Coronary Microvascular Dysfunction: *Can we open the "Black Box"?*

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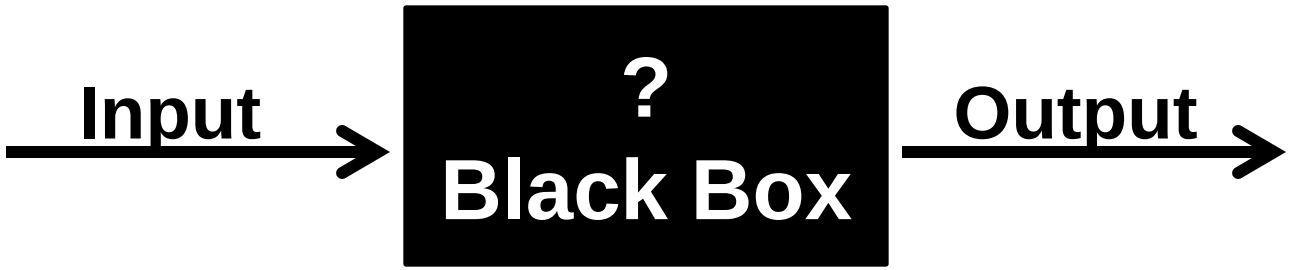
Disclosure Slide:

- Institutional Research Grant
  - St. Jude Medical
- Advisory Board
  - HeartFlow, Inc.

What is a “Black Box”?

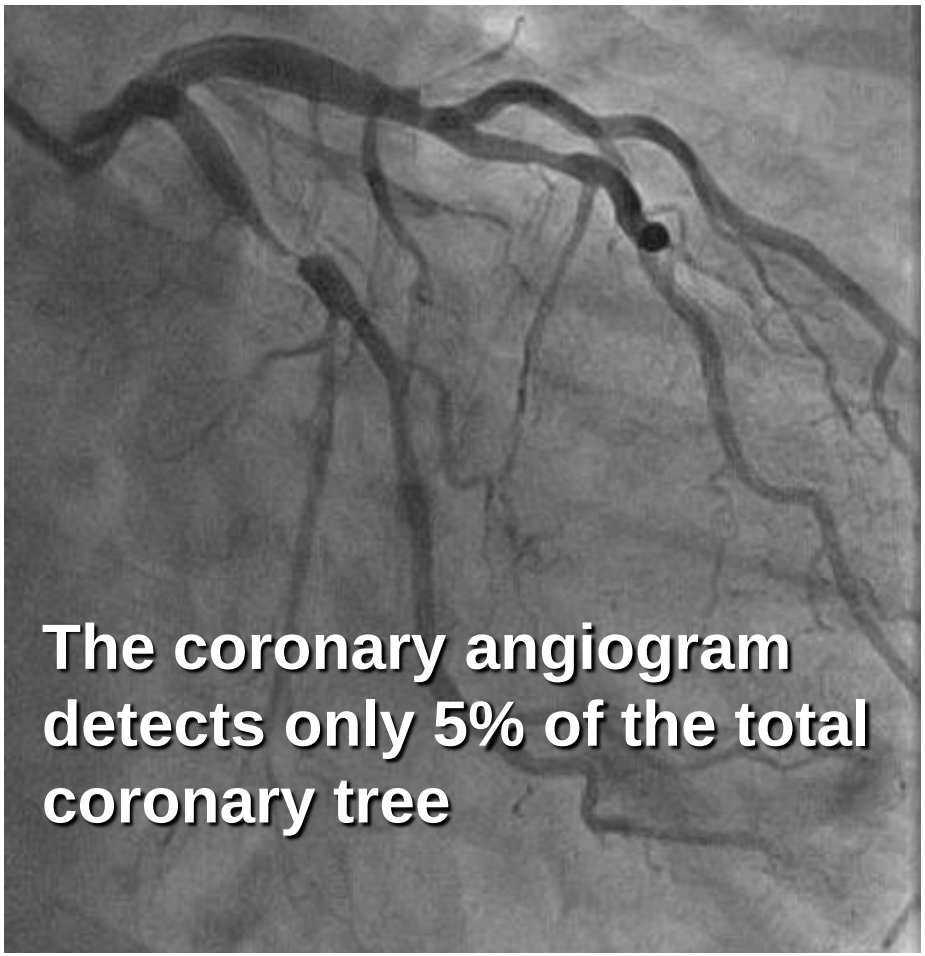
- **A device, system or object which can be viewed in terms of its input, output and transfer characteristics without any knowledge of its internal workings. Its implementation is "opaque" (black).**

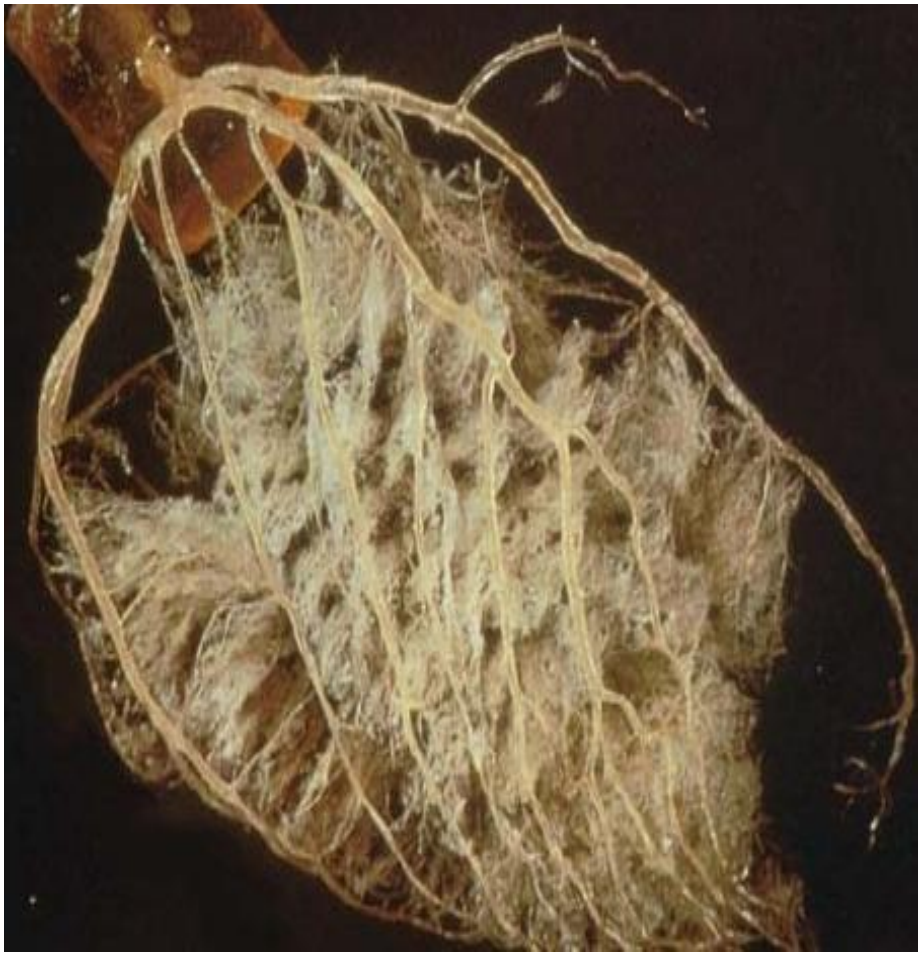


Microvasculature

Wikipedia (April 2013)

What is the Microvasculature?





