
Invasive Evaluation of the Patient with Chest Pain and Non-Obstructive CAD (NOCAD)

William F. Fearon, MD
Professor of Medicine
Director, Interventional Cardiology
Stanford University



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

- Grant/Research Support
- Consulting Fees/Honoraria
- Major Stock Shareholder/Equity
- Royalty Income
- Ownership/Founder
- Intellectual Property Rights
- Other Financial Benefit

Company

- St. Jude Medical, Medtronic
- Medtronic, HeartFlow



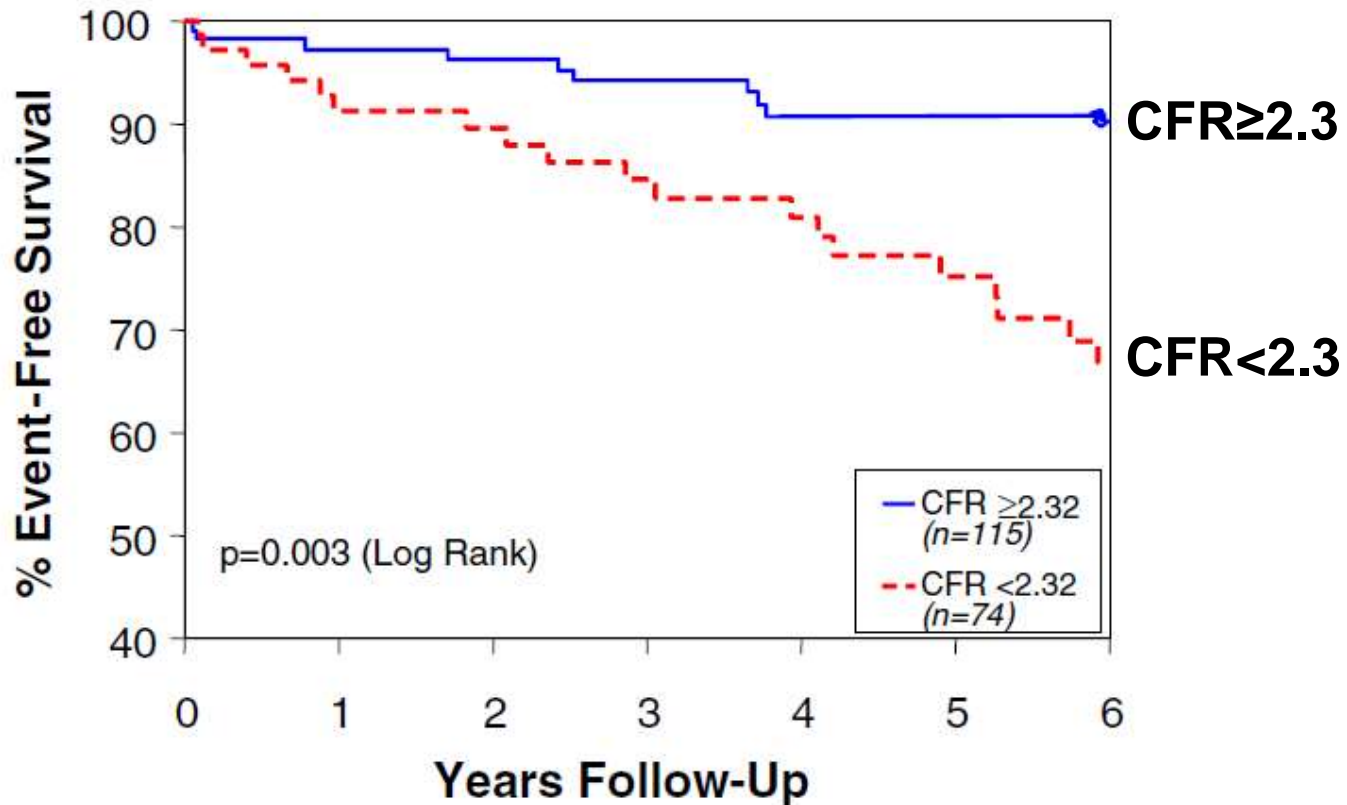
Why is the Evaluation of NOCAD Important?

- ~20% of patients with chest pain are found to have NOCAD
- Up to 30% of patients continue to have angina despite successful coronary revascularization
- Microvascular dysfunction predicts adverse outcomes in a variety of clinical settings



Importance of the Microcirculation

**189 women with chest pain and NOCAD:
% free of Death, MI, CVA, or CHF**



Determinants of Myocardial Flow

■ Epicardial Coronary Flow

- Functional Impairments → **Ach Testing**
 - Endothelial dysfunction (Variant Angina, CAD)
- Structural Impairments → **FFR**
 - Obstructive coronary stenosis (CAD)

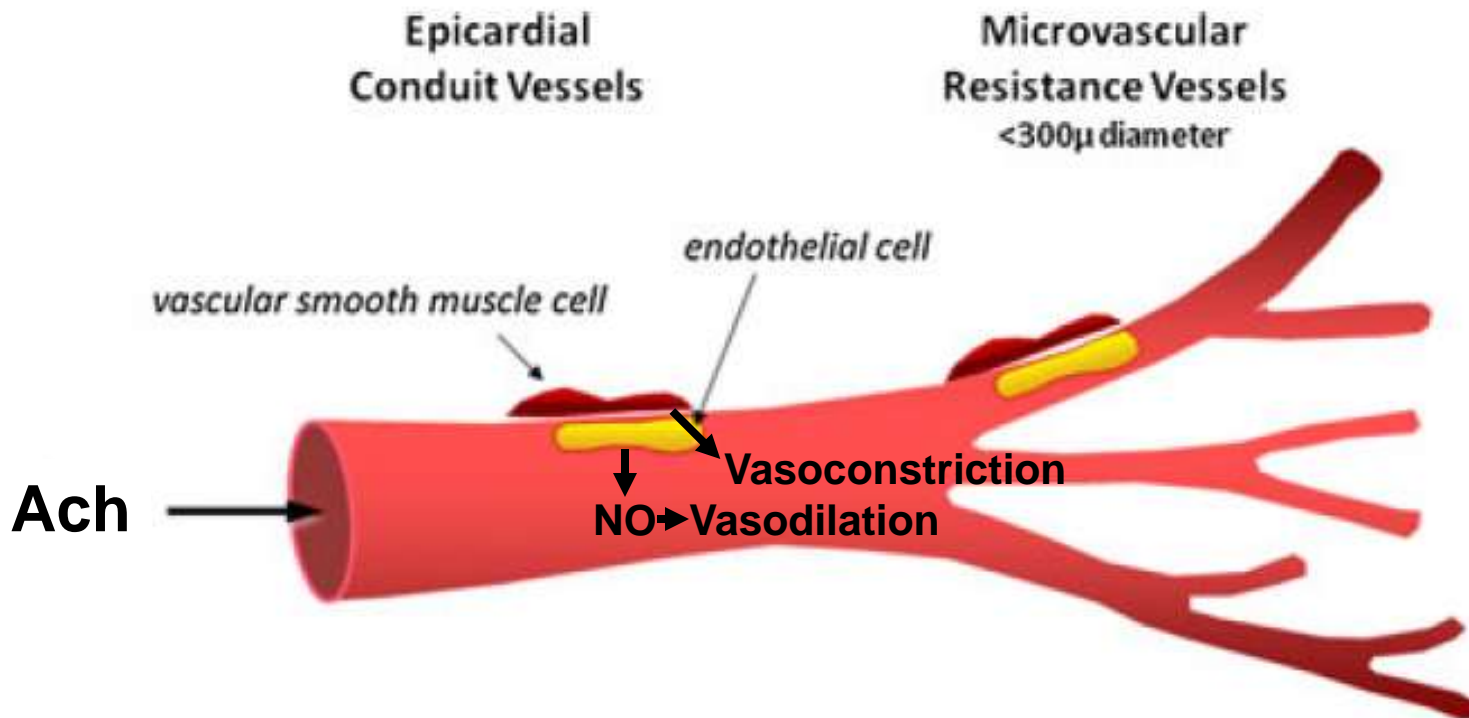
■ Microvascular Flow

- Functional Impairments → **Ach Testing**
 - Endothelial dysfunction (DM, dyslipidemia)
- Structural Impairments → **IMR**
 - Atherosclerosis, fibrosis, decreased vessel density (MI)



Determinants of Myocardial Flow

Endothelial (Dys)Function

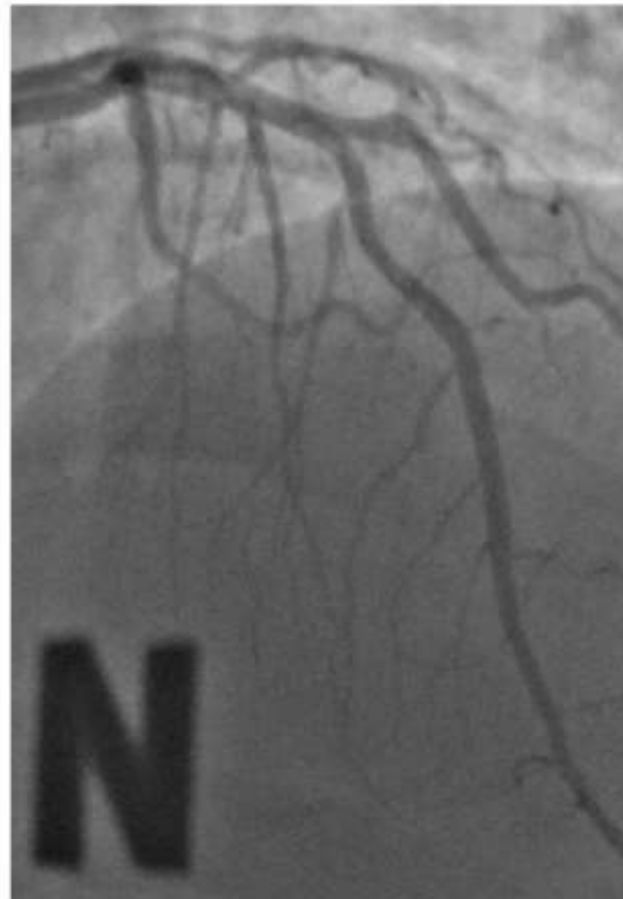


Endothelial Dysfunction:

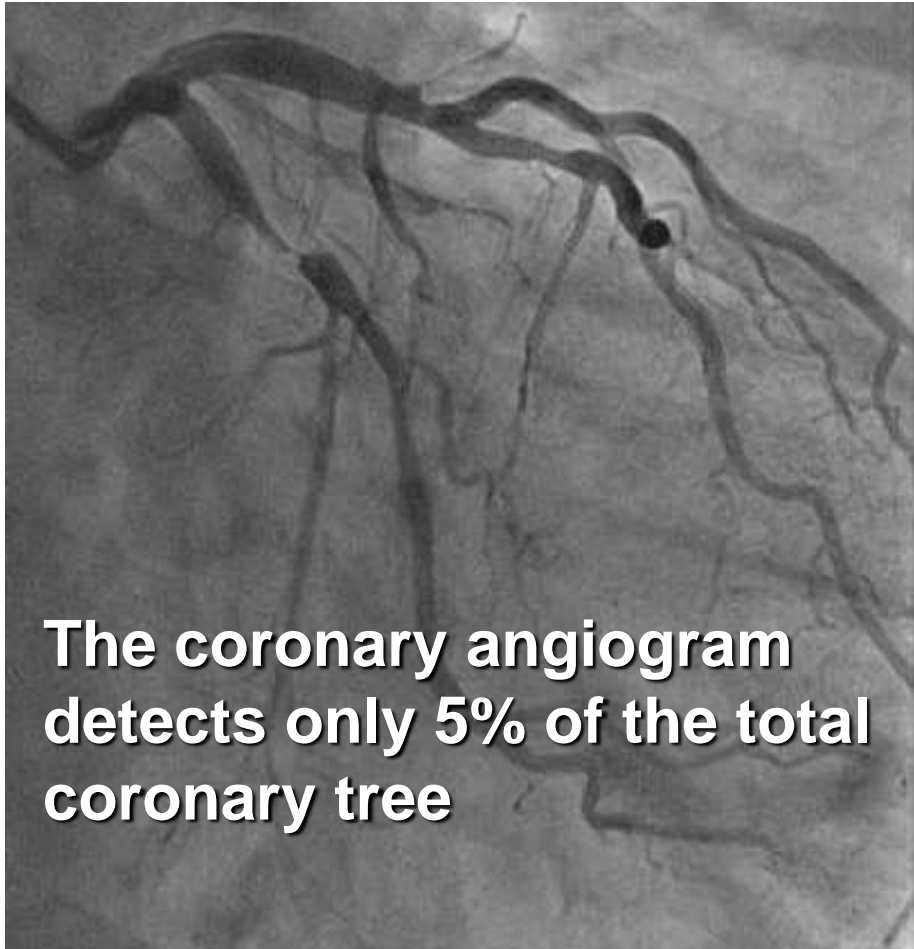
After Acetylcholine



After Nitroglycerin



What is the Microvasculature?

