How to Evaluate Microvascular Function and Angina

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Angina without Coronary Artery Disease (CAD)

- Prevalence: 20-30% going c-angiography, with a higher prevalence (almost 50%) in women.
- The 5-year rate of MACE outcomes were 3-fold higher in symptomatic women with normal coronary arteries and approximately 8-fold higher in symptomatic women with nonobstructive CAD compared with asymptomatic women without CAD.

Gulati M, et al. Arch Intern Med 2009;169:843-50

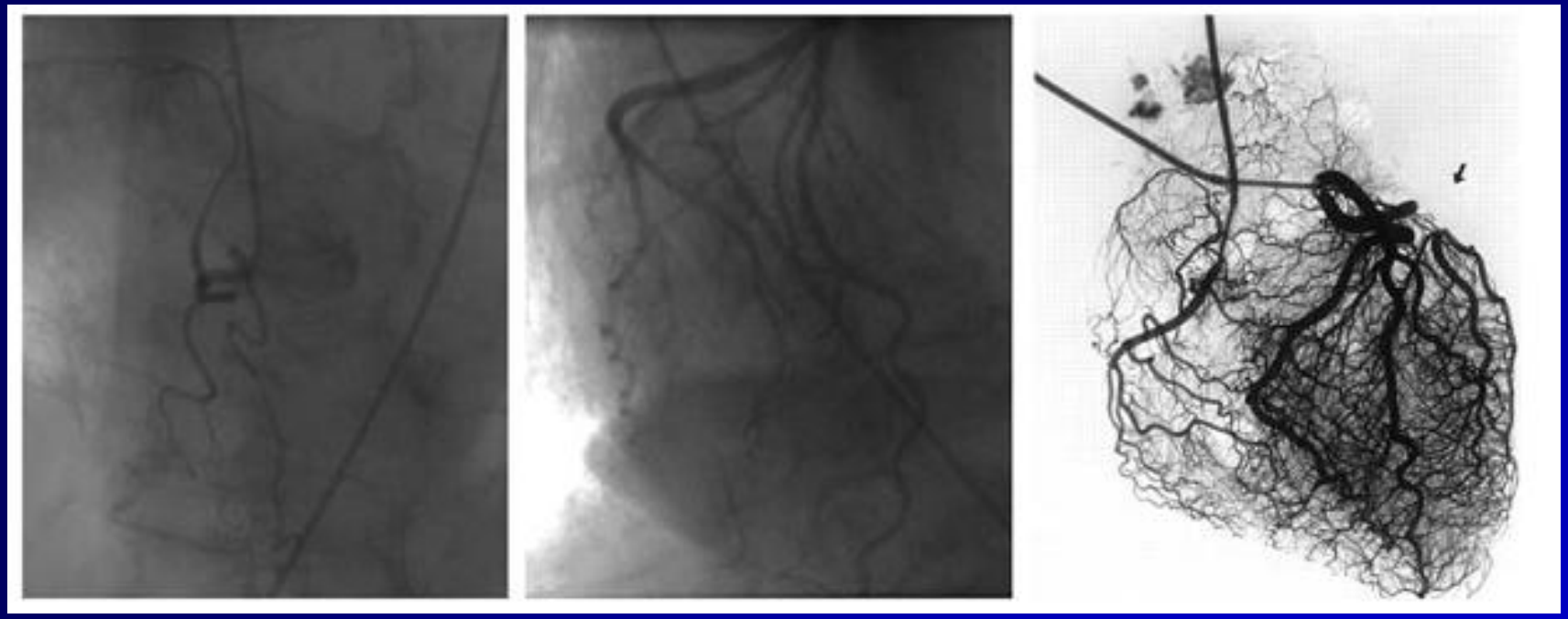
Angina Pectoris and Myocardial Ischemia Without Obstructive CAD

- Cardiac syndrome X (CSX)
  1) Typical exercise-induced angina
  2) Documented stress-induced myocardial ischemia
  3) Absence of obstructive atherosclerotic CAD
  4) Absence of vasospastic angina
  - Female predominance: 70% of CSX
  - In WISE study, almost half of the women with no obstructive CAD showed abnormal CFR consistent with coronary microvascular dysfunction (CMD)

Angina Pectoris and Myocardial Ischemia in the Absence of Obstructive CAD

- Microvascular angina
  - 1)+2)+3)+4)+5) Active demonstration of CMD (positive acetylcholine and/or adenosine test results)
  - As many as 50% to 65% of angina patients without obstructive CAD are believed to have CMD, also known as microvascular angina.

Coronary Microvascular Circulation



- Current cardiovascular imaging technologies are unable to image the vessels that are smaller than 500 μm in diameter.