Courtesy of Bernard De Bruyne, MD,PhD

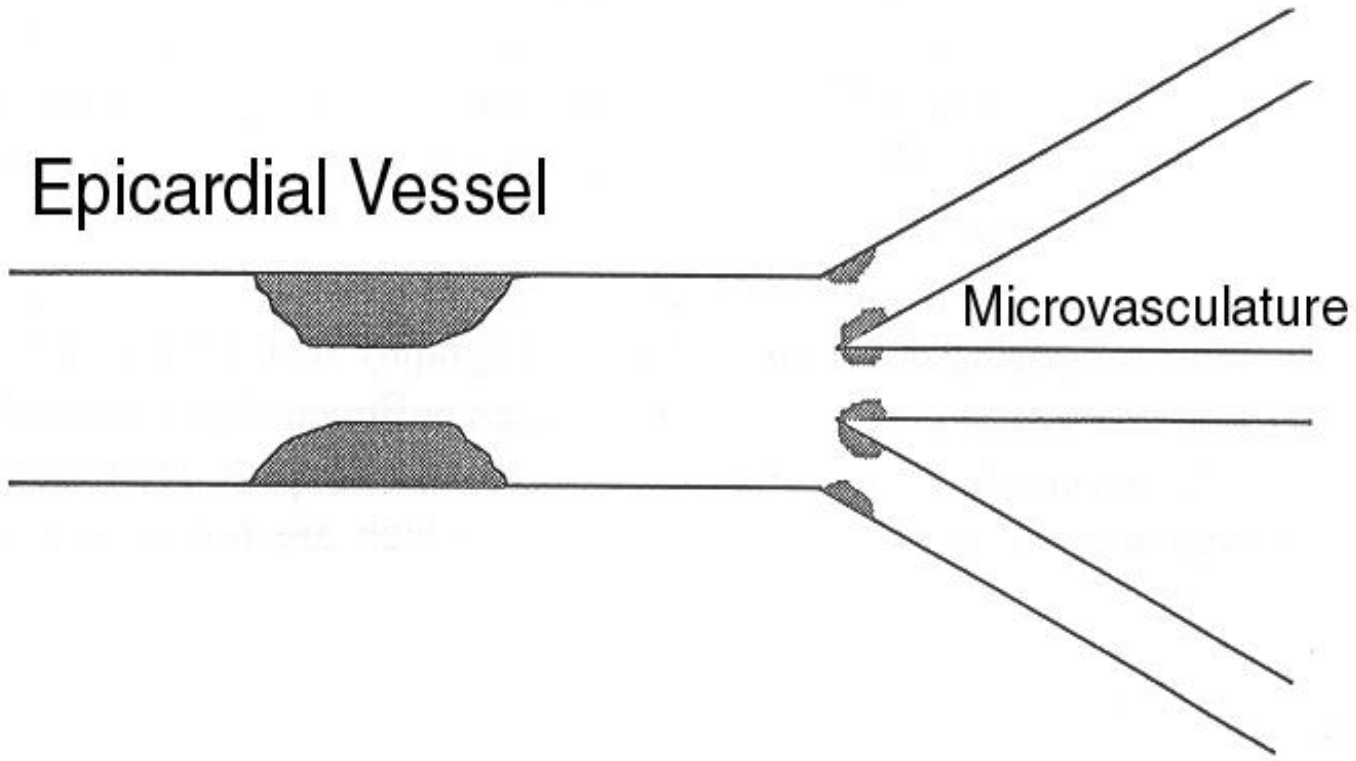
Why is it a “Black Box”?

- Cannot image *in vivo* (~0.5 mm resolution of angiography)
- Animal models are not great representations
- Myocardial biopsy only includes <0.2 mm vessels and patchy
- Noninvasive imaging is challenging because of need to separate epicardial vessel and because of patchy nature (often no wall motion abnormality)
- Therefore, assessment of the microvasculature is primarily *functional* and not *anatomic*

Beltrame, et al. Heart, Lung and Circulation 2009;18:19–27

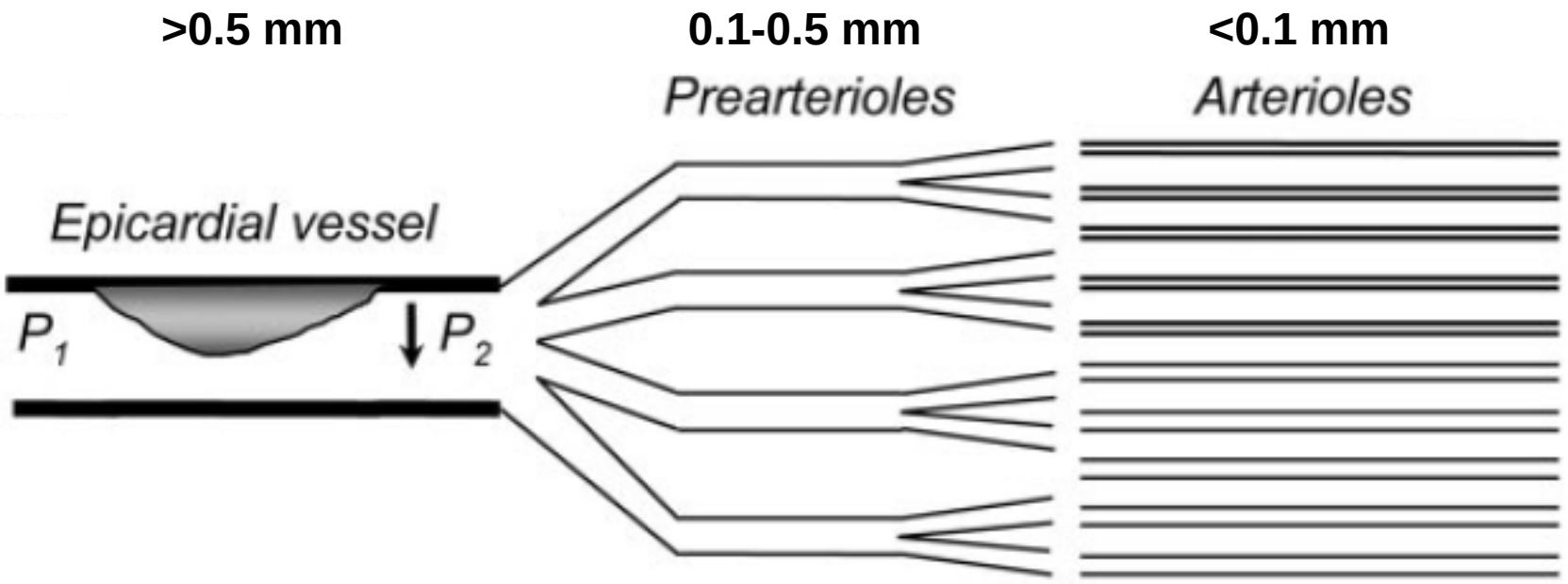
What is the Microvasculature?

Two Compartment Model



What is the Microvasculature?

