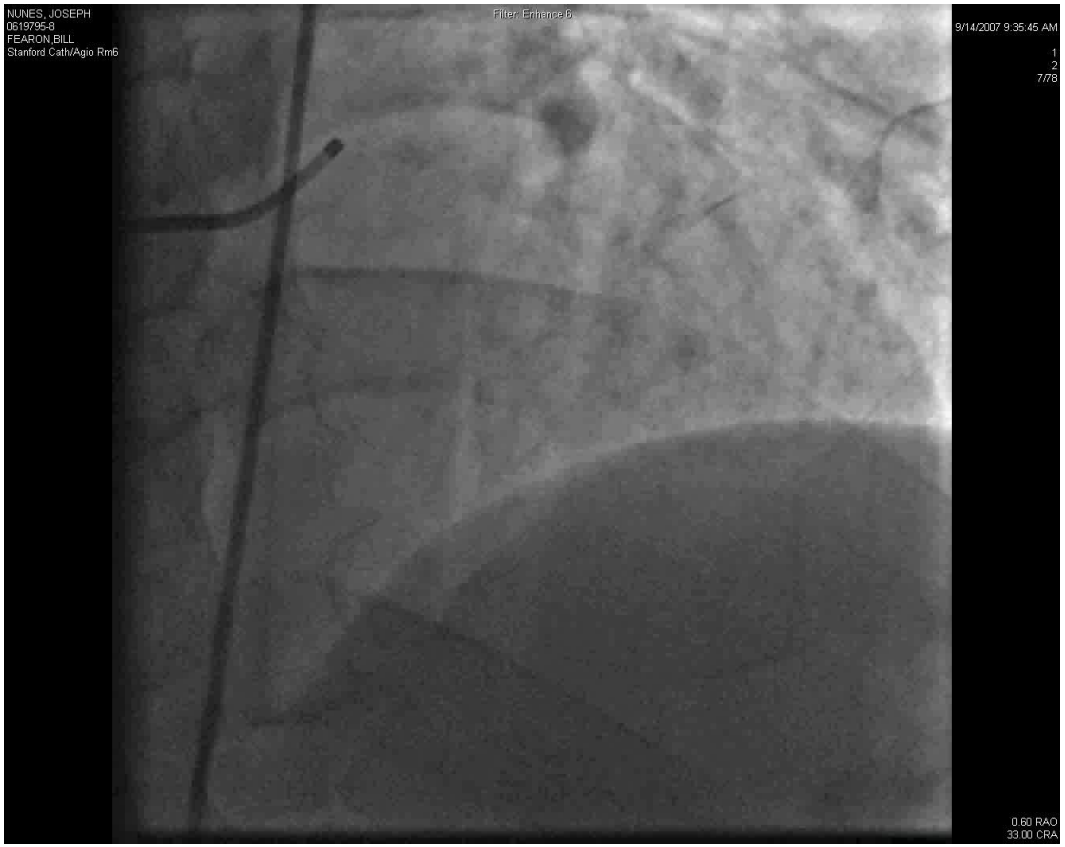


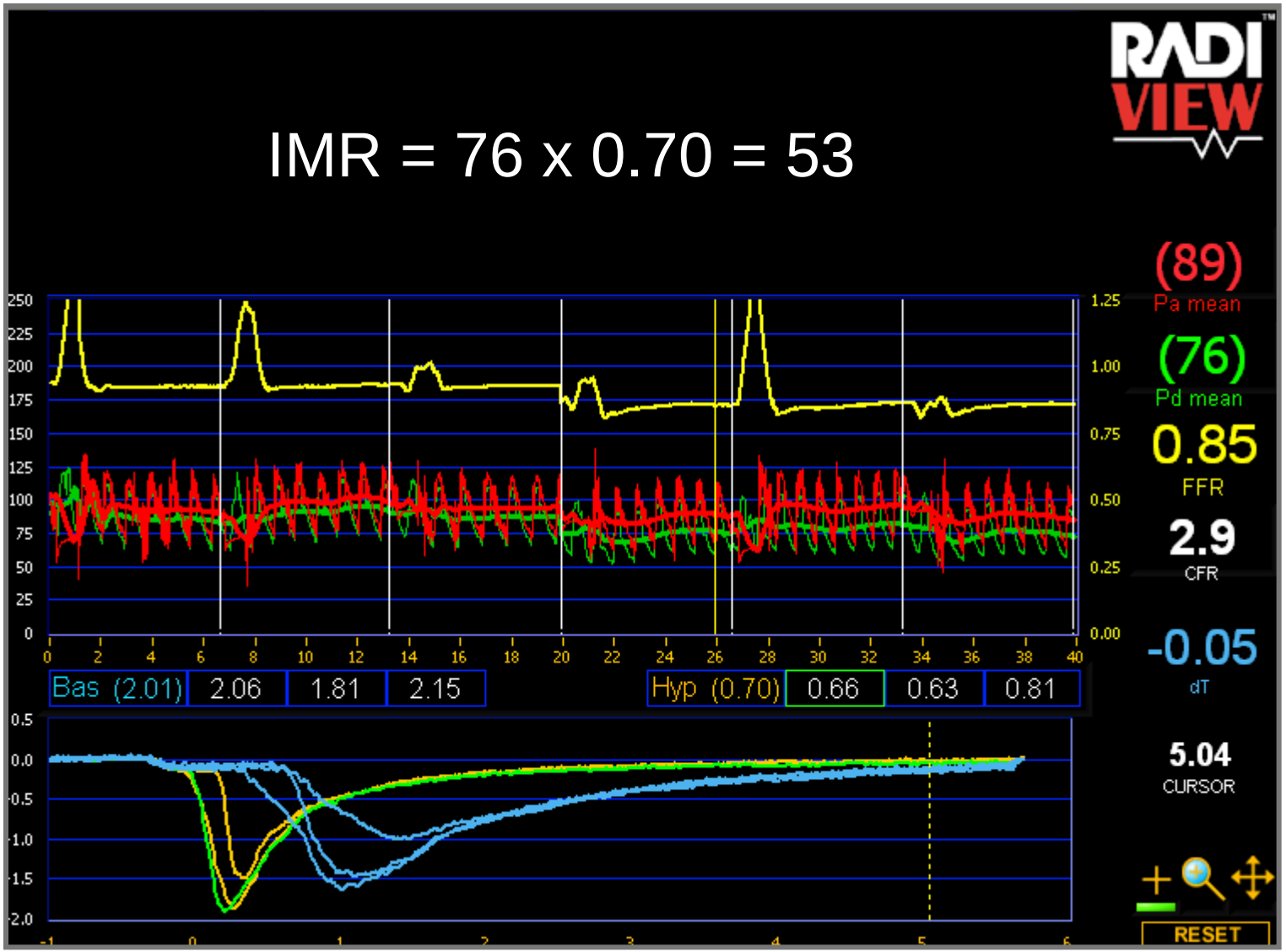


Yong, et al. J Am Coll Cardiol Intv 2013;6:53-8.

Clinical Application of IMR

59 year old man with HTN, dyslipidemia and chest pain with emotional stress and septal ischemia on Nuclear Scan




IMR = 76 x 0.70 = 53
RADI VIEW
(89)
Pa mean
(76)
Pd mean
0.85
FFR
2.9
CFR
-0.05
dT
5.04
CURSOR
RESET
Bas (2.01) 2.06 1.81 2.15
Hyp (0.70) 0.66 0.63 0.81

Chest Pain and “Normal Coronaries”

- 139 patients referred for coronary angiography because of symptoms and/or abnormal stress test and found to have “normal” appearing coronaries

- FFR, IMR, CFR, IVUS and acetylcholine challenge were performed down the LAD

Lee BK, et al. Circulation. 2013;128:A19113

Chest Pain and “Normal Coronaries”

Patient Characteristic	n=139
Age (years)	54 ±11
Female	77%
Hypertension	53%
Diabetes	23%
Dyslipidemia	63%
Tobacco Use	8%

Lee BK, et al. Circulation. 2013;128:A19113

Chest Pain and "Normal Coronaries"

- The mean IMR was 19.6 ±9.1
- Microvascular dysfunction was present in 21% (defined as IMR ≥ 25)
- Predictors of microvascular dysfunction were age, diabetes, HTN, and BMI

Lee BK, et al. Circulation. 2013;128:A19113

Chest Pain and "Normal Coronaries"