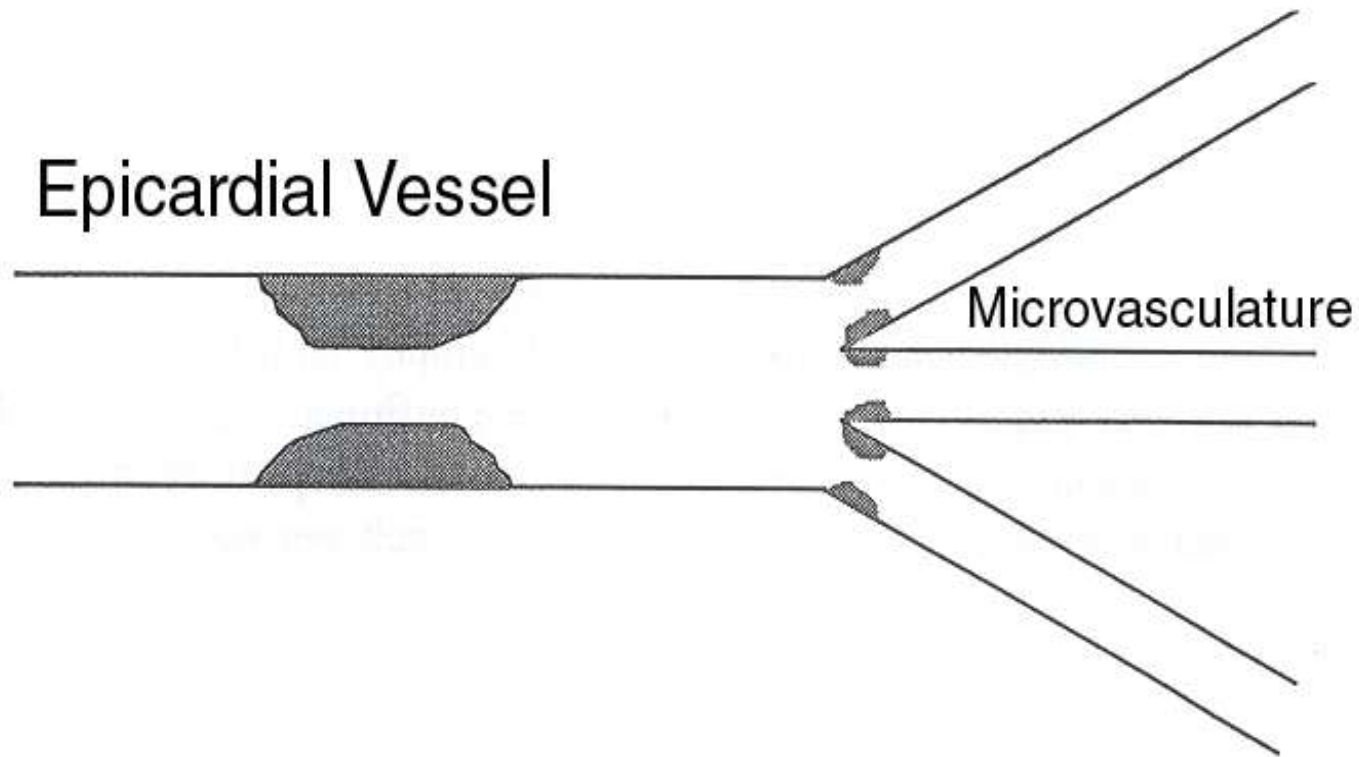


Courtesy of Bernard De Bruyne, MD, PhD



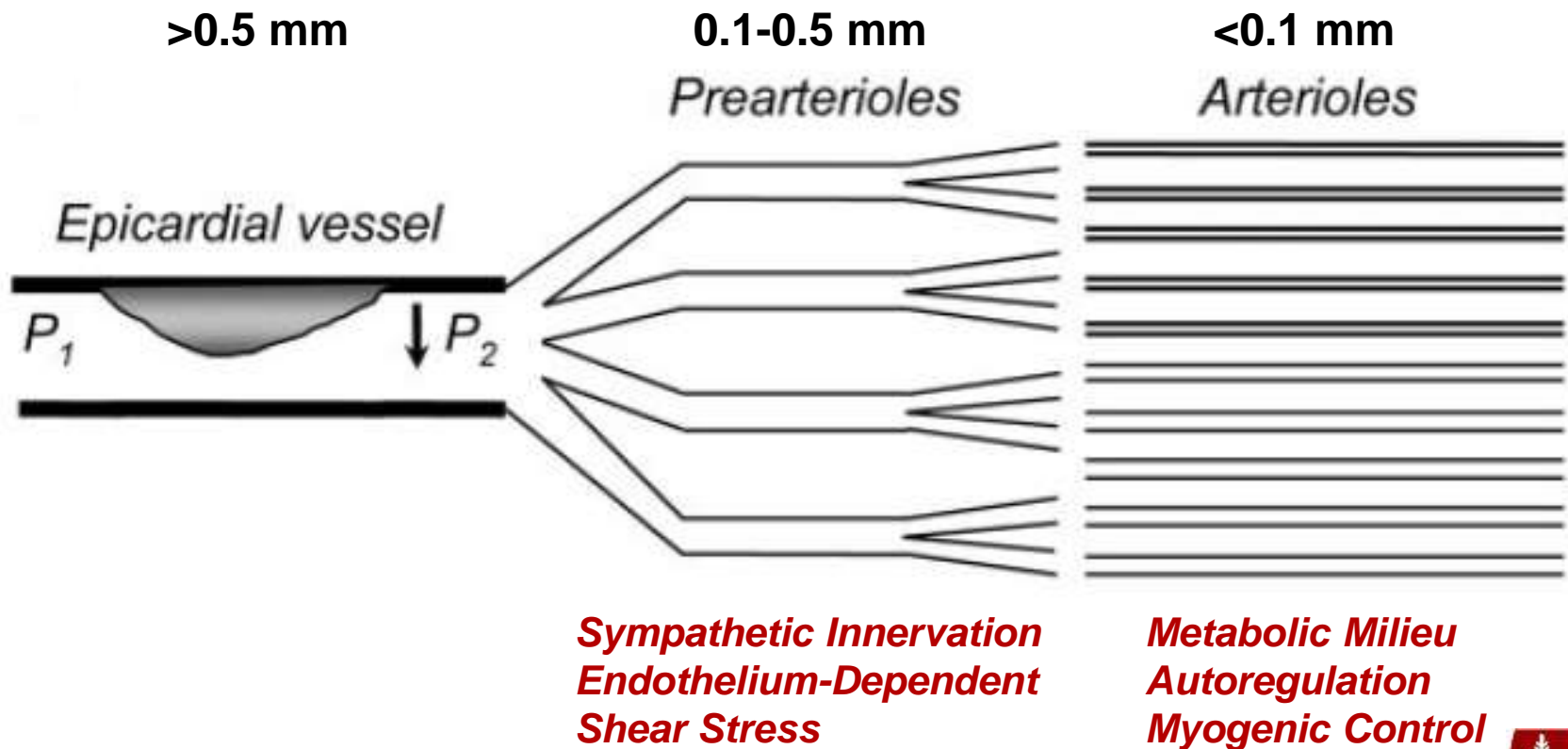
What is the Microvasculature?

Two Compartment Model



What is the Microvasculature?

Three Compartment Model

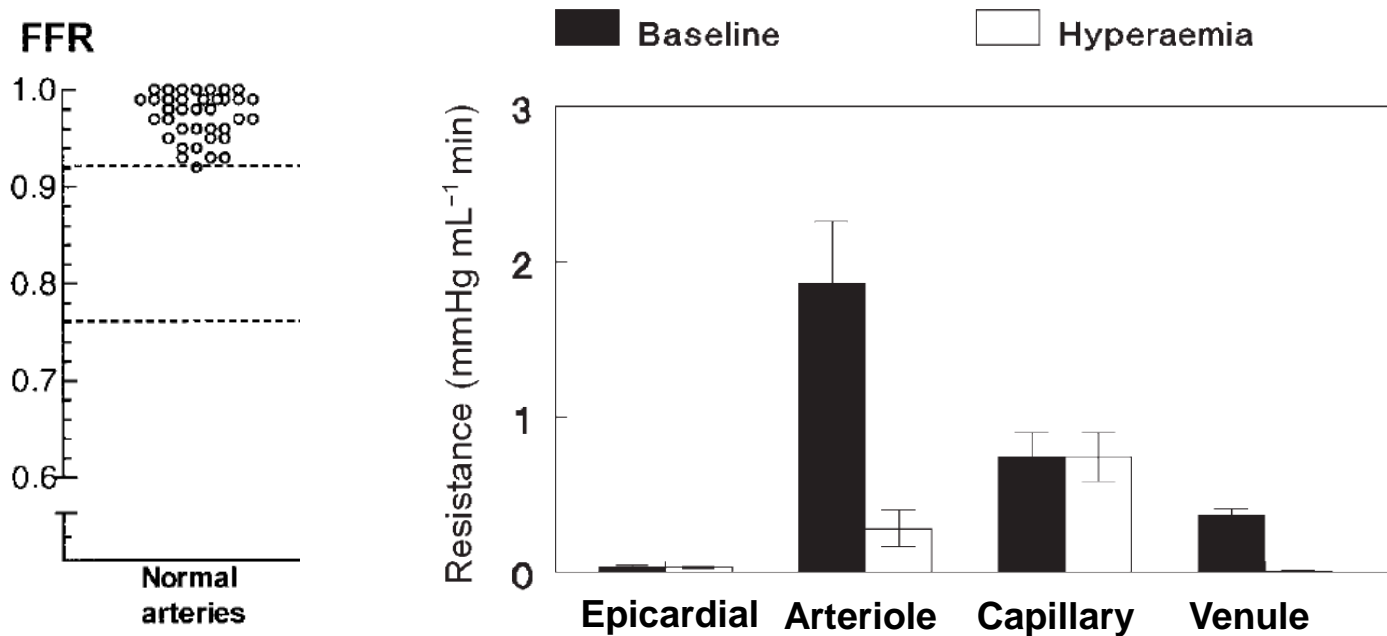


Adapted from: Lanza and Crea. Circulation 2010;121:2317-2325.



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 pre-arteriole and arteriole



What is Microvascular Dysfunction?

- **Coronary microvascular dysfunction (CMD) is defined as abnormal coronary microvascular resistance (either arteriolar or pre-arteriolar)**



What is Microvascular Dysfunction?

- **Coronary microvascular dysfunction (CMD) is defined as abnormal coronary microvascular resistance (either arteriolar or pre-arteriolar) that is clinically evident as an inappropriate coronary blood flow response, impaired myocardial perfusion and/or myocardial ischemia**



What is Microvascular Dysfunction?

- **Coronary microvascular dysfunction (CMD) is defined as abnormal coronary microvascular resistance (either arteriolar or pre-arteriolar) that is clinically evident as an inappropriate coronary blood flow response, impaired myocardial perfusion and/or myocardial ischemia that cannot be accounted for by abnormalities in the epicardial coronary arteries.**



Microvascular Dysfunction:

Classification

- Without myocardial/coronary disease
- With associated myocardial disease
- With associated epicardial disease
- Iatrogenic