Three Compartment Model

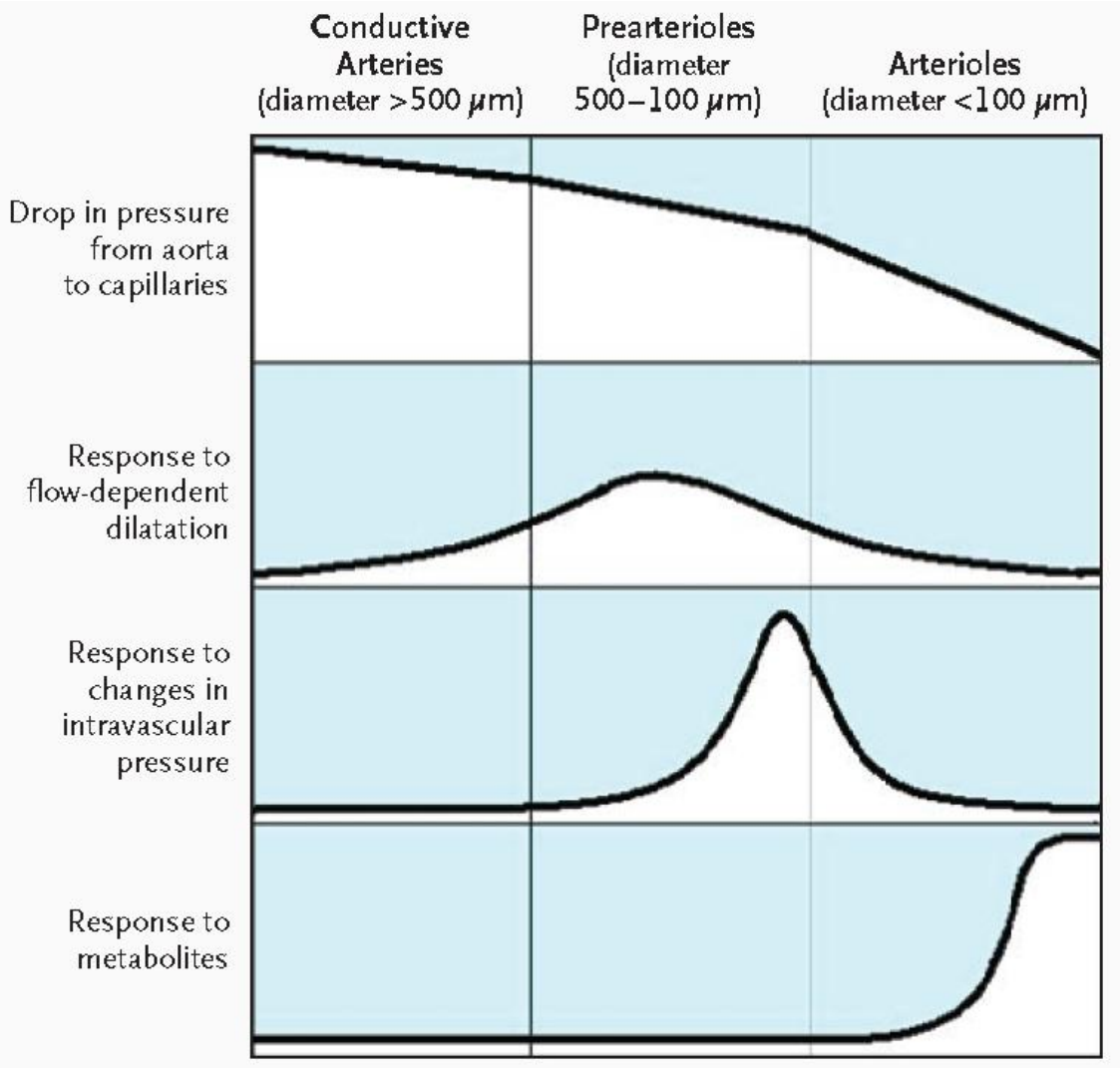


Sympathetic Innervation
Endothelium-Dependent
Shear Stress

Metabolic Milieu
Autoregulation
Myogenic Control

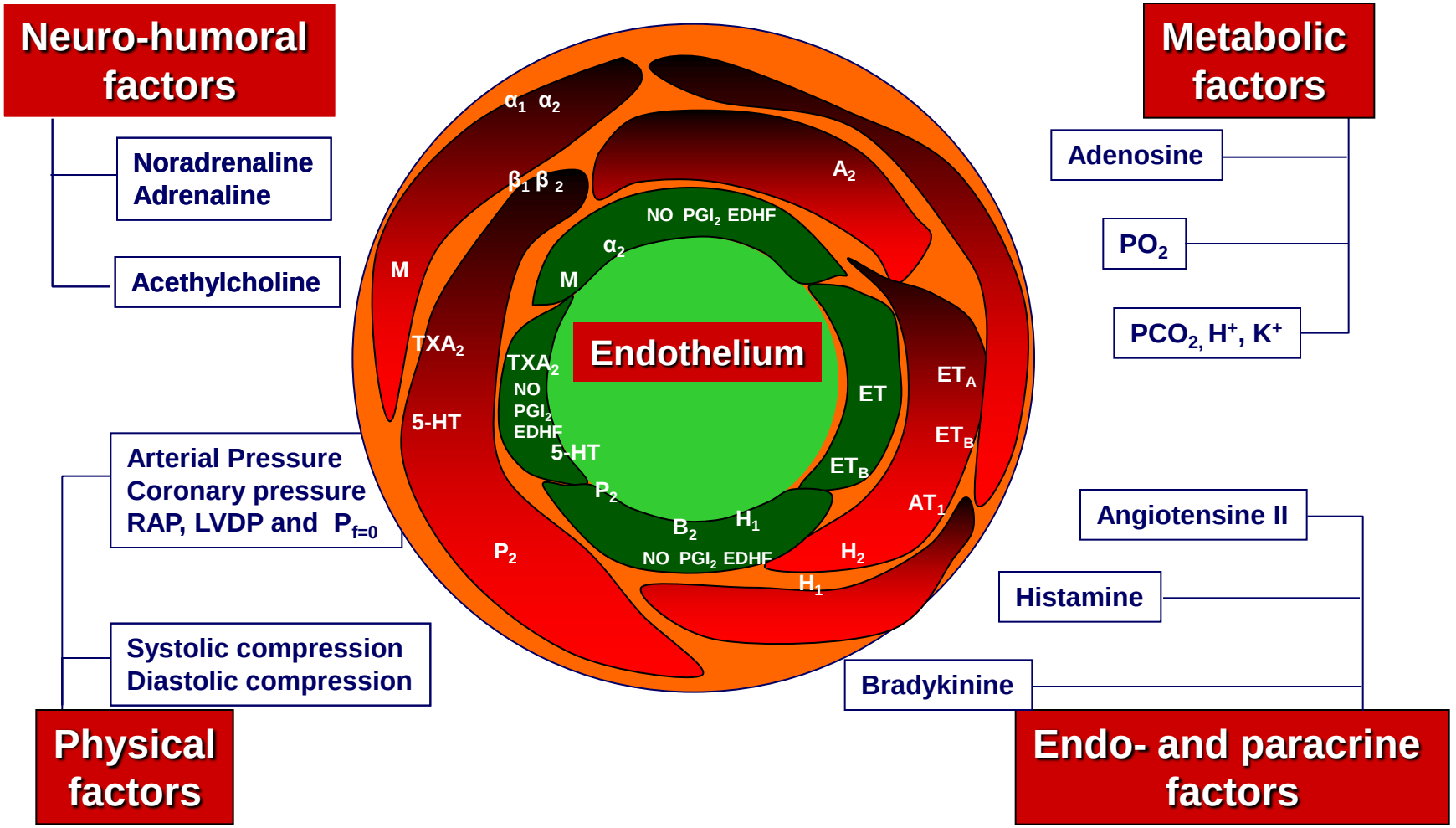
Adapted from: Lanza and Crea. Circulation 2010;121:2317-2325.

What is the Microvasculature?



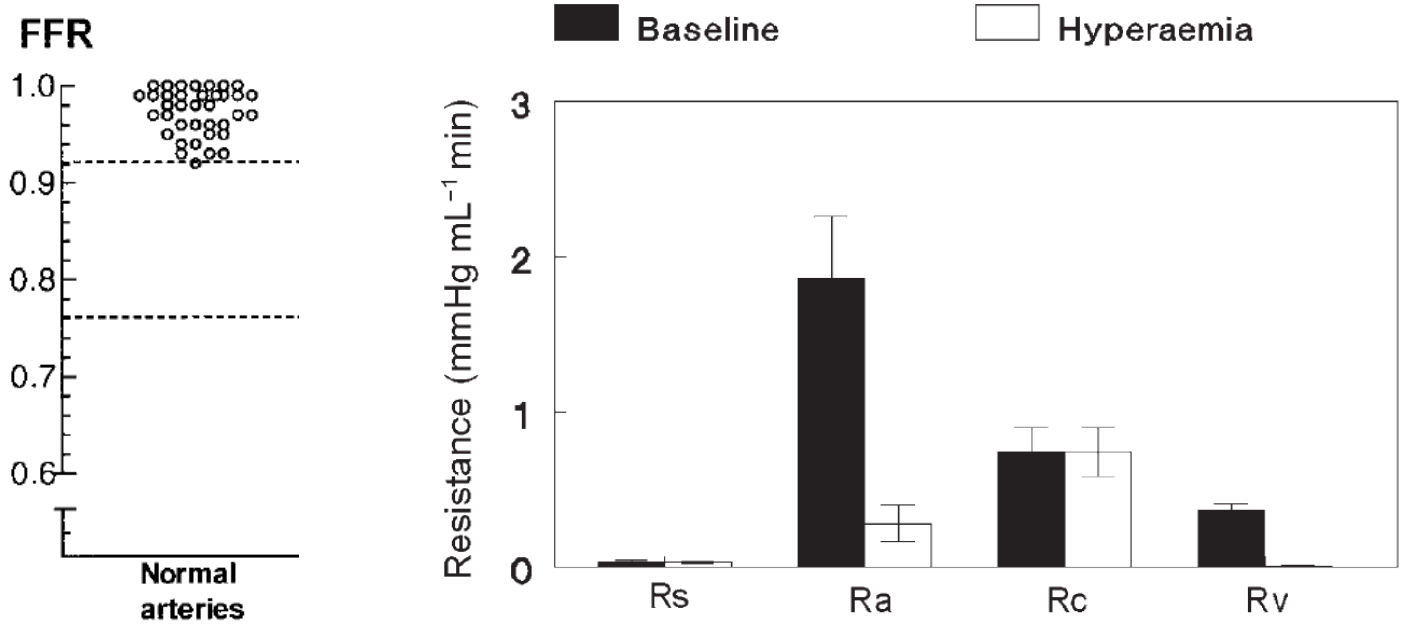
Camici and Crea. New Engl J Med 2007;356:830-840.

Determinants of Myocardial Flow



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



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

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.**

Beltrame, et al. Heart, Lung and Circulation 2009;18:19–27.

What is Microvascular Dysfunction?

- **Pathophysiology:**
  - **Structural**
    - **Decreased lumen size**
    - **Decreased capillary number**
  - **Functional**
    - **Inappropriate vasoconstrictor response**
    - **Inadequate vasodilator response**
    - **Resulting from an intravascular issue (e.g., endothelial dysfunction) or extravascular issue (e.g., autonomic or humoral dysfunction)**

Beltrame, et al. Heart, Lung and Circulation 2009;18:19–27.