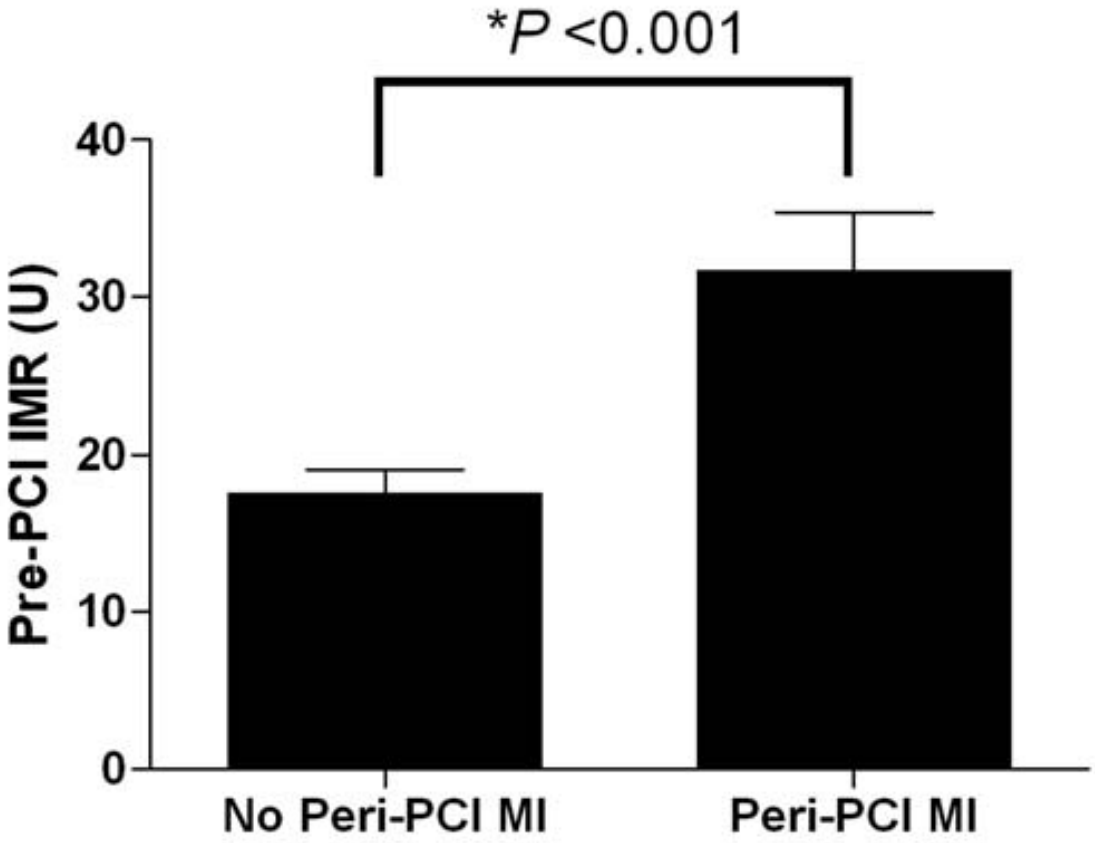
- 5% of patients had an FFR of the LAD ≤ 0.80
- 44% had epicardial endothelial dysfunction
- 58% had a myocardial bridge

- 24% had nonischemic FFR, normal IMR, no endothelial dysfunction and no "bridge"