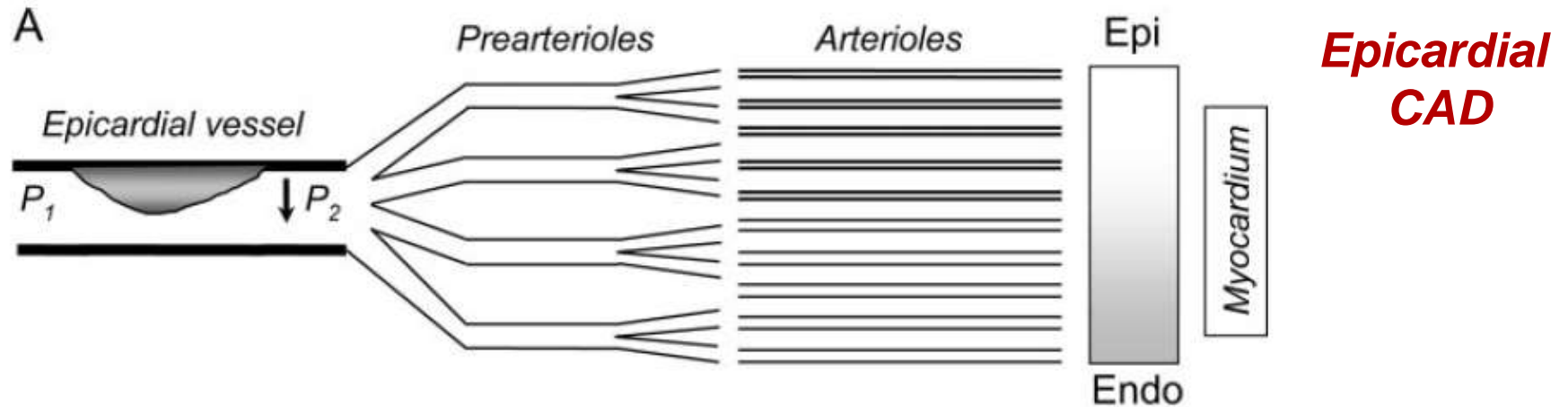
Assessment of the Microvasculature

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



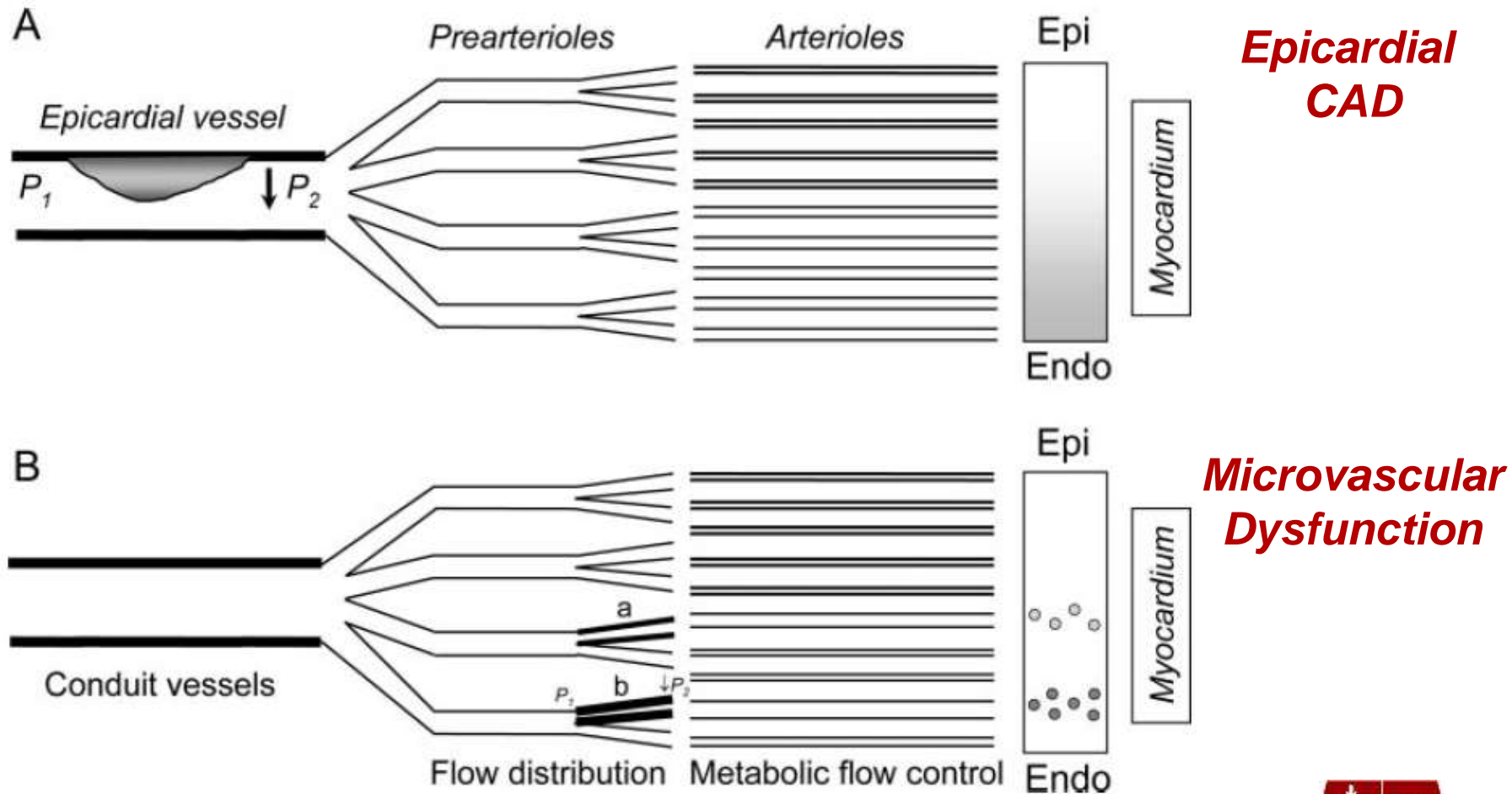
Assessment of the Microvasculature

Diagnostic Challenge



Assessment of the Microvasculature

Diagnostic Challenge



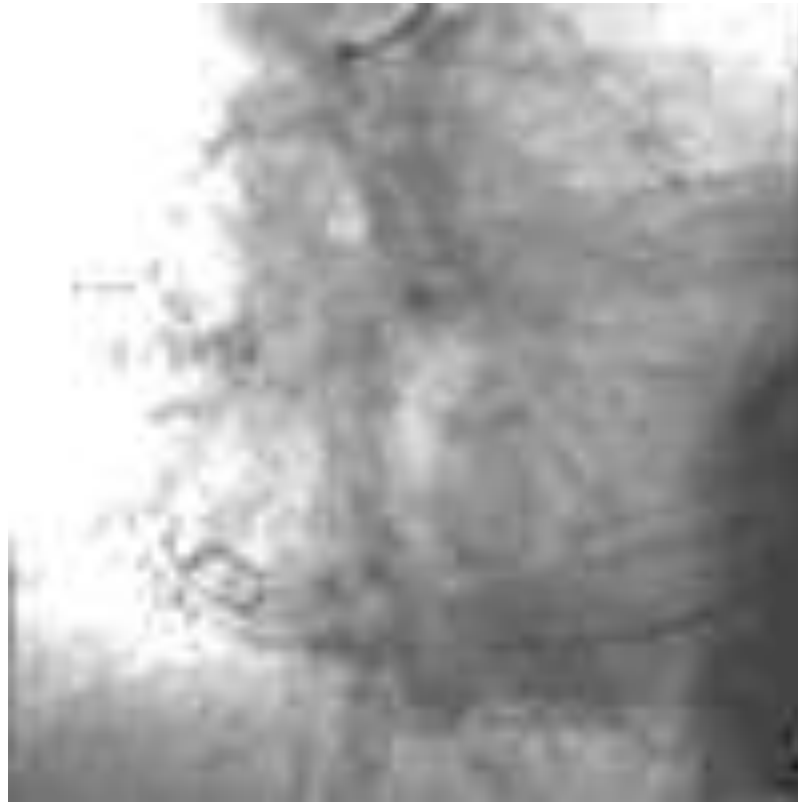
Assessment of the Microvasculature

- 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 *physiologic* 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 AMI studies

Drawbacks:

- Qualitative

- Interobserver variability

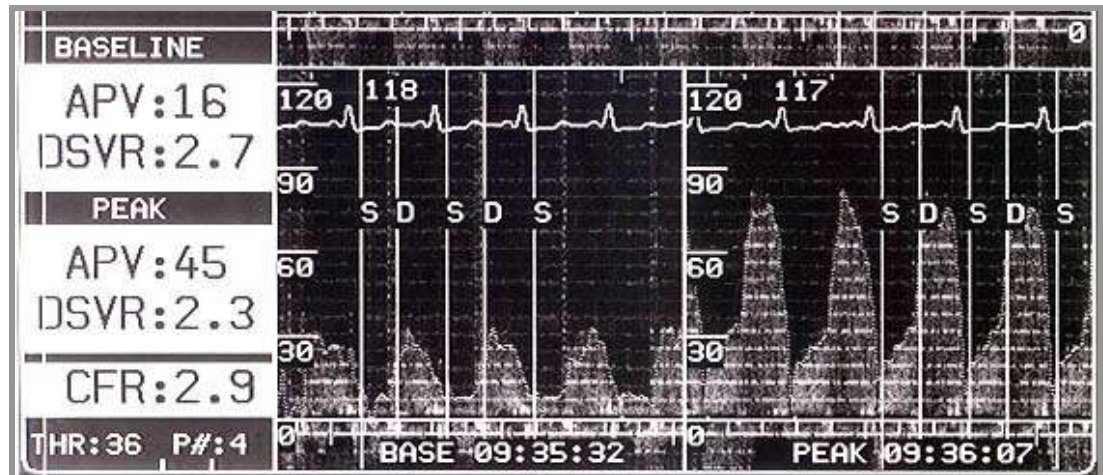
- Not as useful in smaller studies or stable patients



Doppler Wire Coronary Flow Reserve

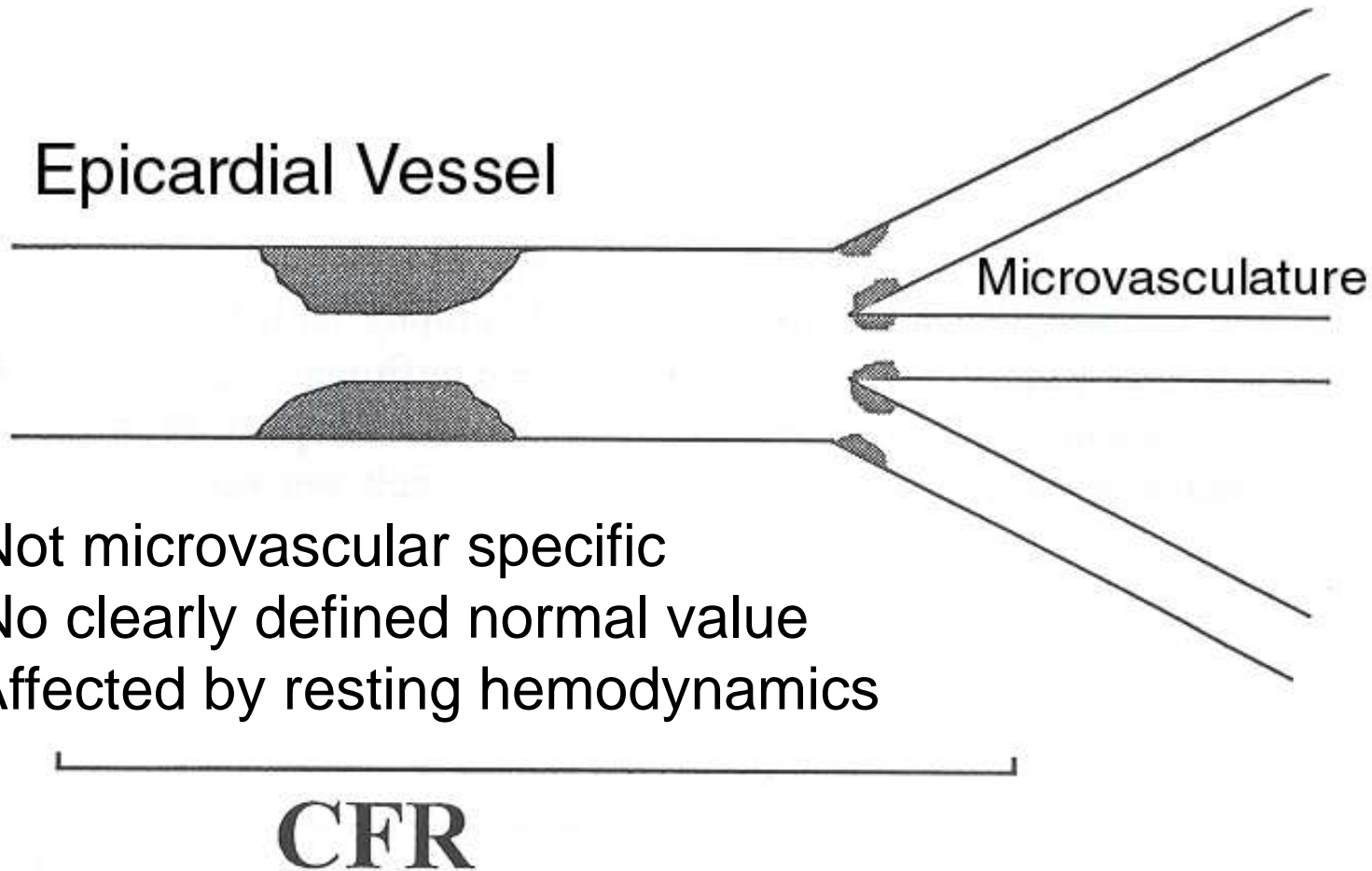


$$CFR = \frac{\text{Hyperemic Flow}}{\text{Resting Flow}}$$



Coronary Wire-Based Assessment

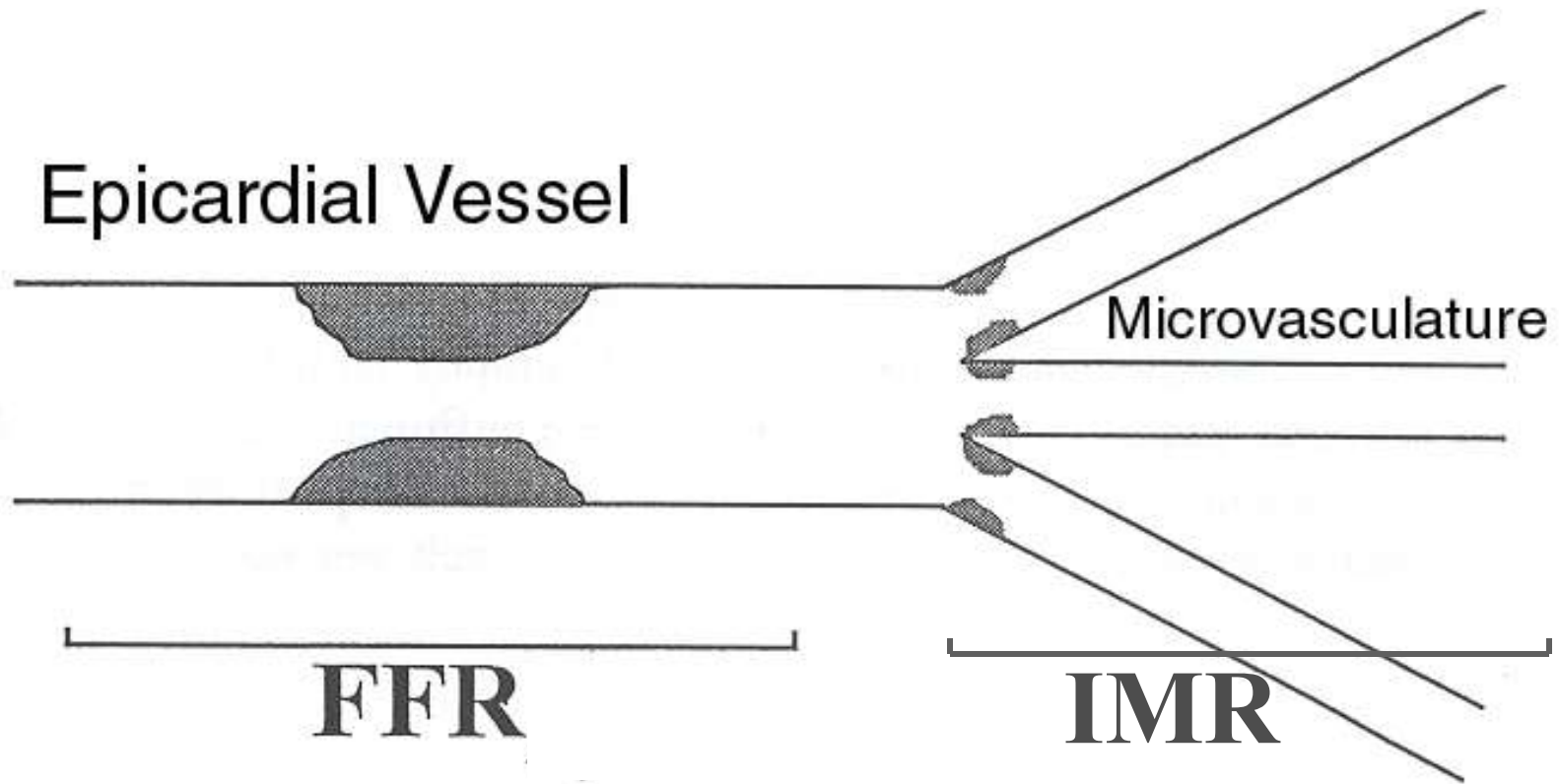
Coronary Flow Reserve



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



Index of Microcirculatory Resistance



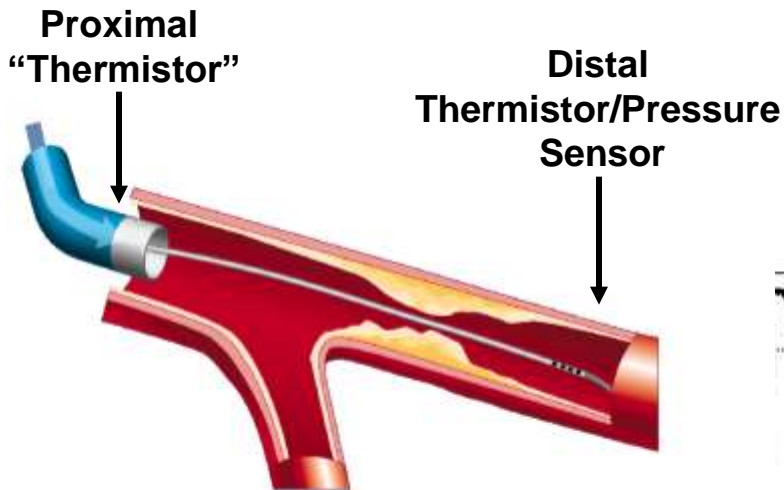
Index of Microcirculatory Resistance

Potential Advantages:

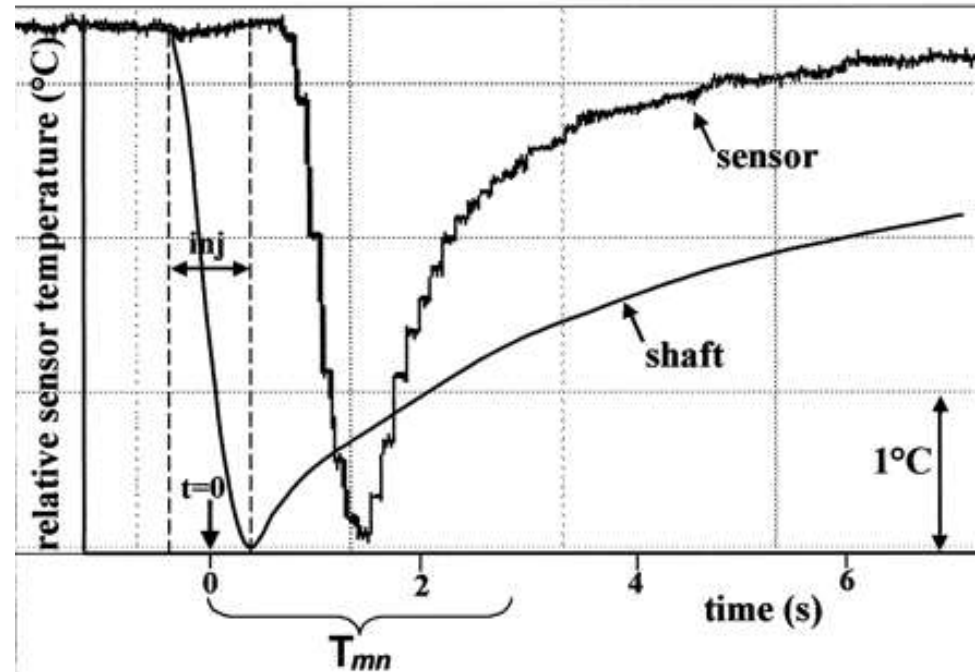
- ❑ Readily available in the cath lab
- ❑ Specific for the microvasculature
- ❑ Quantitative and reproducible
- ❑ Predictive of outcomes



Estimation of Coronary Flow



Calculation of mean transit time



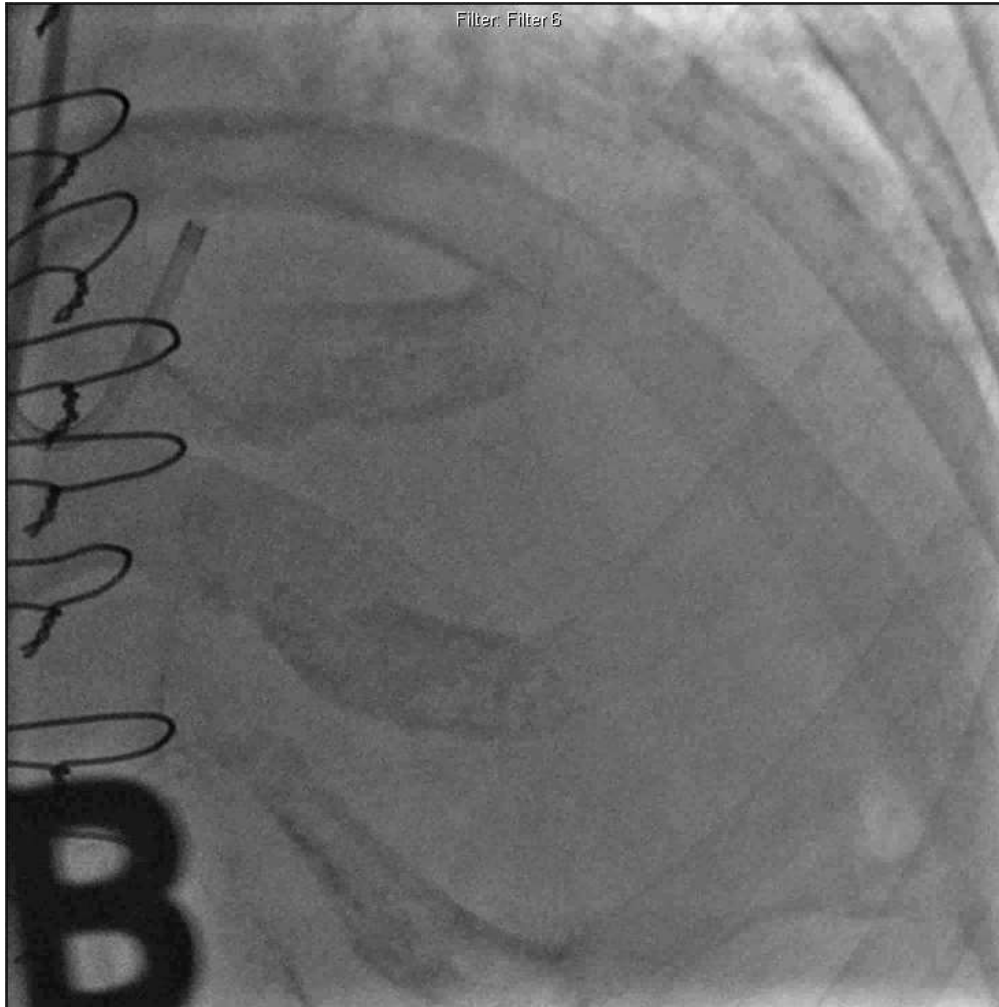
Derivation of IMR:

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



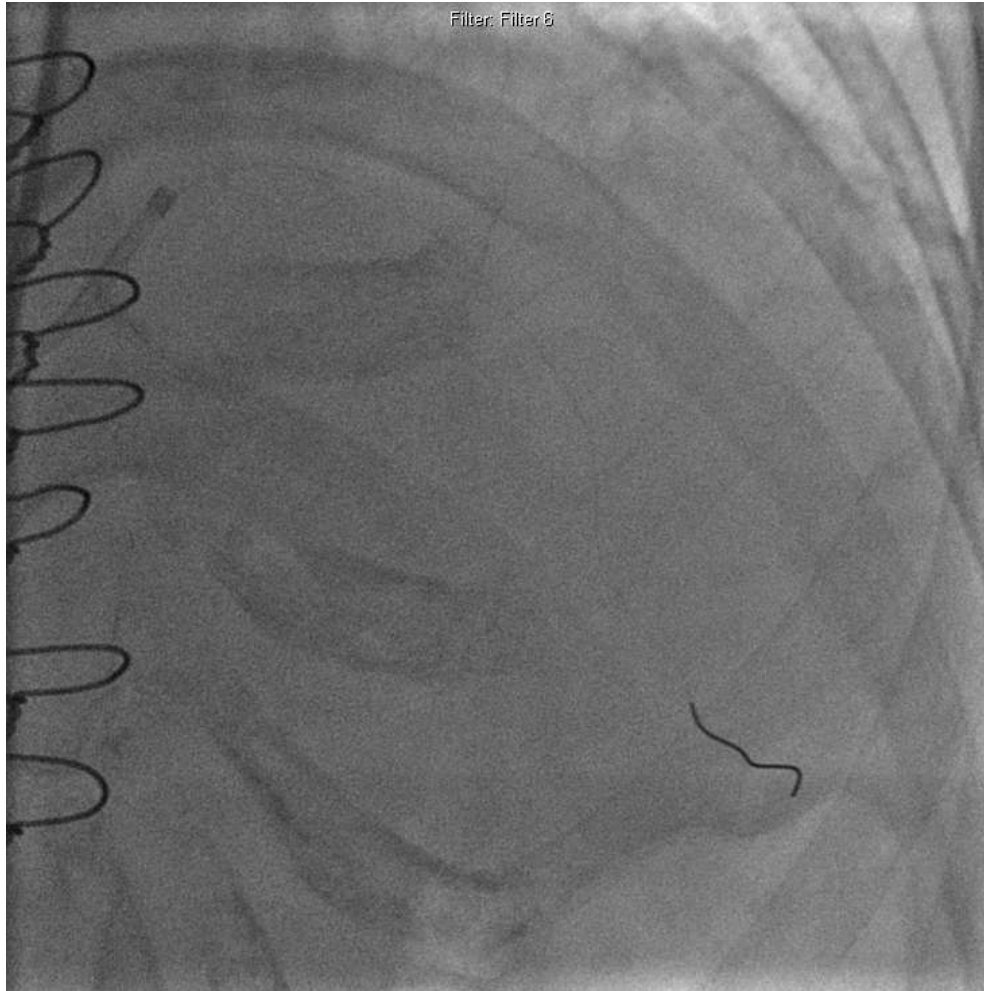
IMR Case Example

Cardiac transplant recipient enrolled in study evaluating ACE inhibition



IMR Case Example

Cardiac transplant recipient enrolled in study evaluating ACE inhibition



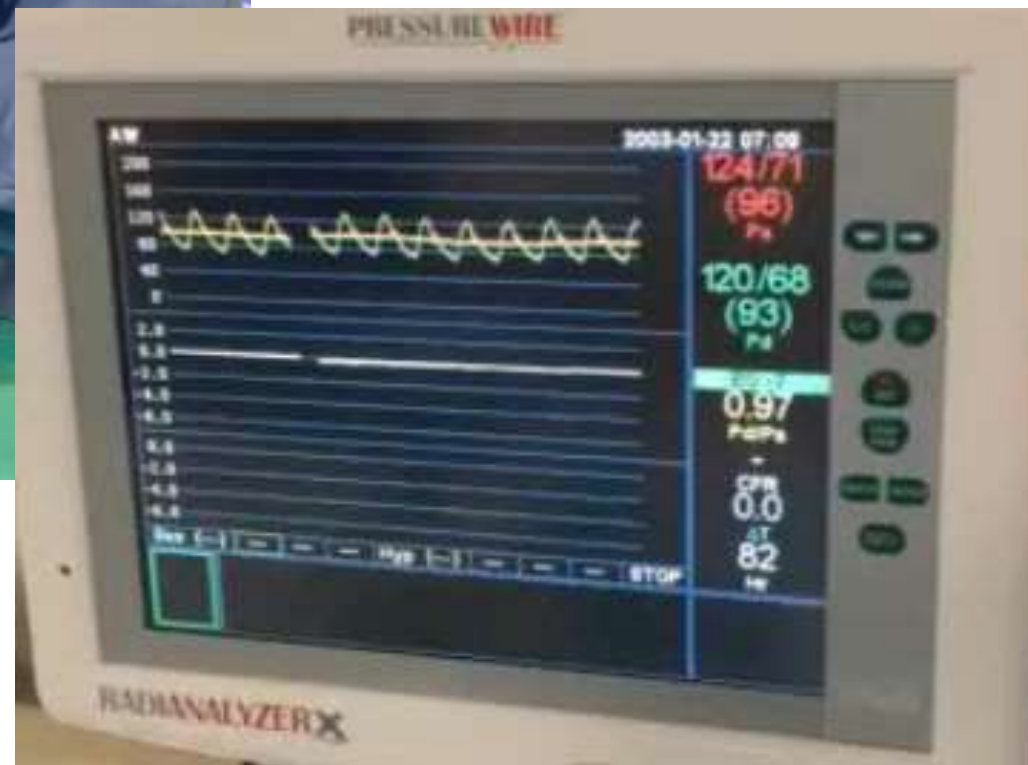
Accessing IMR



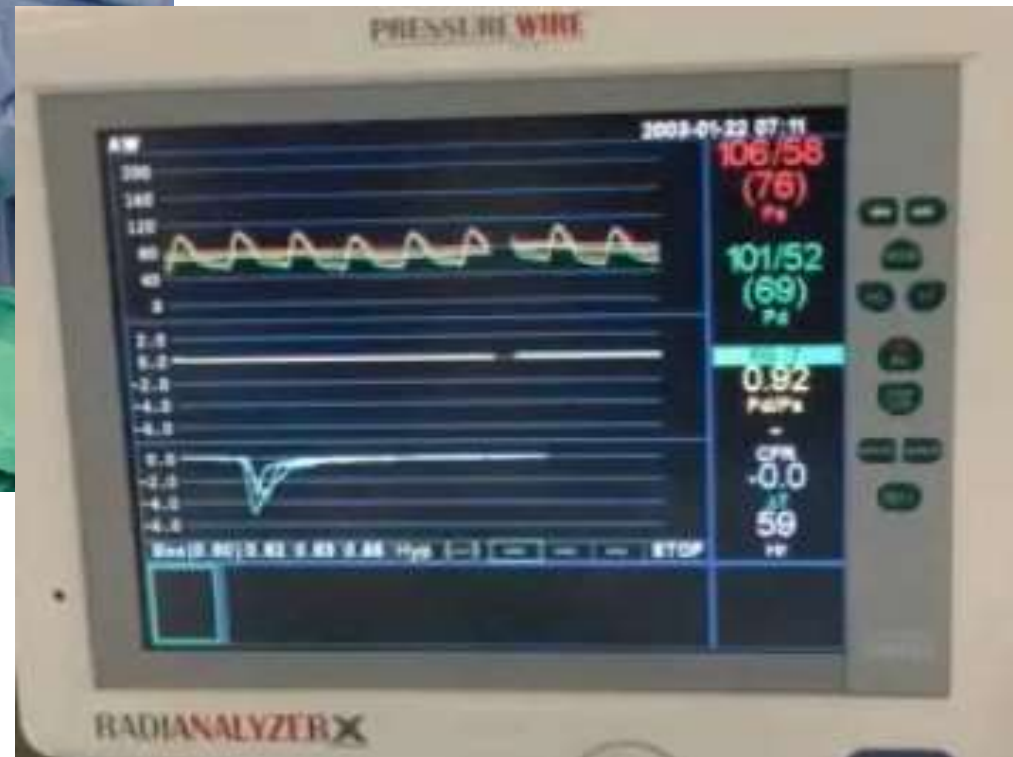
Flushing the System



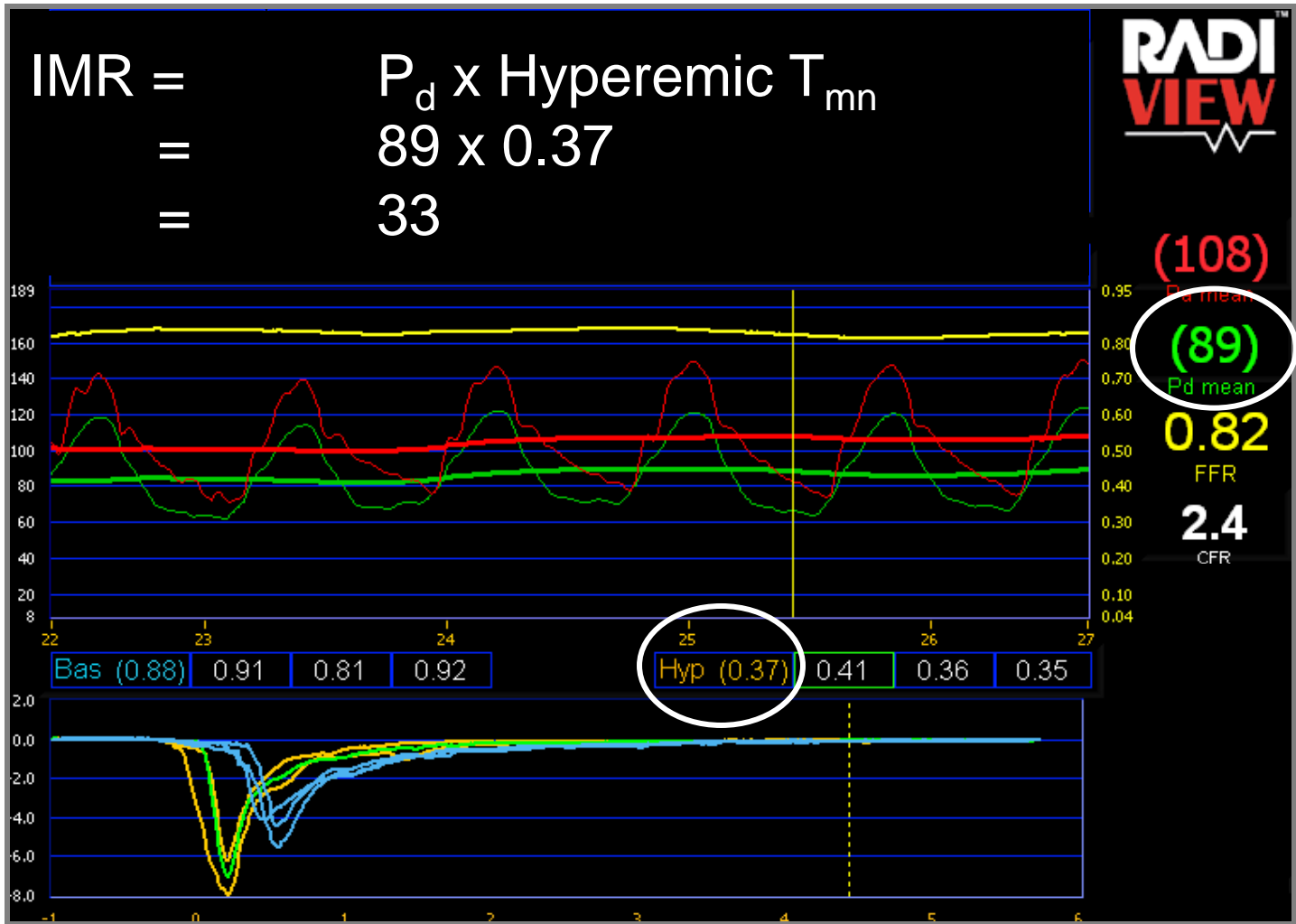
Resting T_{mn} Measurements



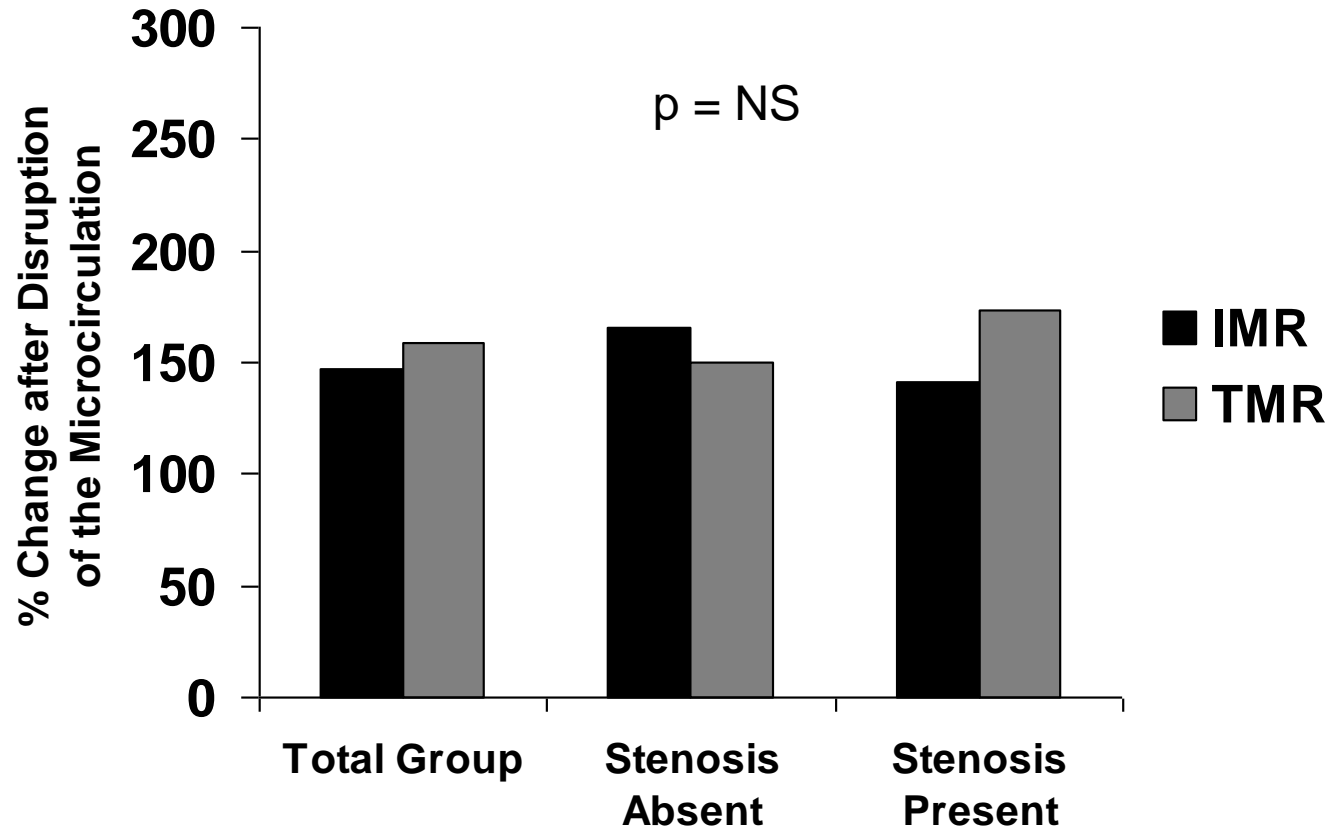
Hyperemic T_{mn} Measurements



Practical Measurement of IMR



Animal Validation of IMR



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

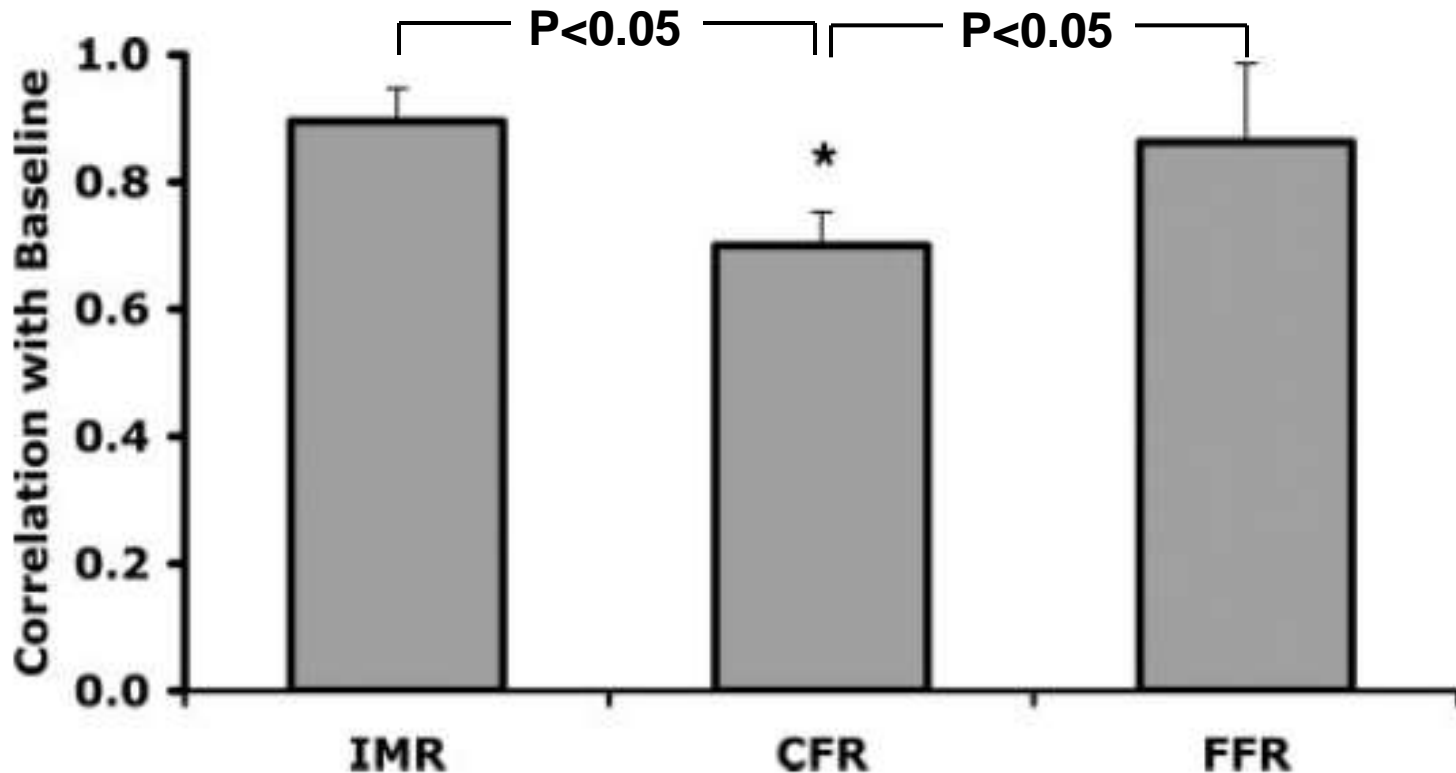
Change in LV Contractility and FFR/CFR/IMR

	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



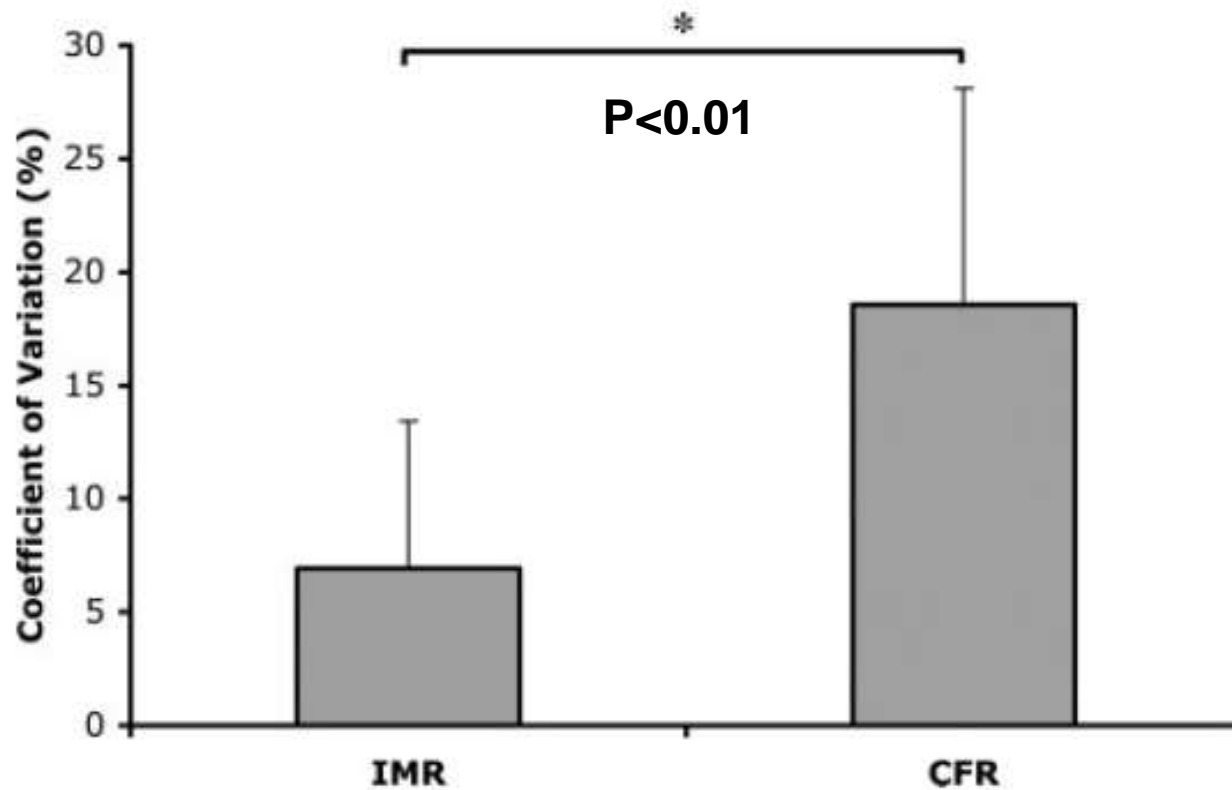
Reproducibility of IMR

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



Reproducibility of IMR

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



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], $P=0.48$).