Microvascular Dysfunction:

Classification

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

Camici and Crea. New Engl J Med 2007;356:830-840.

Microvascular Dysfunction:

Classification

- **Without myocardial/coronary disease**
  - Smoking
  - Dyslipidemia
  - Hypertension
  - Diabetes
  - Microvascular Angina/Syndrome X
- With associated myocardial disease
- With associated epicardial disease
- Iatrogenic

Camici and Crea. New Engl J Med 2007;356:830-840.

Syndrome X

- **Introduced in the 1970s as an explanation for chest pain in patients without CAD**
- **Characterized by:**
  - **Exertional angina**
  - **Typical ST segment depression on exercise stress testing**
  - **Angiographically normal epicardial coronary arteries**
  - **No other explanation for microvascular dysfunction (e.g., HTN)**

Arbogast and Bourassa. Am J Cardiol 1973;32:257-63.

Microvascular Angina

- **Introduced in the 1980s**
- **Characterized by:**
  - **Angina**
  - **No ST segment depression on exercise stress testing**
  - **Angiographically normal epicardial coronary arteries**
  - **Abnormal coronary blood flow response to vasodilatory stimuli (e.g., pacing, adenosine, dipyridamole)**

Cannon, et al. J Am Coll Cardiol 1983;1:1359-73.

Microvascular Dysfunction:

Classification

- Without myocardial/coronary disease
- **With associated myocardial disease**
  - Hypertrophic cardiomyopathy
  - Dilated cardiomyopathy
  - Infiltrative cardiomyopathies
- With associated epicardial disease
- Iatrogenic

Camici and Crea. New Engl J Med 2007;356:830-840.

Microvascular Dysfunction:

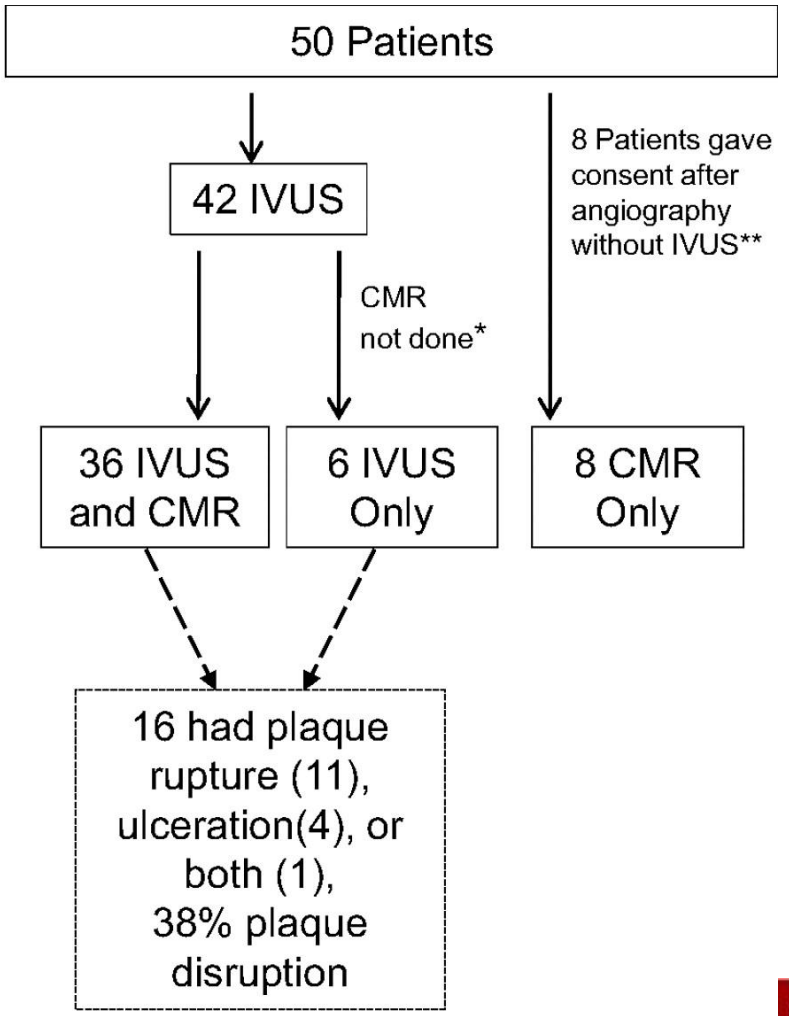
Classification

- Without myocardial/coronary disease
- With associated myocardial disease
- **With associated epicardial disease**
  - Acute Myocardial Infarction
  - Inappropriate pre-arteriole/arteriole vasoconstriction?
- Iatrogenic

Camici and Crea. New Engl J Med 2007;356:830-840.

AMI and Normal Coronaries

50 women presenting with AMI and found to have "normal" appearing coronaries underwent IVUS followed by cardiac MR



Reynolds, et al. Circulation 2011;124:1414-1425.

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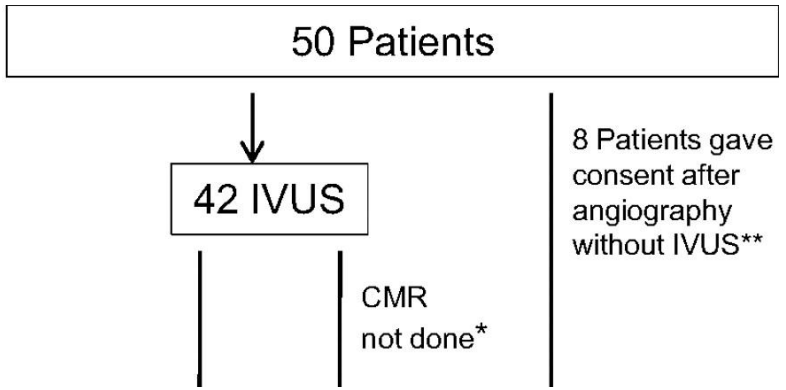
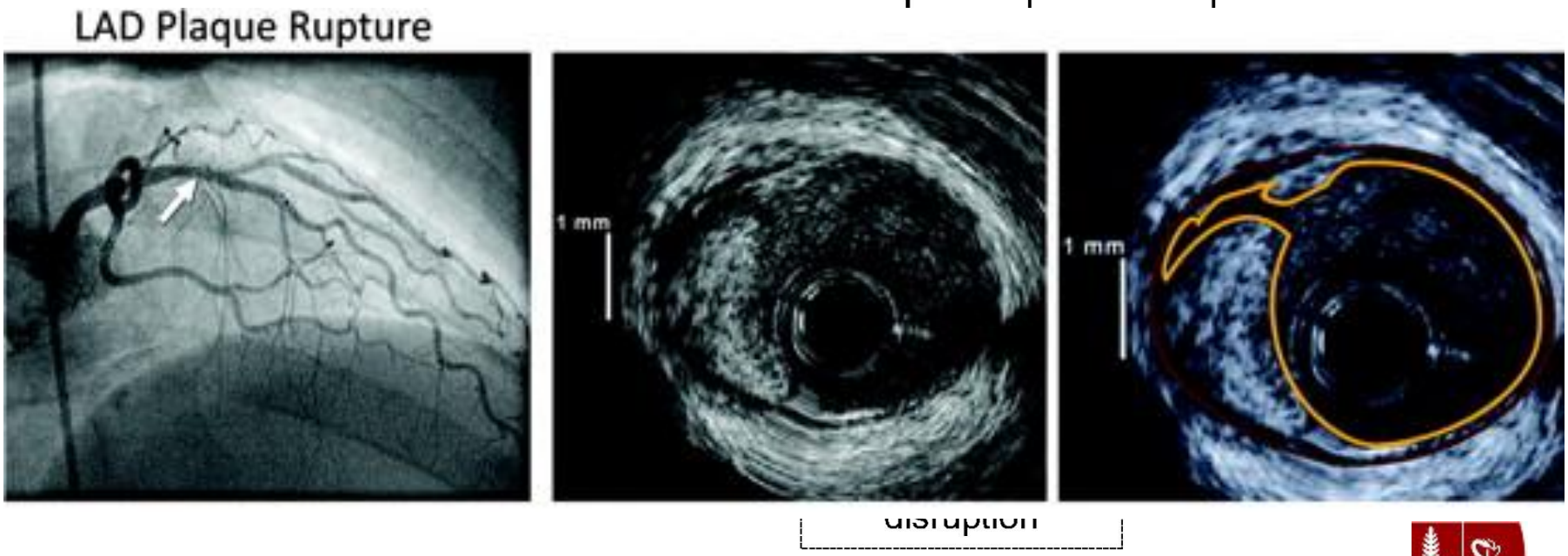




Reynolds, et al. Circulation 2011;124:1414-1425.