Lee BK, et al. Circulation. 2013;128:A19113

IMR *Before* PCI in Stable Patients

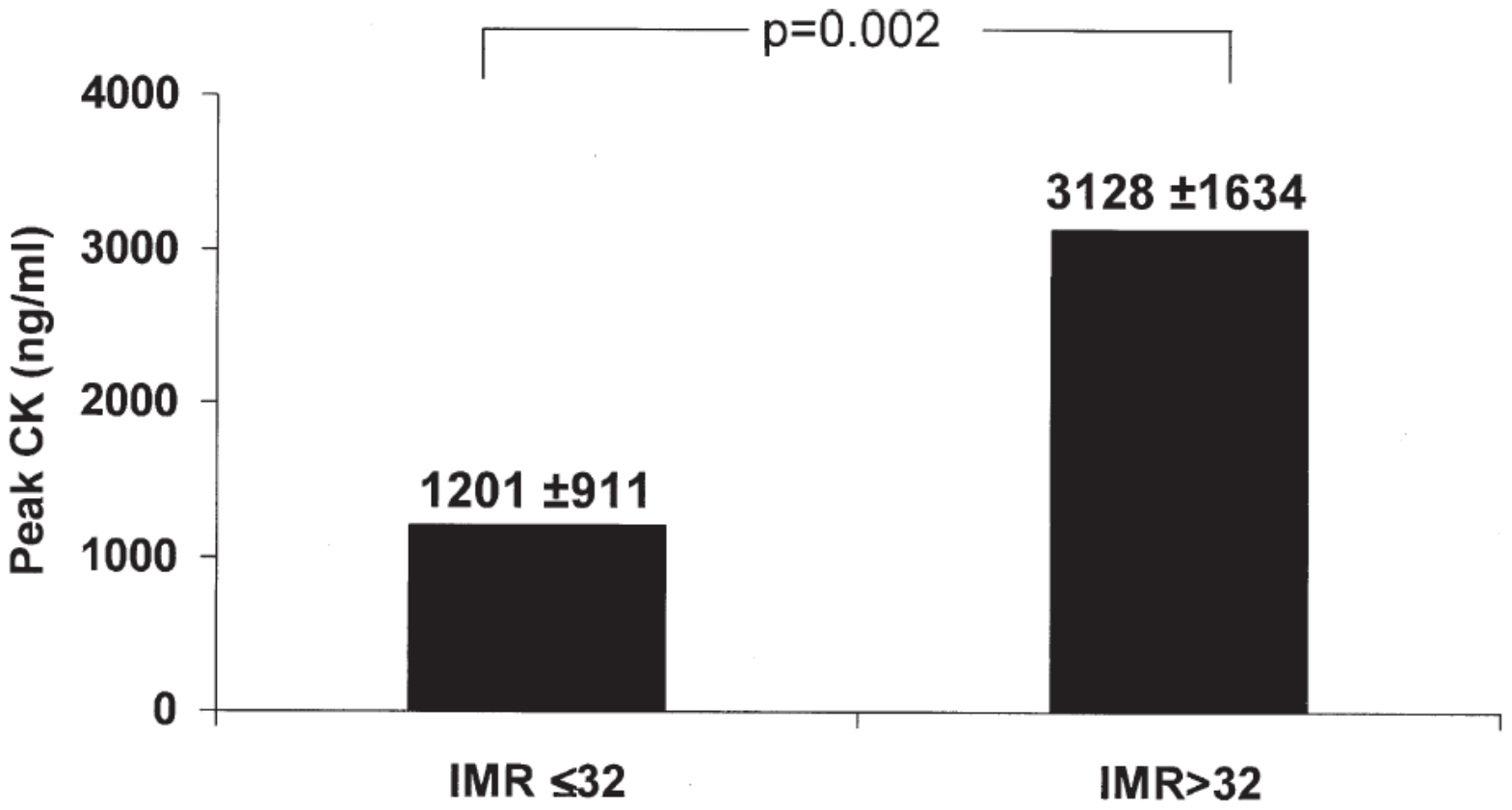
IMR measured before PCI in 50 stable patients undergoing LAD PCI



Ng, et al. Circ Cardiovasc Interv 2012;5:515-22.

Predictive Value of IMR after PCI for STEMI

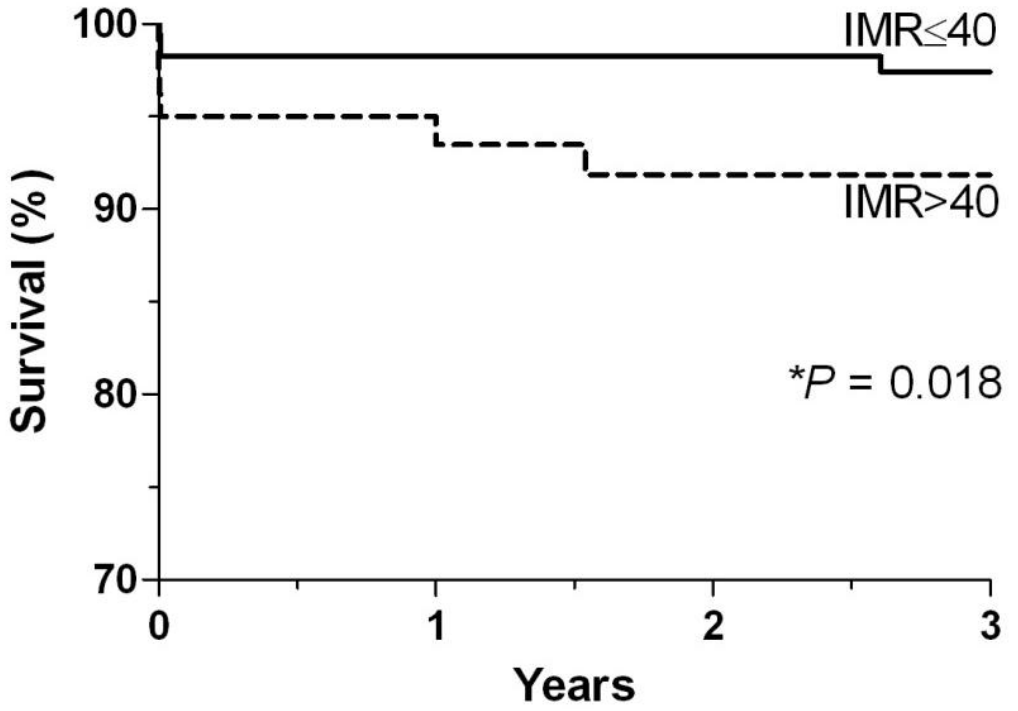
IMR predicts peak CK in patients with STEMI