Sex Differences and CFR

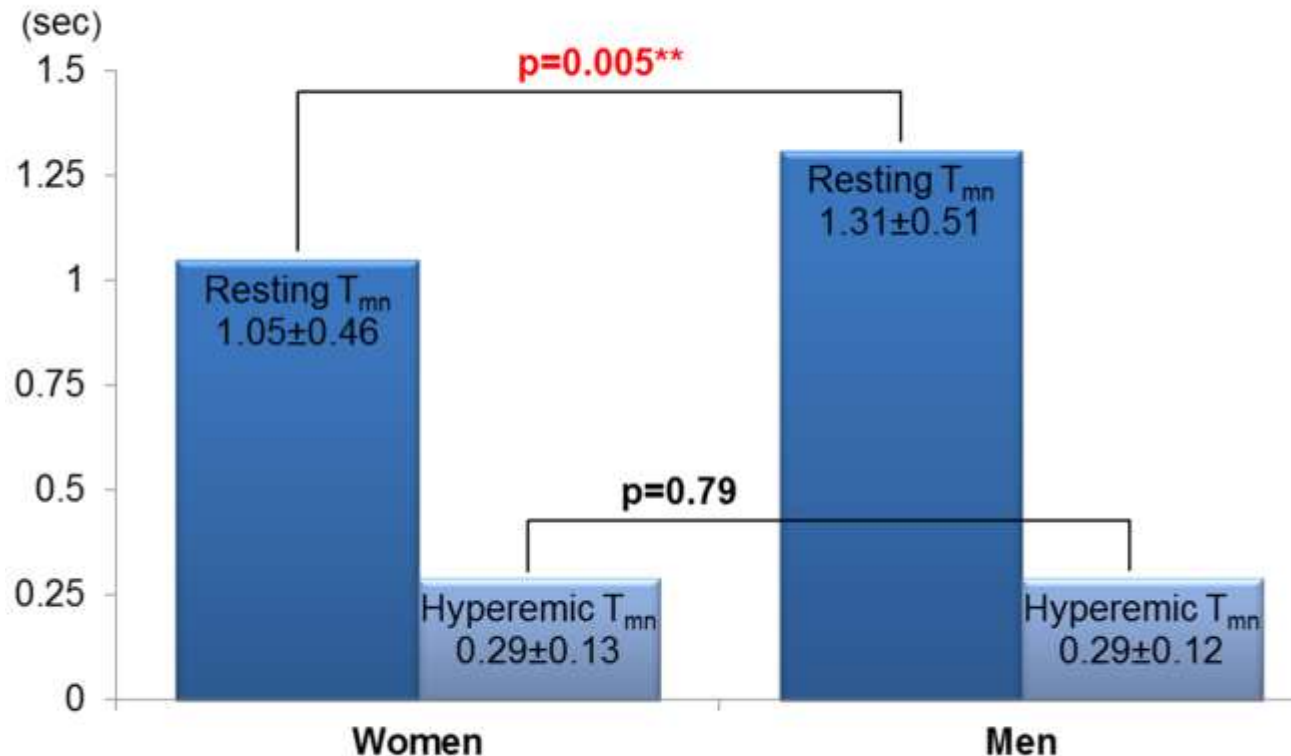
FFR, IMR and CFR measured in 157 patients (40 men) with NOCAD

- IMR was similar between the sexes (20.7 ± 9.8 vs. 19.1 ± 8.0 , $p=0.45$), but CFR was lower in women (3.8 ± 1.6 vs. 4.8 ± 1.9 , $p=0.004$).
- This was primarily due to a shorter resting T_{mn} in women ($p=0.005$).
- Hyperemic T_{mn} was identical ($p=0.79$).
- On multivariate analysis, female sex was an independent predictor of lower CFR and shorter resting T_{mn} , but not a predictor of IMR or hyperemic T_{mn} .



Sex Differences and CFR

FFR, IMR and CFR measured in 157 patients (40 men) with NOCAD

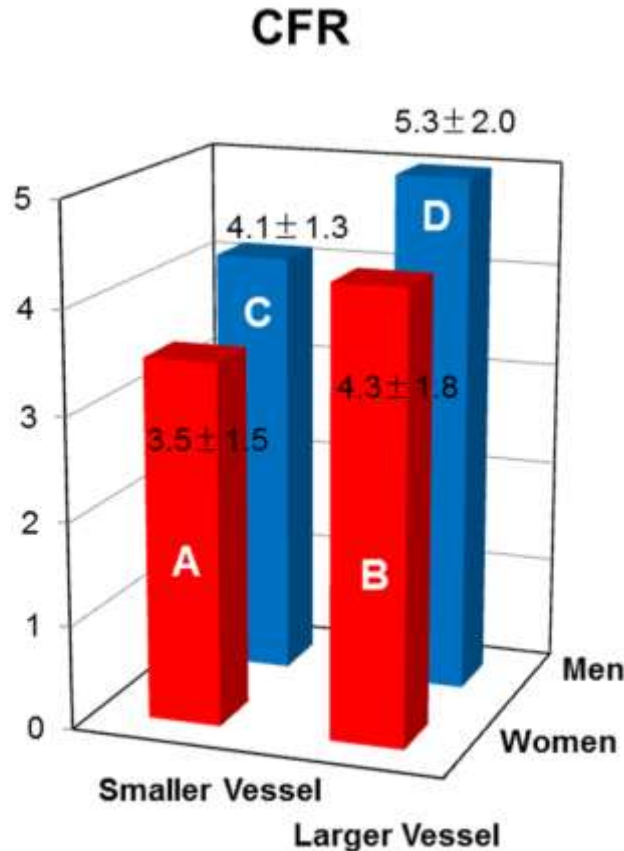


T_{mn}: an inverse correlate to absolute coronary flow

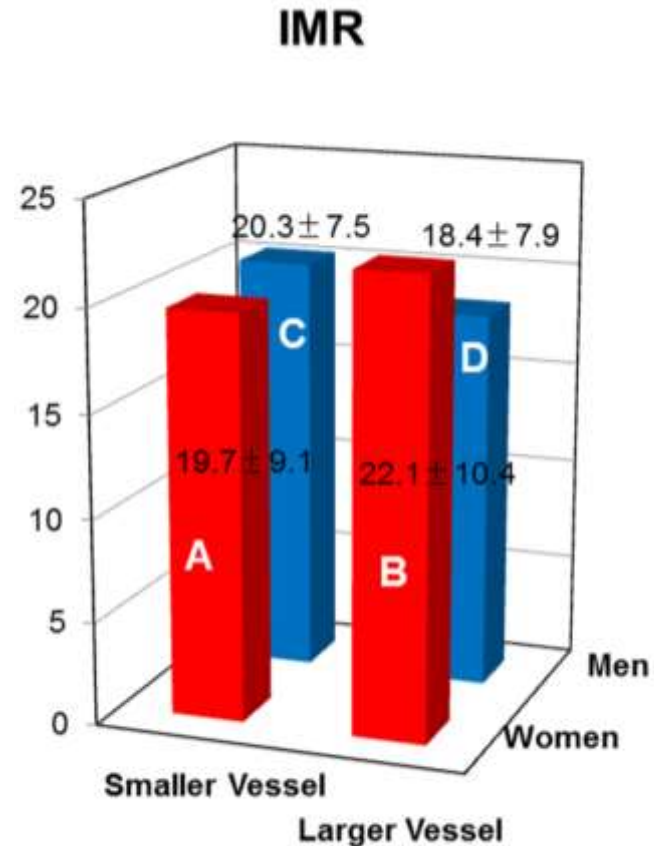


Sex Differences and CFR

FFR, IMR and CFR measured in 157 patients (40 men) with NOCAD



ANOVA $p=0.002$ (A vs. D, $p=0.002$)



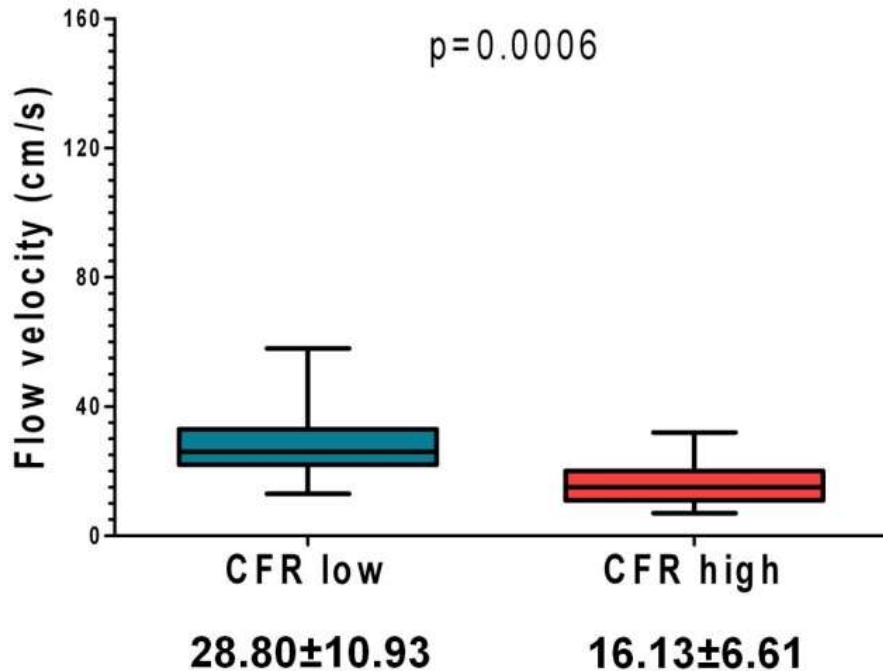
ANOVA $p=0.41$



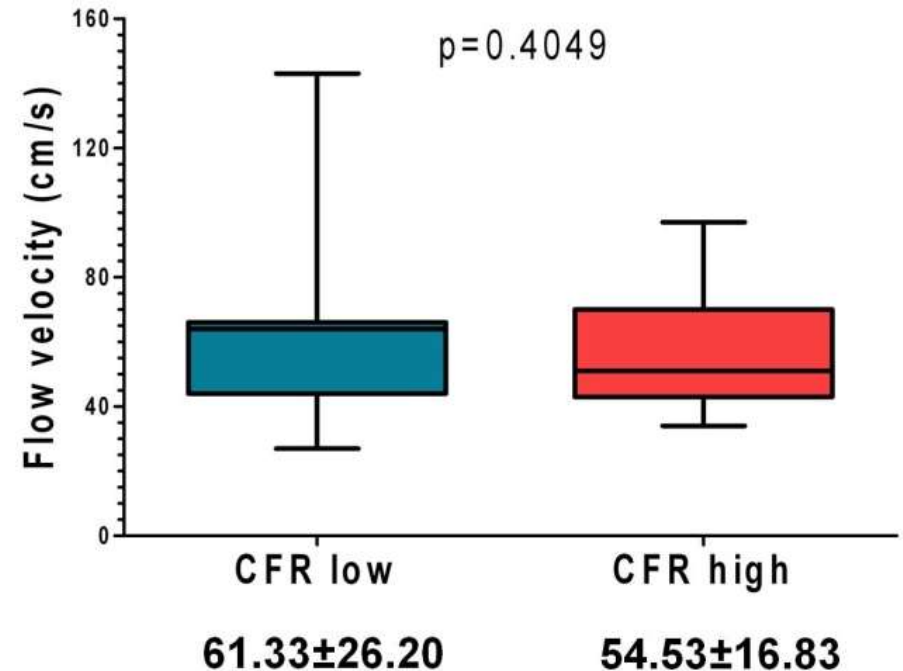
“Resting Flow” and CFR

Doppler wire-derived CFR measured in 30 patients

Baseline flow



Hyperemic flow



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 .
- The mean IMR in 20 subjects with no CAD or risk factors was 14.0 with all values <23.

Melikian, et al. Eurointervention 2010;5:939-945.

Luo, et al. Circ Cardiovasc Interv 2014;7:43-48.

Solberg, et al. Eurointervention 2014;9:1069-75.



Evaluation of NOCAD:

Case Example

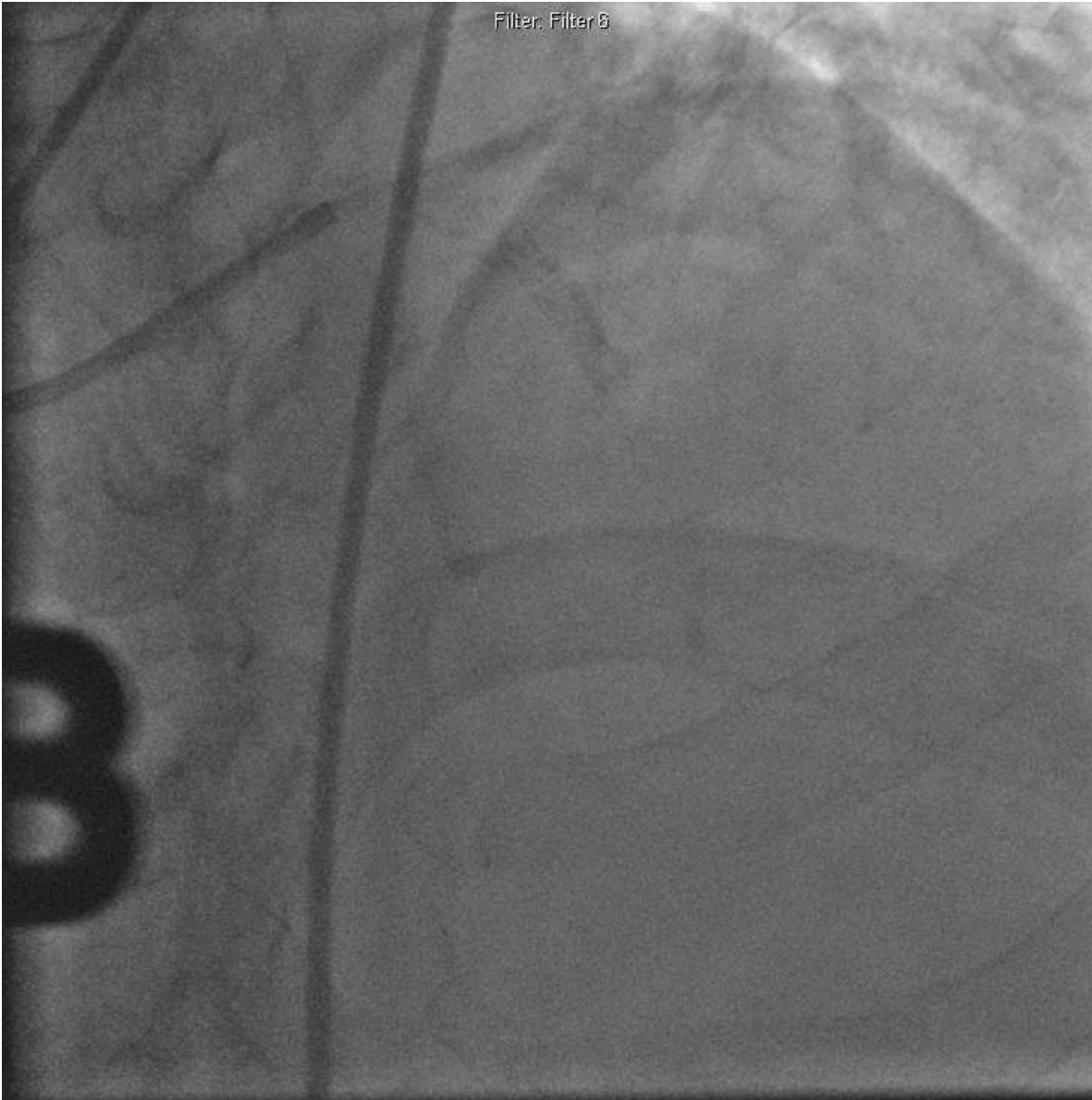
- 72 year old retired naval officer
- HTN and dyslipidemia
- PCI of proximal LAD in 2006
- Some relief of angina
- Recent worsening angina
- Multiple stress tests (mild apical ischemia) and coronary angiograms