Microvascular Dysfunction and CAD

51 patients presenting with stable angina, abnormal stress test, or stabilized ACS and found to have no CAD had CFVR and IVUS performed to identify VH-TCFA

Variable	Frequency of TCFA		
	Beta	SE	*p*-Value
Age	0.30	0.36	0.121
Gender	−0.04	7.65	0.825
HTN	0.02	8.11	0.934
DM	0.14	6.53	0.400
BMI	−0.02	0.59	0.914
Smoking	−0.25	6.58	0.177
Log hs-CRP	−0.11	6.32	0.567
Impaired microvascular function (CFVR < 2.0)	0.42	6.90	0.033

Dahwan, et al. Atherosclerosis 2012;223:384-88.

Microvascular Dysfunction:

Classification

- Without myocardial/coronary disease
- With associated myocardial disease
- With associated epicardial disease
- **Iatrogenic**
  - Plaque embolization related to PCI

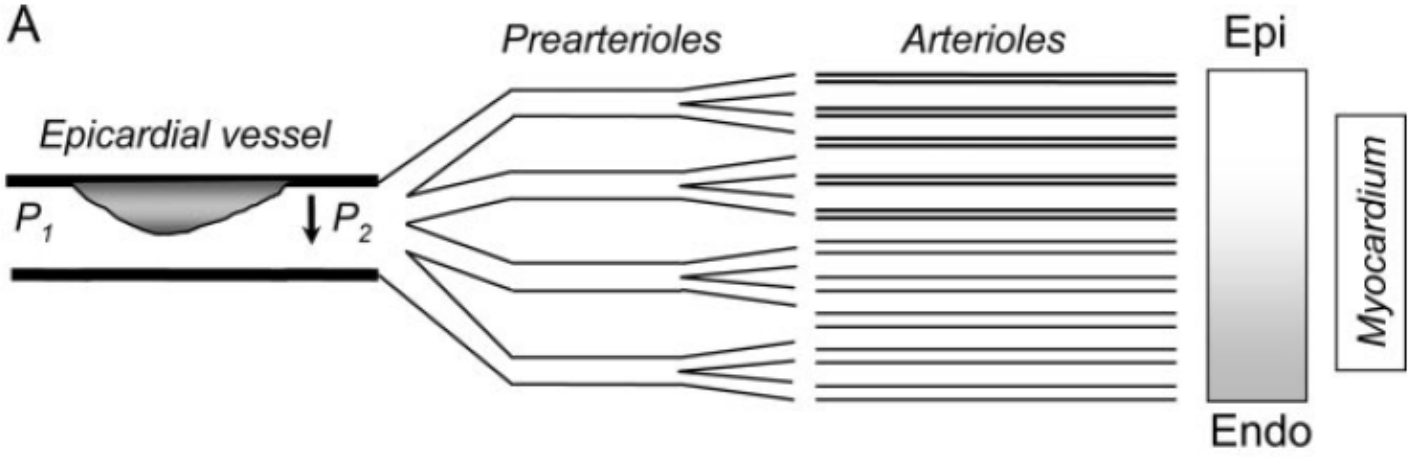
Camici and Crea. New Engl J Med 2007;356:830-840.

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

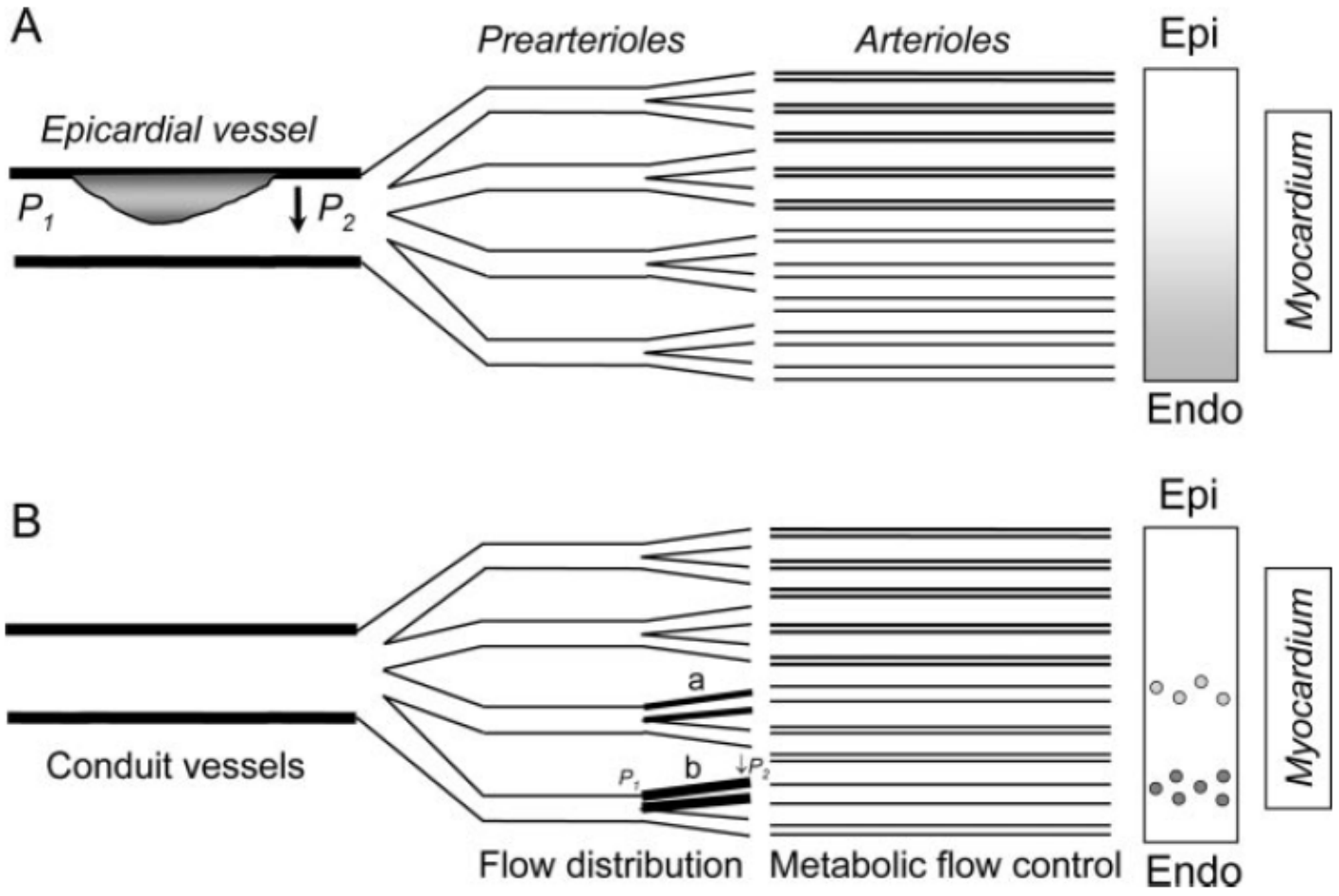


Epicardial CAD

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

Evaluating the Microcirculation…
…in the Cath Lab

TIMI Myocardial Perfusion Grade:

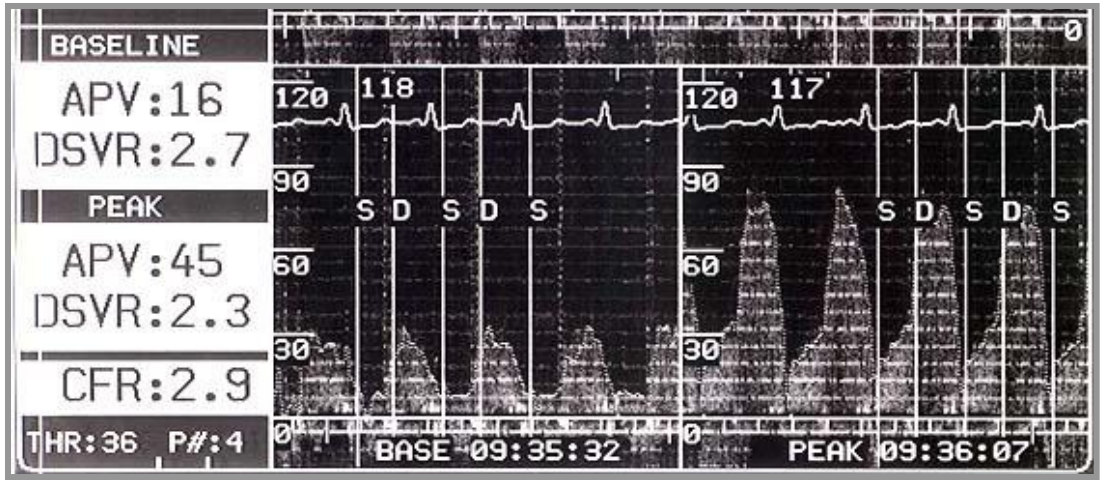
- Easy to obtain
- Specific for microvasculature
- Predictive of outcomes in large studies