J Am Coll Cardiol 2008;51:560-5

IMR and Outcomes post STEMI

Multicenter study evaluating relationship between IMR and longer-term outcomes in 253 STEMI patients

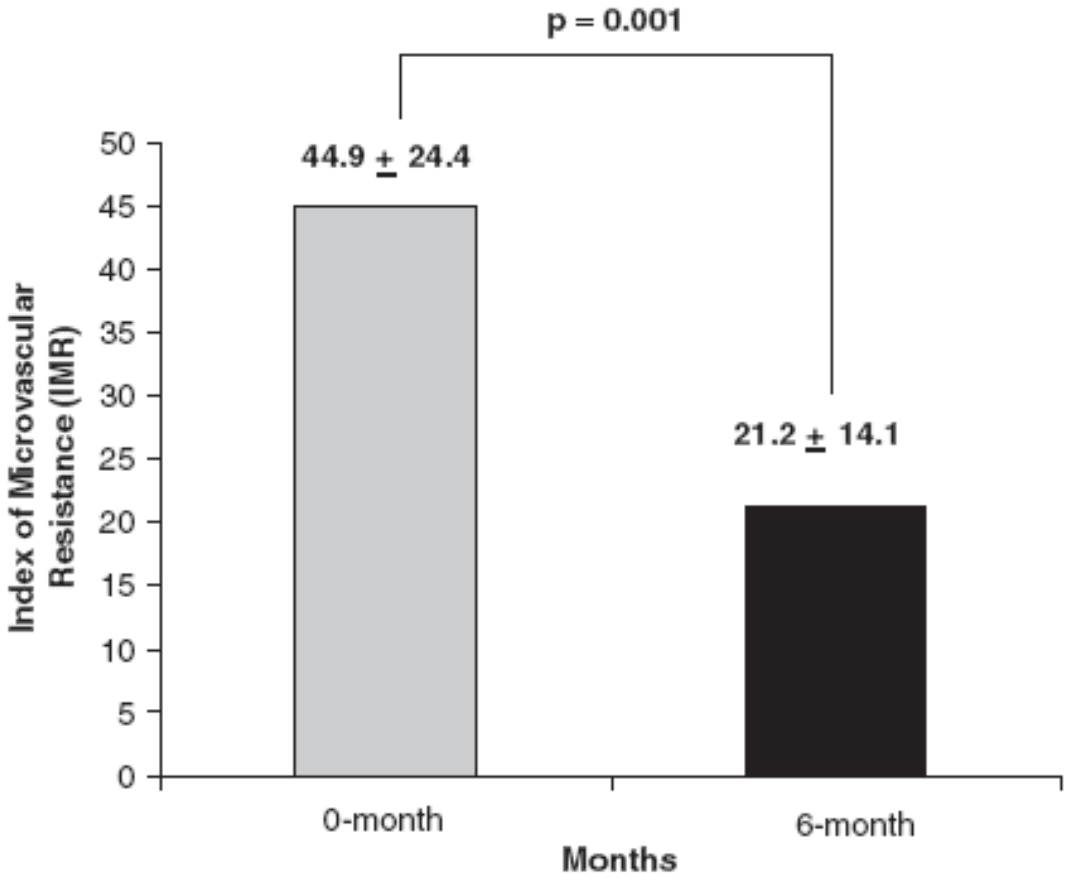


No. at risk:				
IMR ≤40	173	154	149	84
IMR >40	80	69	63	33

Circulation 2013; 127:2436-2441.