Filter: Filter6



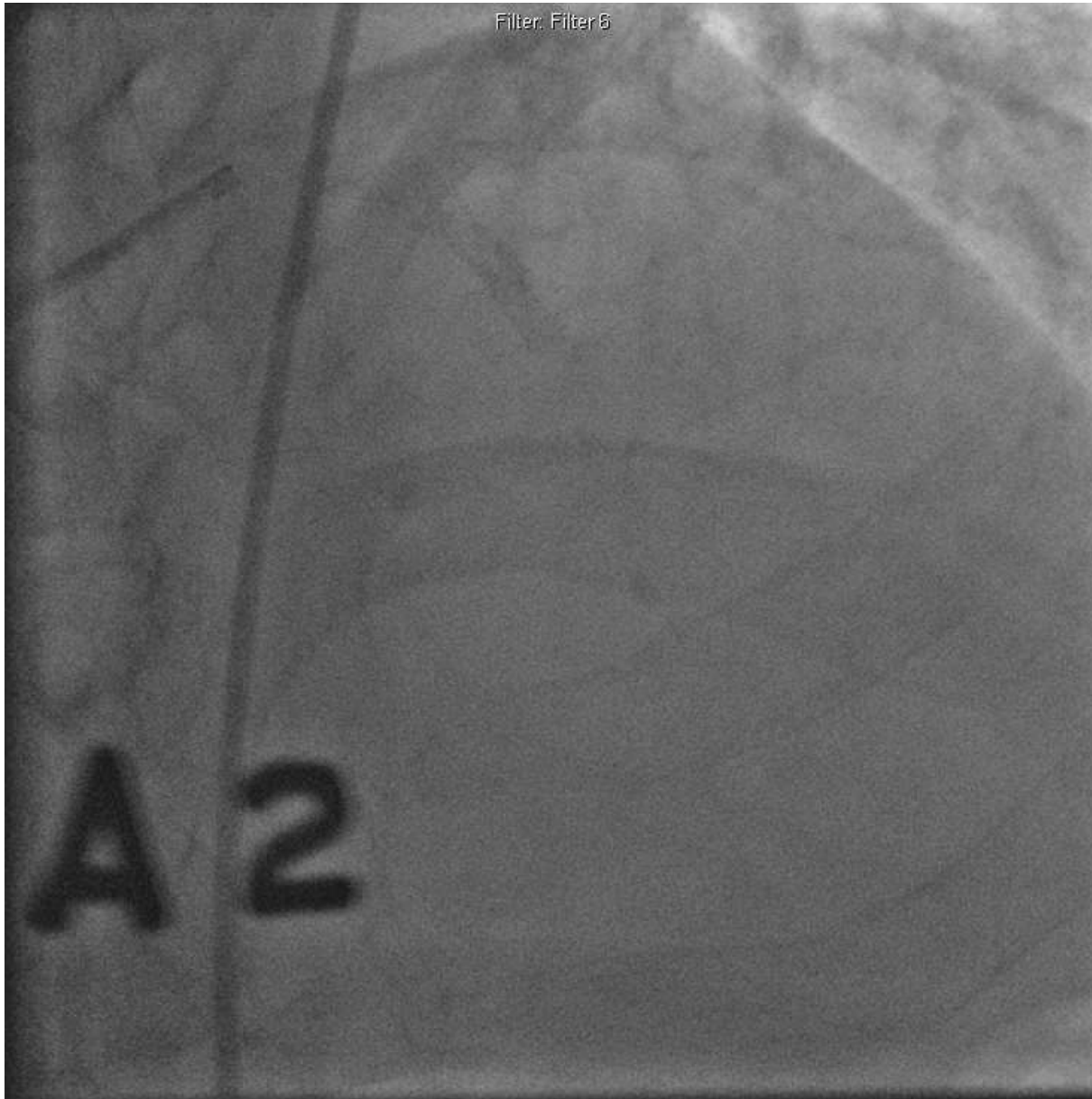
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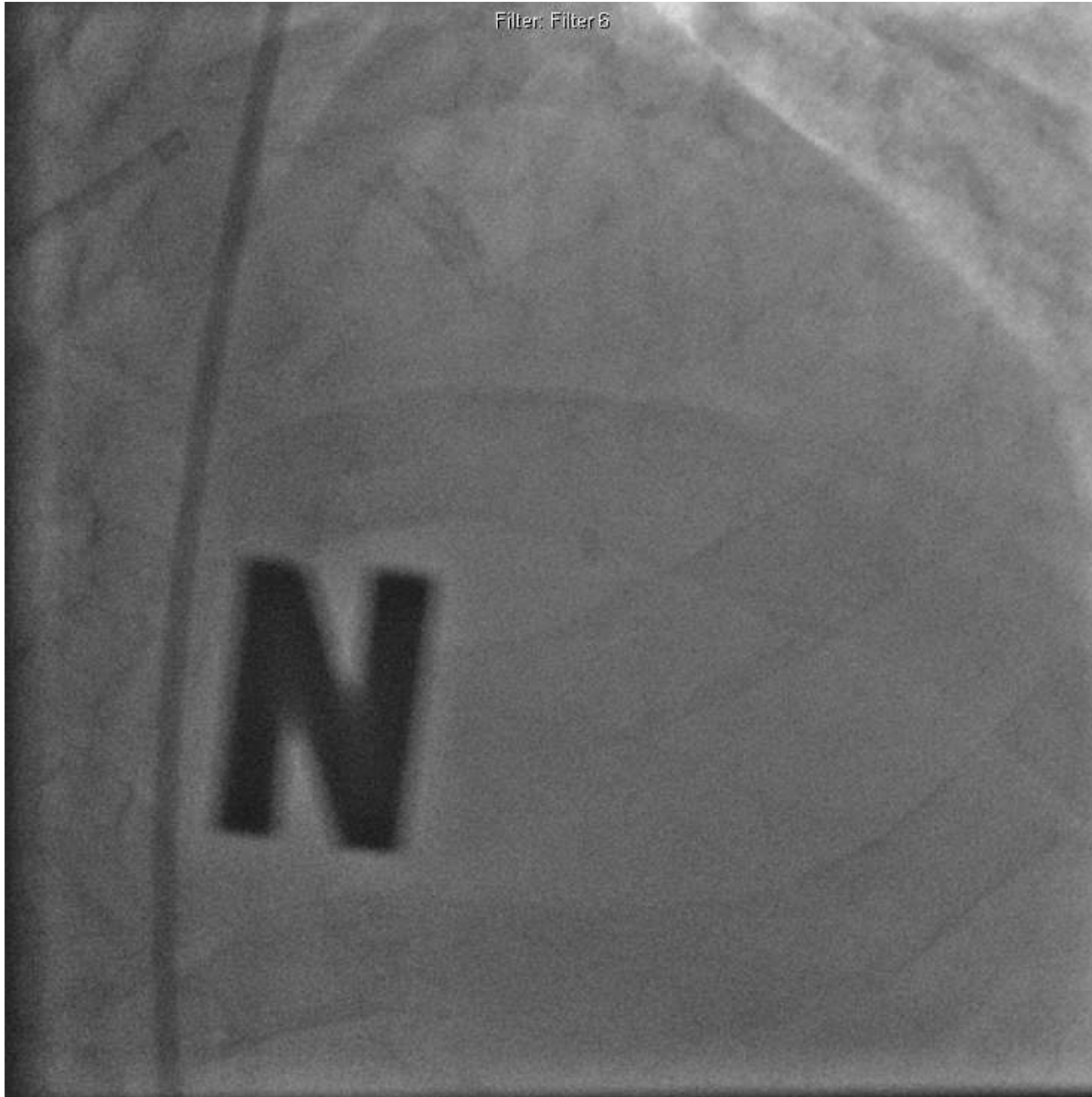
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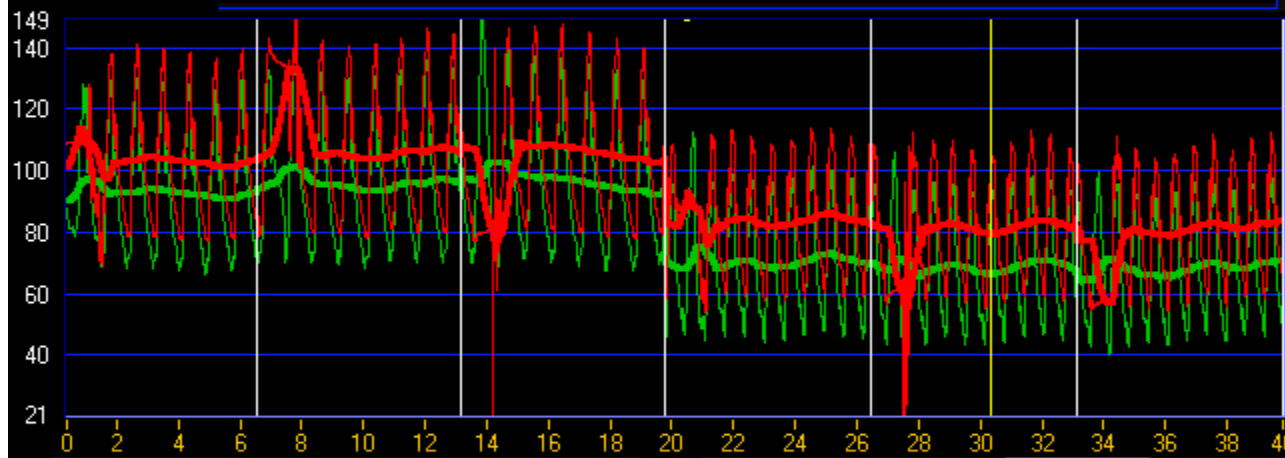
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IMR of LAD = 28

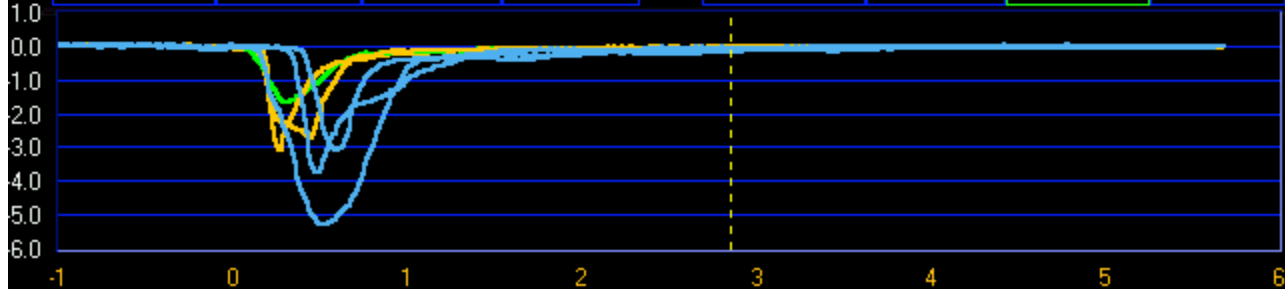


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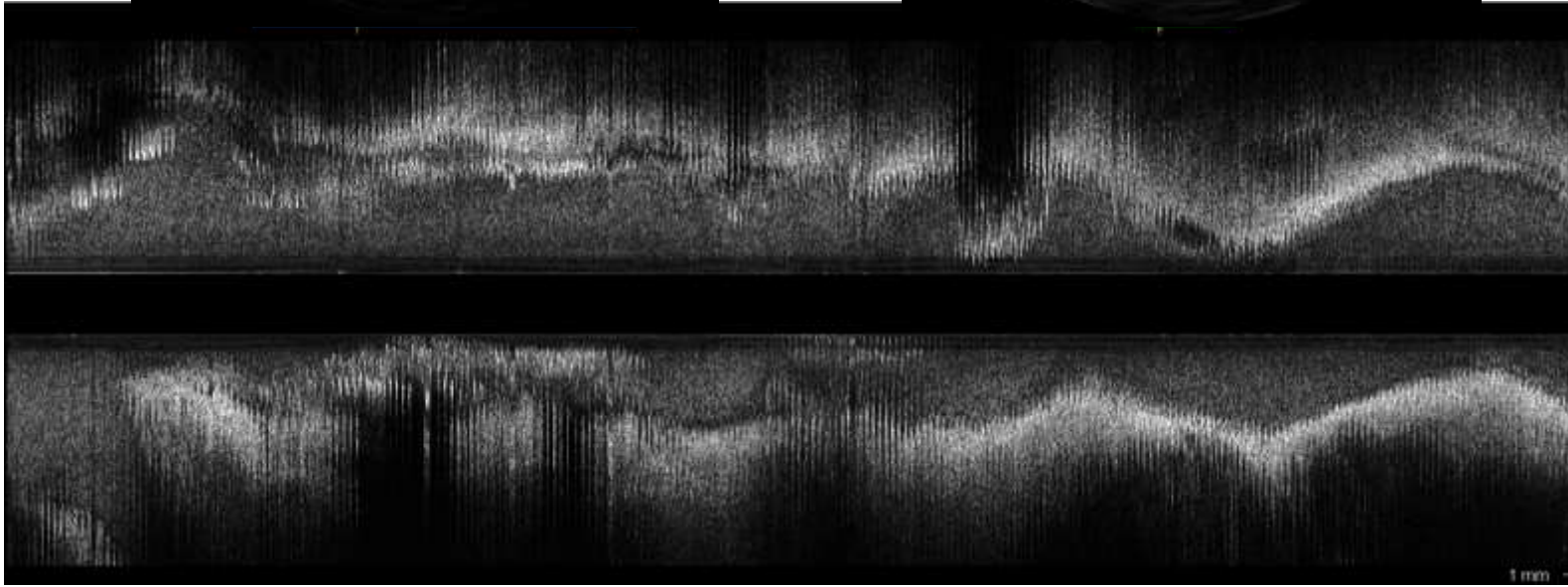
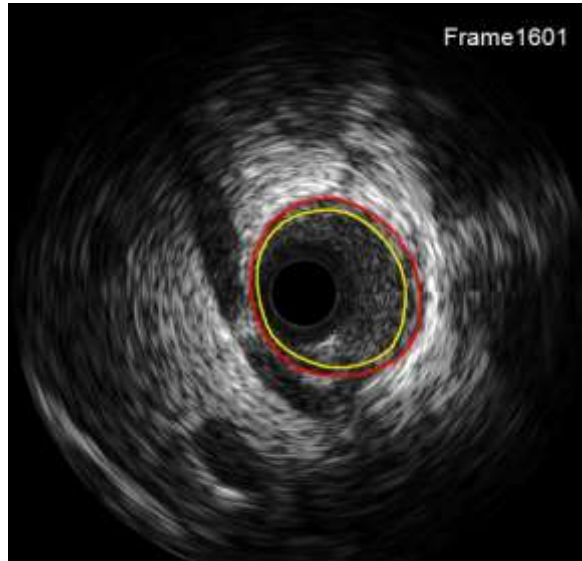
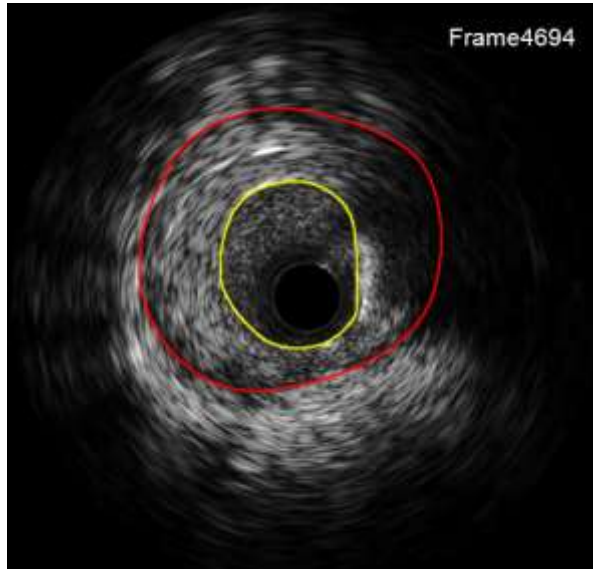
80
Pa mean
66
Pd mean
0.83
FFR
1.6
CFR
-0.03
dT
2.9
CURSOR