Drawbacks:

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

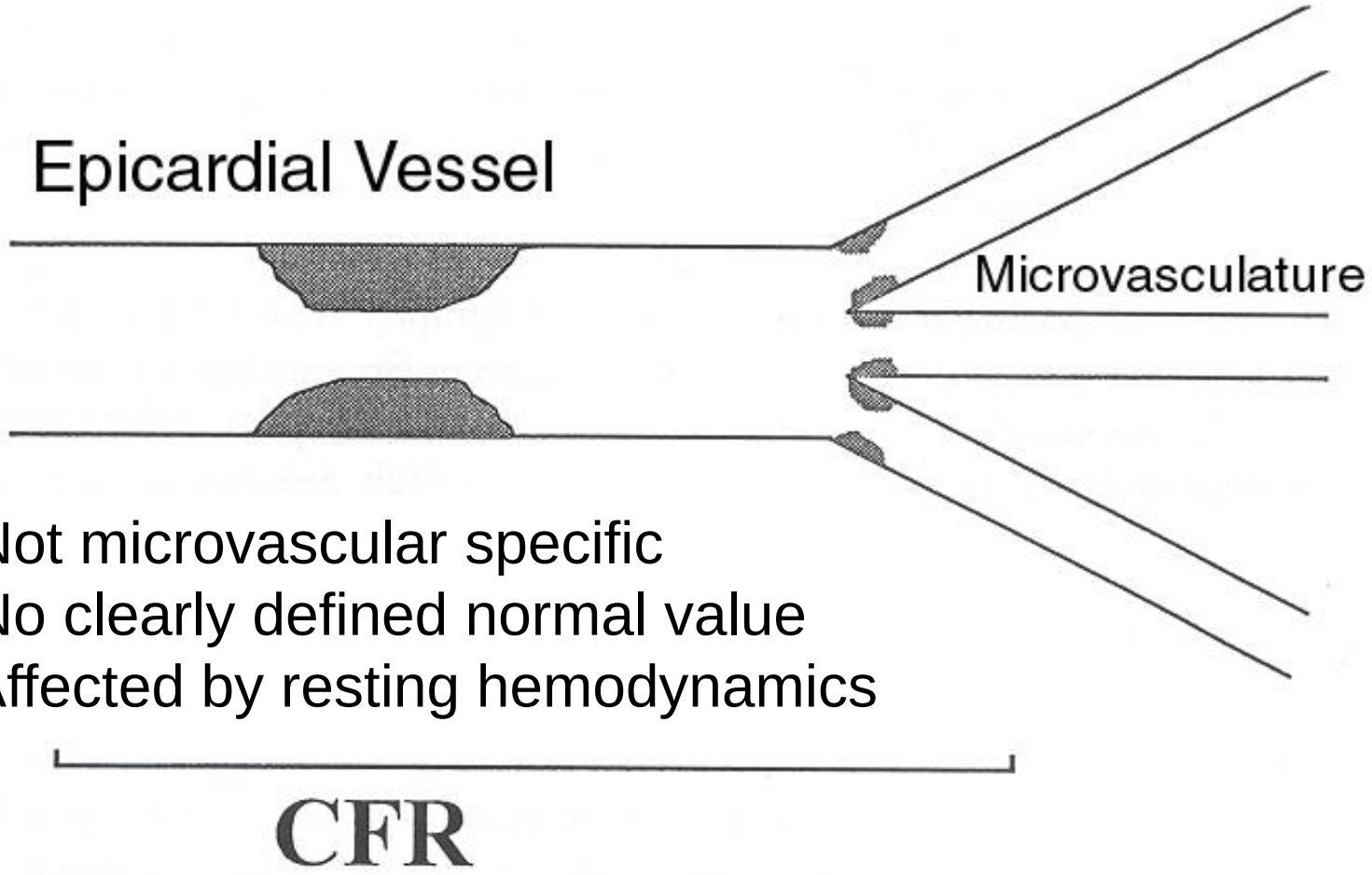
Doppler Wire Coronary Flow Reserve

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



Coronary Wire-Based Assessment

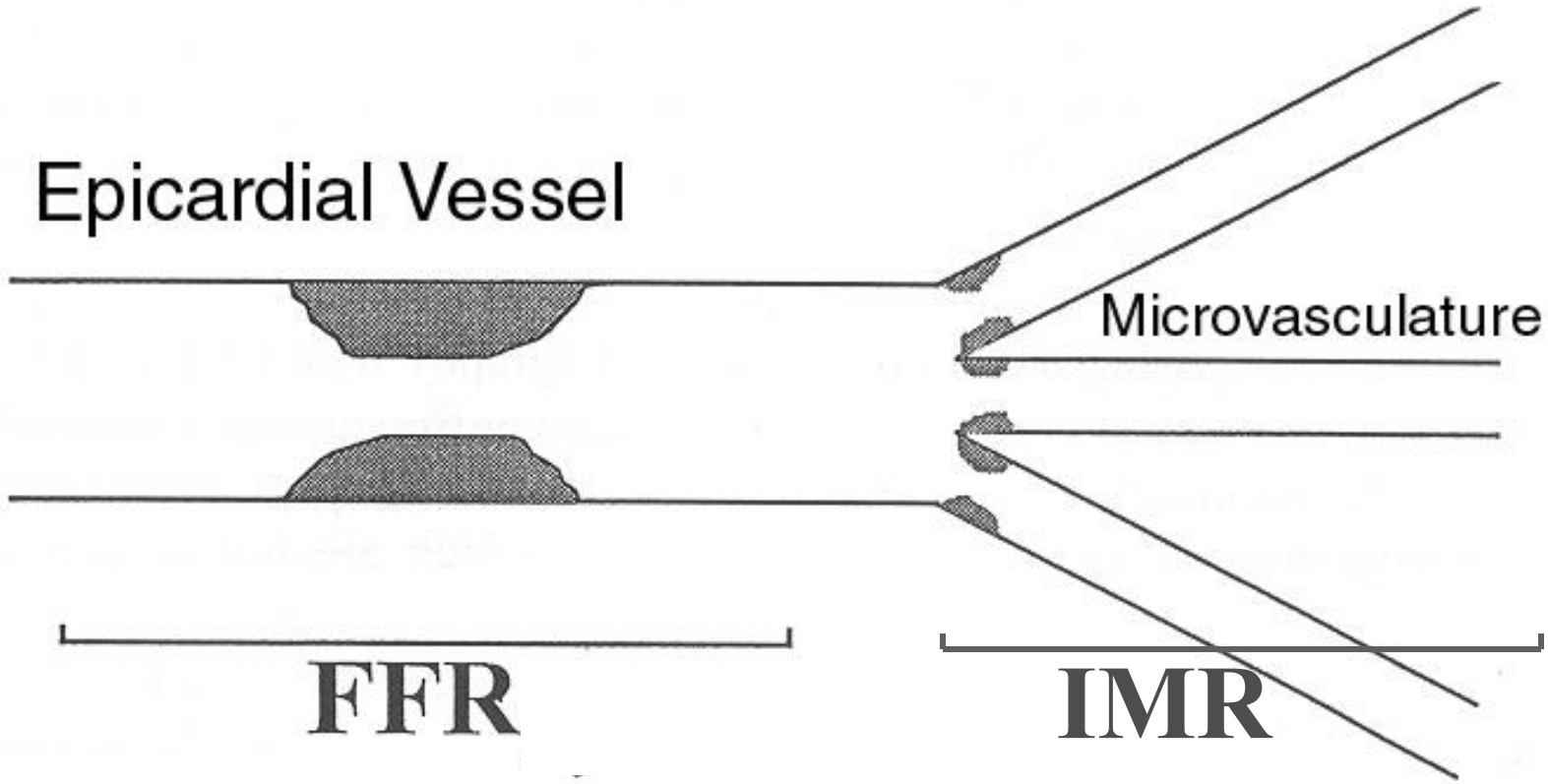
Coronary Flow Reserve



- 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

Methods	Invasiveness	Parameters assessed	Tracers	Qualification	Current clinical usefulness
PET scan	Non-invasive	Myocardial perfusion	Radioisotopes	Myocardial blood flow in ml/time/unit myocardial mass	Gold standard
SPECT	Non-invasive	Myocardial perfusion	Radioisotopes	None	For detection of myocardial ischaemia
MRI	Non-invasive	Myocardial perfusion	Contrast agent (gadolinium)	Myocardial blood flow in ml/time/unit myocardial mass	Moderate
CT scan	Non-invasive	Myocardial perfusion	Contrast agent (x-ray contrast)	Myocardial blood flow	Limited
Doppler echocardiography	Non-invasive	Coronary flow velocity	Echo contrast agents	CFR	Low to moderate
Myocardial contrast echocardiography	Non-invasive	Myocardial perfusion defect	Echo contrast agents	Perfusion defect size	Moderate