IMR post Stem Cell Therapy

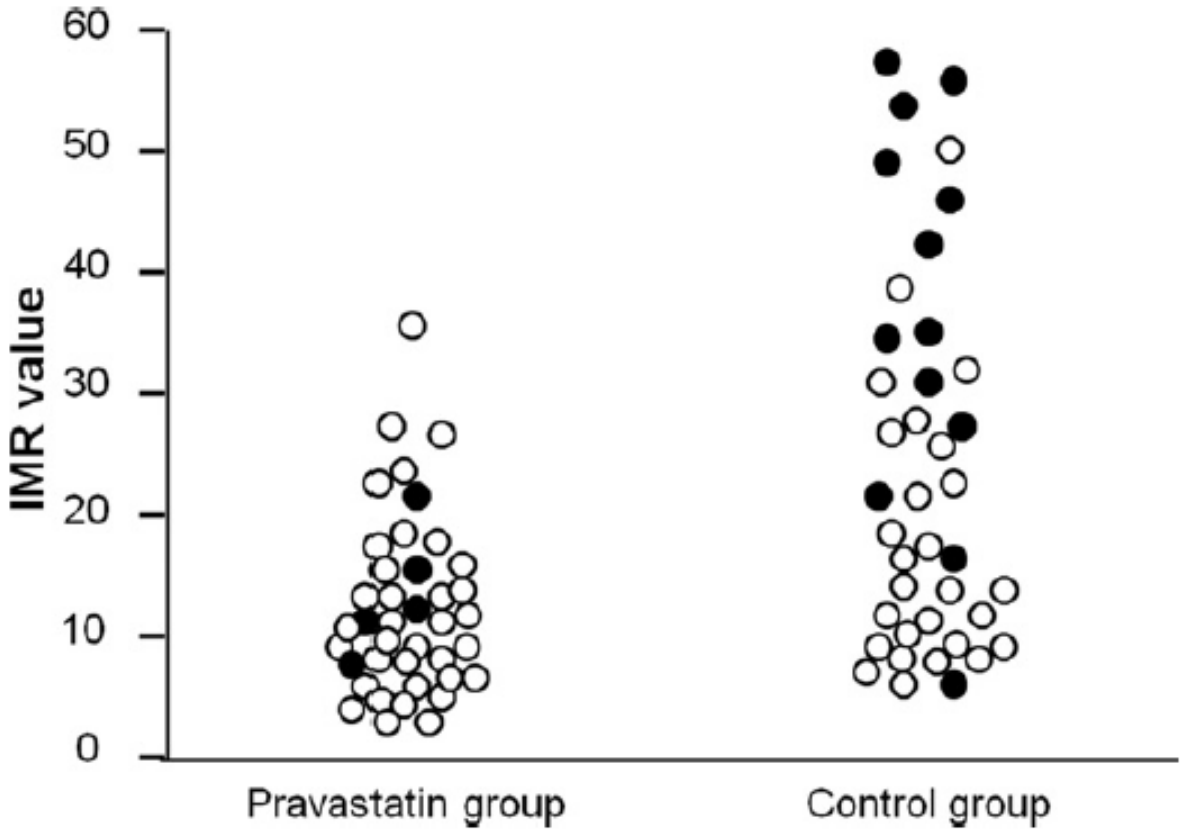
IMR measured in 15 patients with ischemic cardiomyopathy before and 6 months after intracoronary stem cell delivery