Bas(0.66) 0.70 0.70 0.58 Hyp(0.42) 0.38 0.45 0.43



MSA = 4.3 mm²

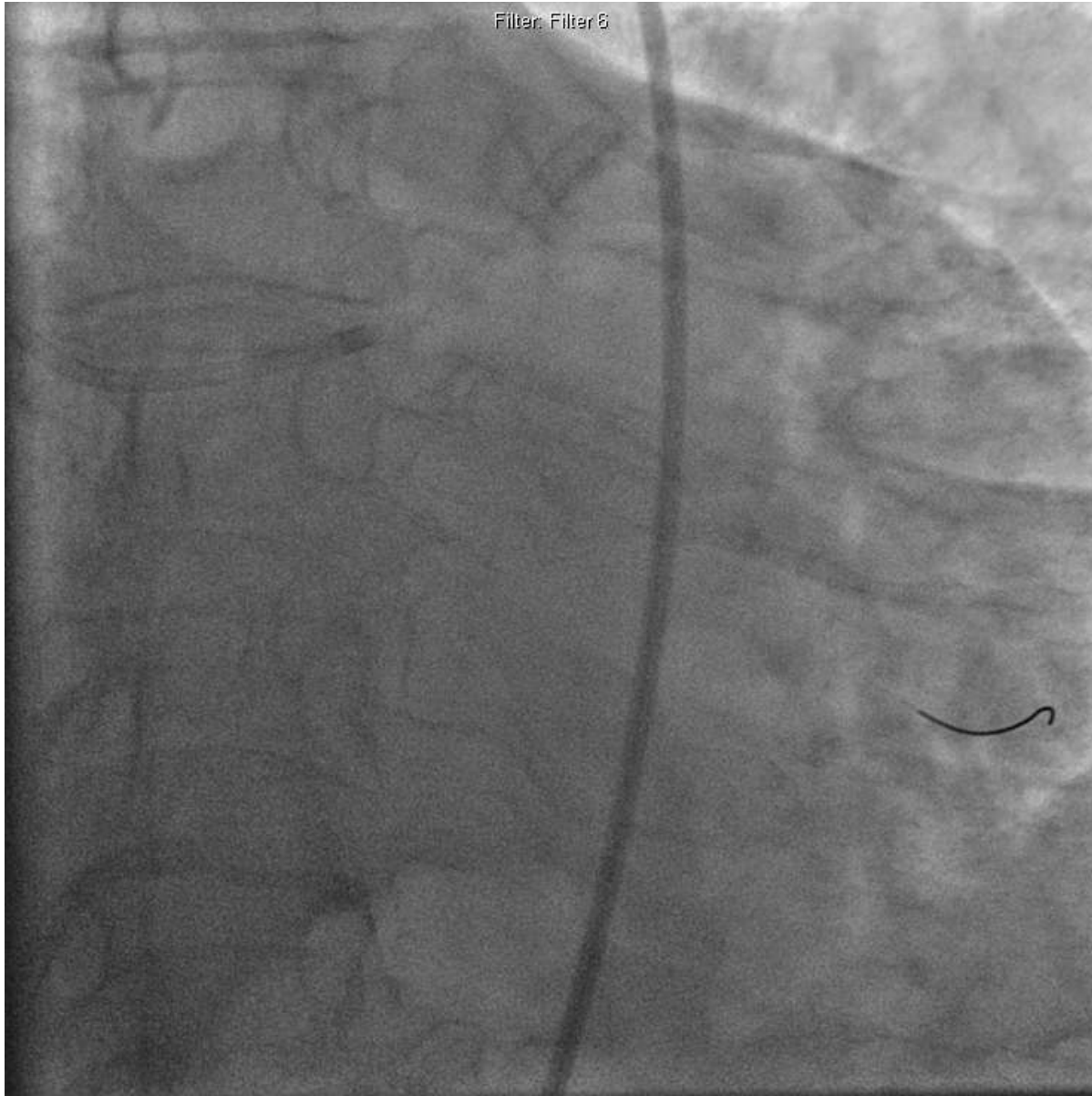
Myocardial Bridge



IVUS of LAD



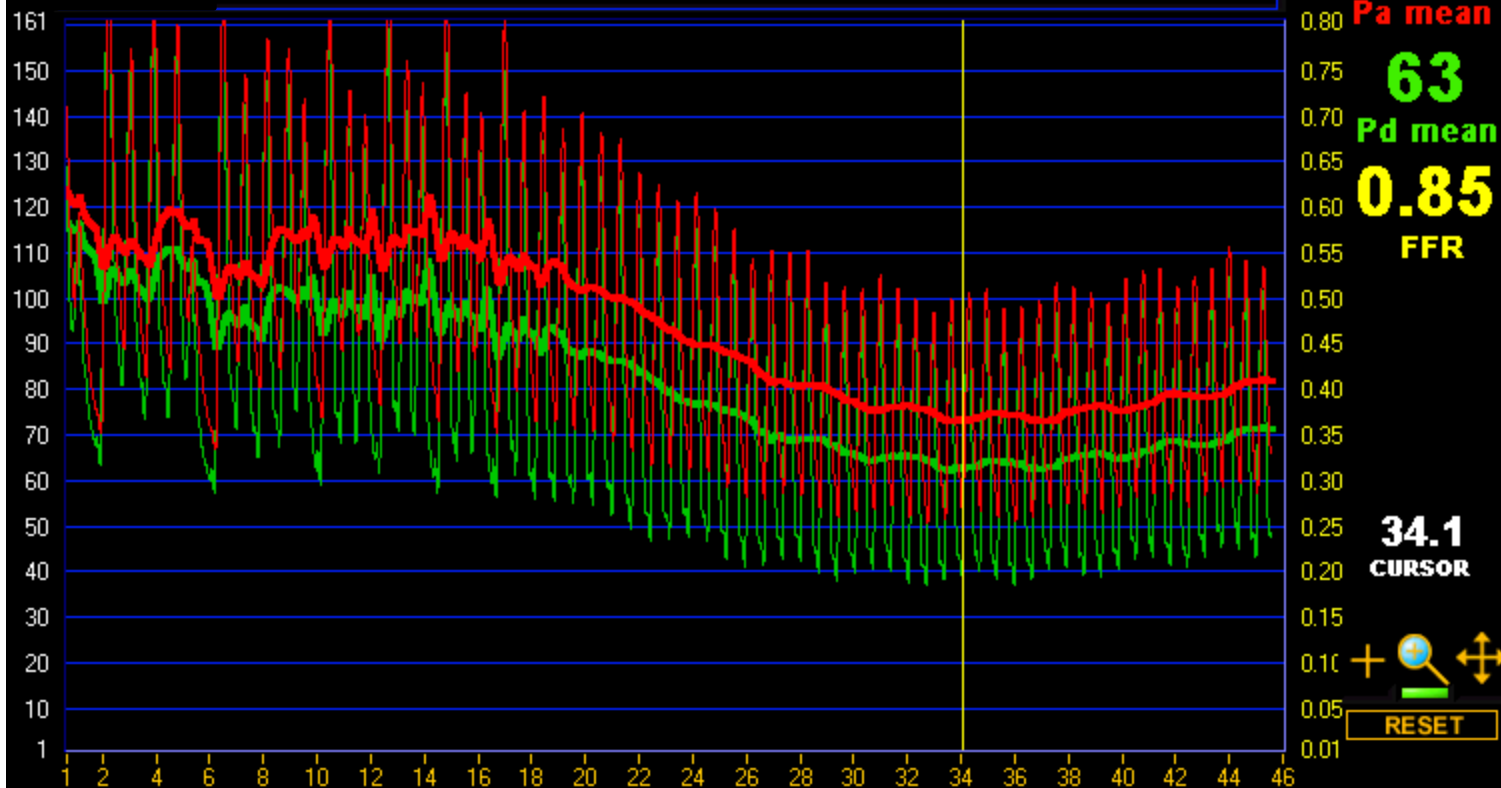
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FFR OM = 0.85



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Case Summary:

- No significant endothelial dysfunction/spasm
- Moderate restenosis of the LAD stent with mild diffuse epicardial atherosclerosis, which is not functionally significant
- Short mild bridging which is not significant
- Evidence for microvascular dysfunction
- Moderate OM disease which is not functionally significant
- Treatment plan: Augment medical therapy (statin, ACE I, carvedilol, nitroglycerin PRN)



Chest Pain and NOCAD

- 139 patients referred for coronary angiography because of symptoms and/or abnormal stress test and found to have NOCAD
- FFR, IMR, CFR, IVUS and acetylcholine challenge were performed down the LAD



Chest Pain and NOCAD

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



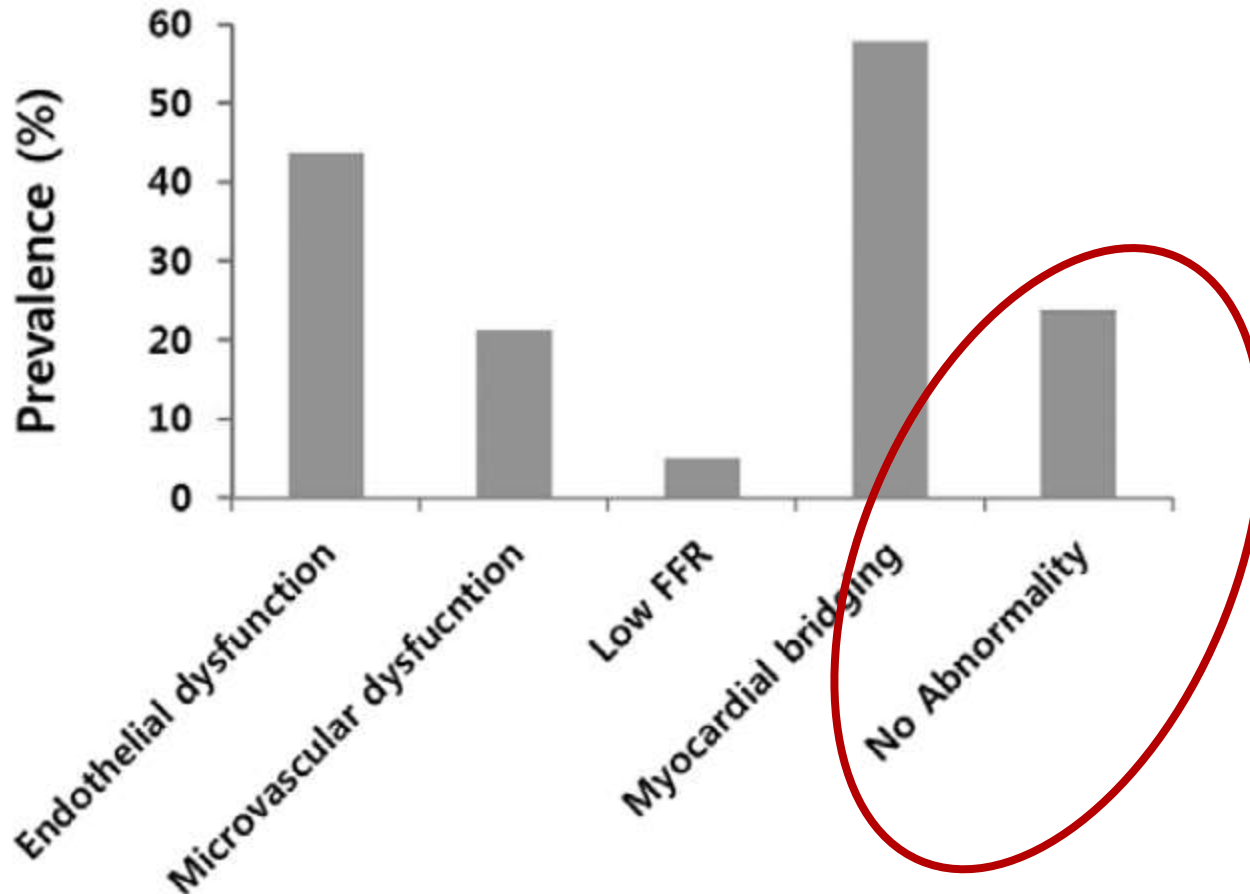
Chest Pain and NOCAD

- The mean IMR was 19.6 ± 9.1
- Microvascular dysfunction was present in 21% (defined as $\text{IMR} \geq 25$)
- Patients with microvascular dysfunction were older and more often hypertensive and diabetic



Chest Pain and NOCAD

77% of patients had at least one occult coronary circulatory abnormality



Conclusion:

- The evaluation of the patient with chest pain and no obstructive coronary artery disease (NOCAD) can be performed safely and relatively easily on a routine basis.
- The information provided will help diagnose the etiology of the patient's chest pain and may help to guide therapy.