Myocardial contrast echocardiography (destruction replenishment imaging)	Non-invasive	Myocardial perfusion	Echo contrast agents	CFR, myocardial blood flow	Moderate
Doppler flow wire	Invasive	Coronary flow velocity	None	CFR	Low to moderate
Temperature and pressure sensor tripped coronary wire	Invasive	Intracoronary pressure and transit time	Saline	CFR, FFR, IMR	High
TIMI frame count and myocardial blush score	Invasive	Myocardial perfusion	Contrast (x-ray)	None	Moderate

Leung, et al. Heart 2011;97:587-95.

Why is Microvascular Dysfunction Important?

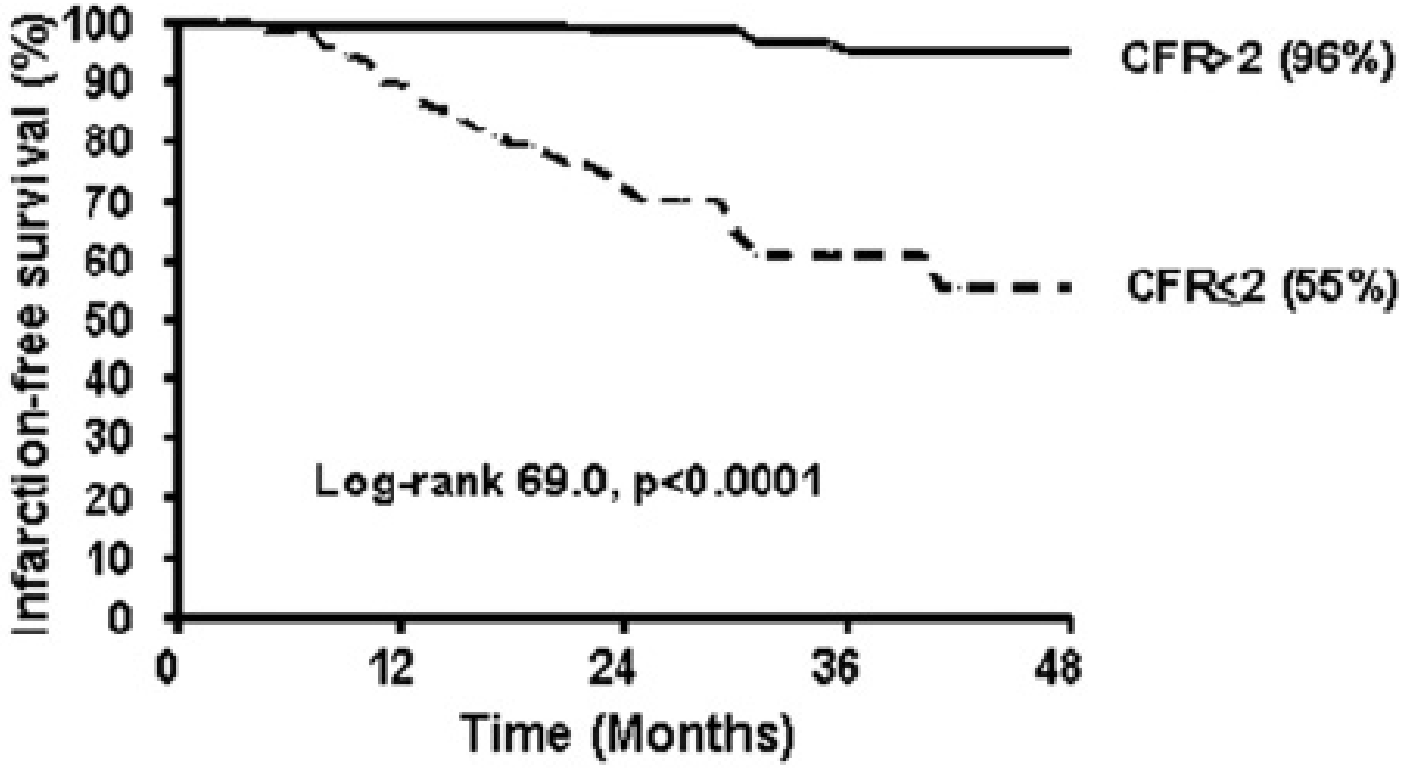
- Up to 30% of patients continue to have angina despite successful coronary revascularization

- ~20% of patients with chest pain are found to have no angiographic apparent CAD

- Microvascular dysfunction predicts adverse outcomes in a variety of clinical settings

Importance of Microvascular Dysfunction

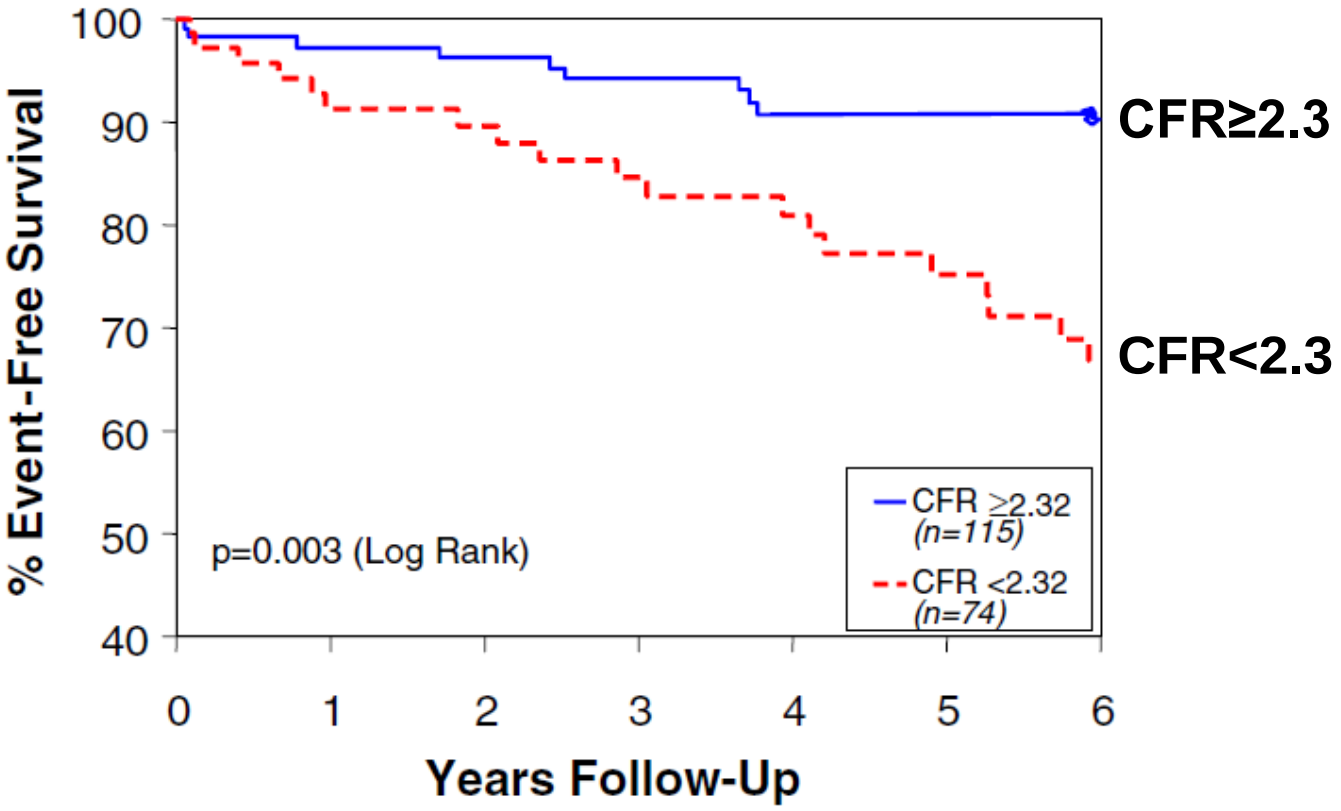
Infarct-Free Survival based on Echo-Derived CFR in 394 Patients with Chest Pain and Normal Coronaries



Sicari, et al. Am J Cardiol 2009;103:626-31.