Tayyareci, et al. Angiology 2008;59:145

IMR post Statin Therapy

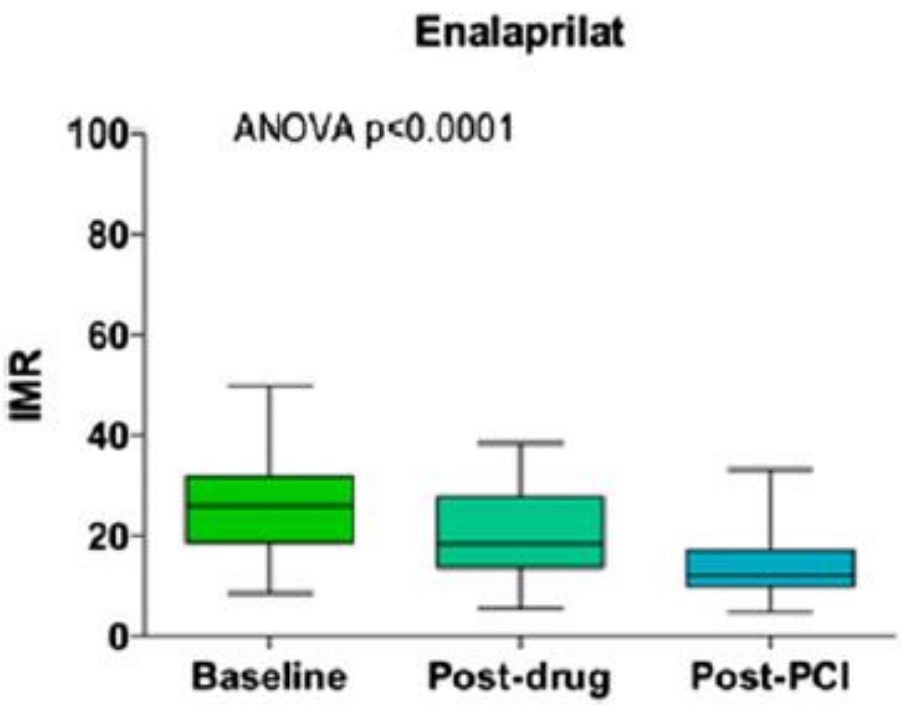
IMR measured after PCI in 80 patients randomized to either 1 month pretreatment with pravastatin or placebo

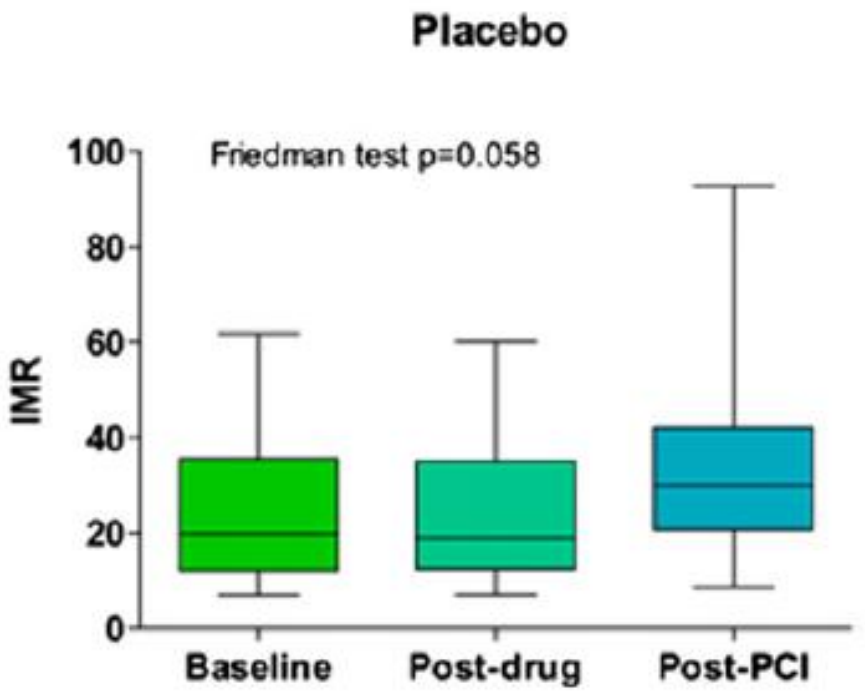


Fujii, et al. J Am Coll Cardiol Intv 2011; 4:513-20.

IMR post ACE Inhibitor Therapy

40 patients randomized to IC enalaprilat or placebo prior to PCI





Mangiacapra, et al. J Am Coll Cardiol 2013; 61:615-21.

Limitations of IMR

- Invasive
- Interpatient and intervessel variability?
  - Sensor distance
- Independent of epicardial stenosis
  - Coronary wedge pressure

Conclusion

Take Home Messages:

- The microvasculature is a complex entity, which is challenging to investigate.
- Measurement of IMR is easy, specific for the microvasculature, quantitative, reproducible, and independent of hemodynamic changes.
- Measurement of IMR may help guide treatment in patients with “normal coronaries” and chest pain. IMR predicts outcomes in acute MI; emerging data suggest its utility in stable PCI patients, as well.