Importance of the Microcirculation

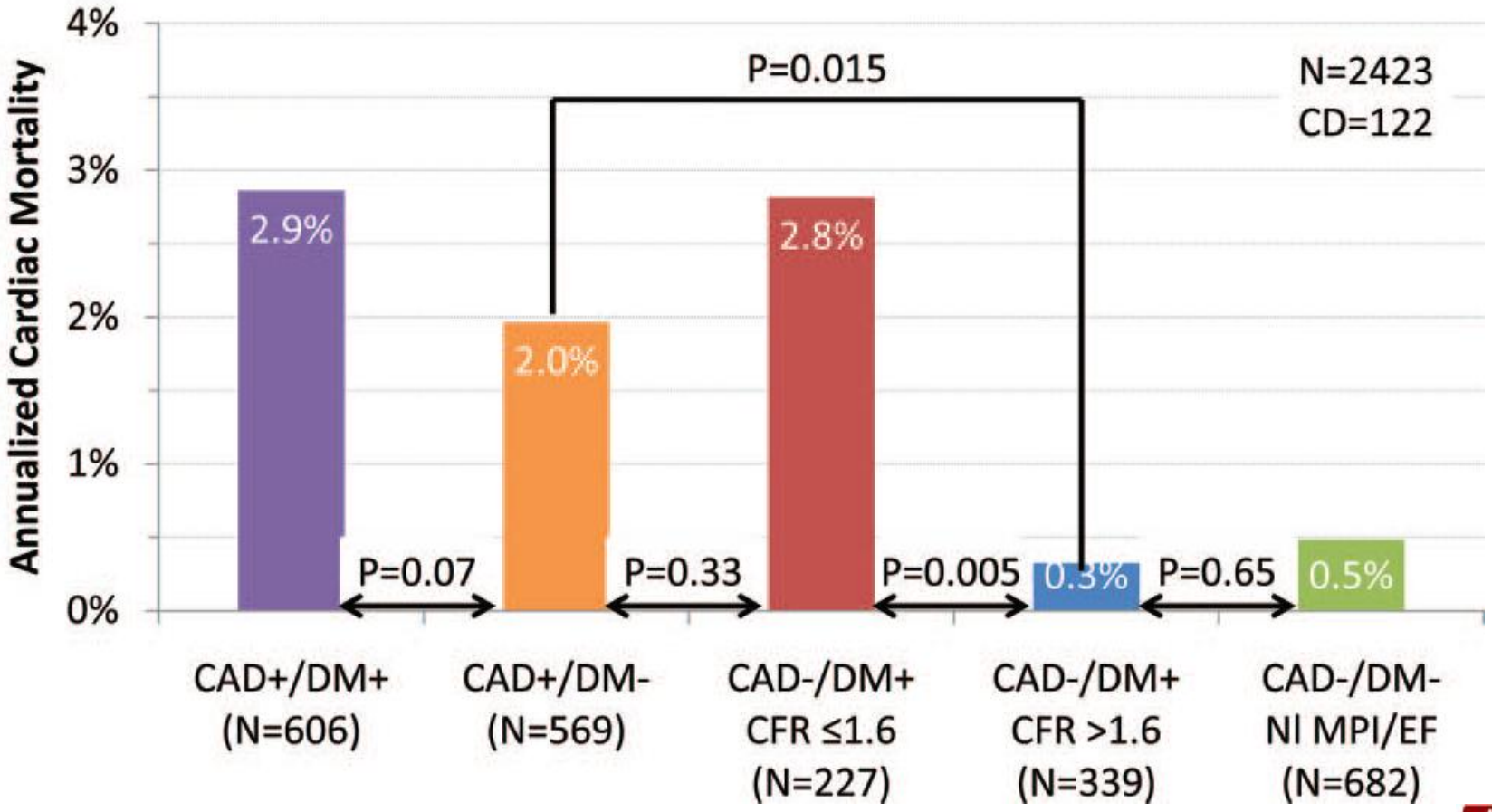
189 women with chest pain and "normal" coronary arteries: % free of Death, MI, CVA, or CHF



Pepine, et al. J Am Coll Cardiol 2010;55:2825-32.

Importance of the Microcirculation

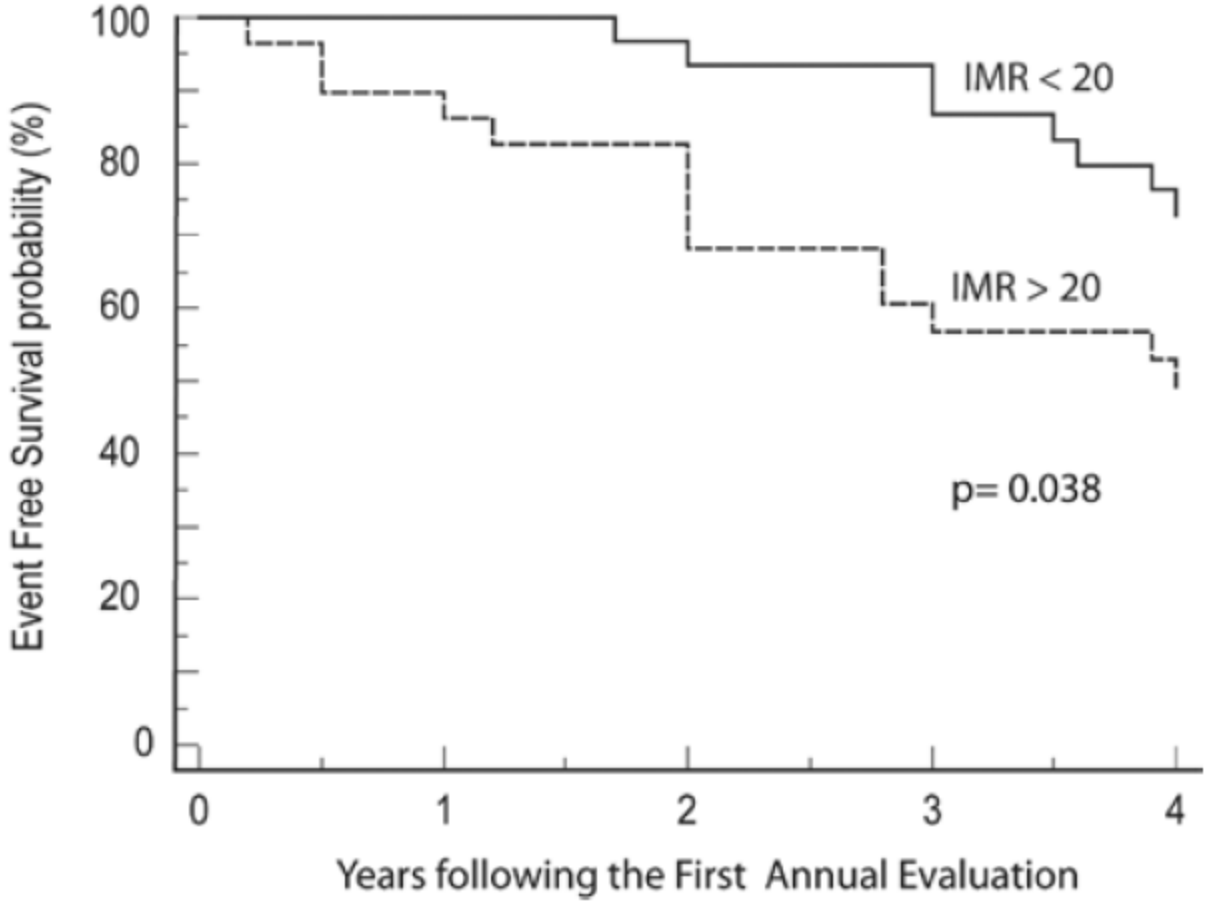
2,423 patients undergoing PET-derived CFR



Murthy, et al. Circulation 2012;126:1858-68.

Importance of Microvascular Dysfunction

IMR measured at 1 year in 63 heart transplant recipients



% Free of Death, Graft Failure, CAV

Haddad, et al. Circ Heart Fail. 2012;5:759-68.

Conclusions:

- The coronary microvasculature is an oft-ignored entity.
- The etiology of coronary microvascular dysfunction is complex and multifactorial.
- Microvascular dysfunction is associated with worse outcomes.
- The invasive assessment of microvascular function will likely play an increasingly important role in patient evaluation.