Assessment of Coronary Microvascular Function

- Study of the coronary microcirculation is indirect parameters, such as coronary blood flow and coronary flow reserve (CFR), which reflect its functional status
- Lack of uniform diagnostic criteria.
- Relative contributions of CMD to pathologic microvascular angina are poorly understood yet.

Prognosis of CMD or Microvascular Angina

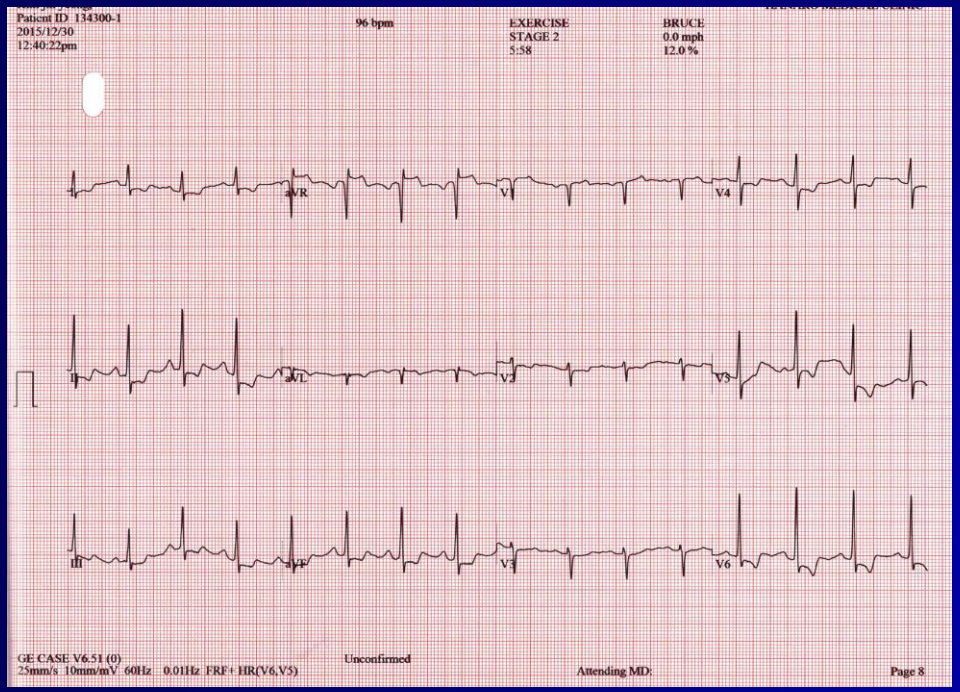
- 20% higher rate of cardiovascular events (death, acute coronary syndromes, stroke, and need for revascularization) at 46-month follow-up.

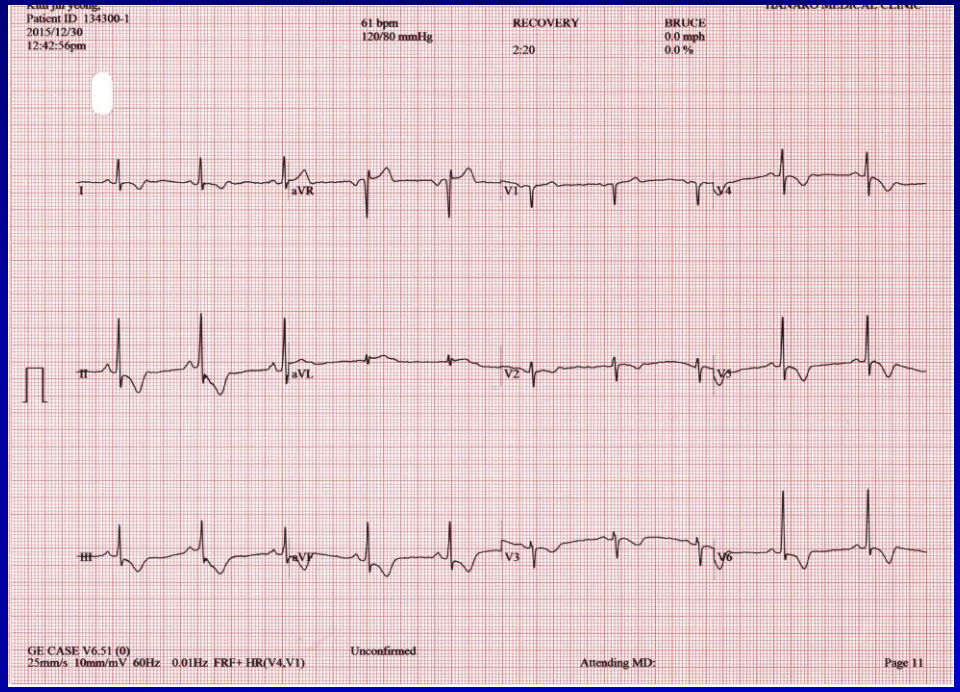
Halcox JP, et al. Circulation 2002;106:653–8

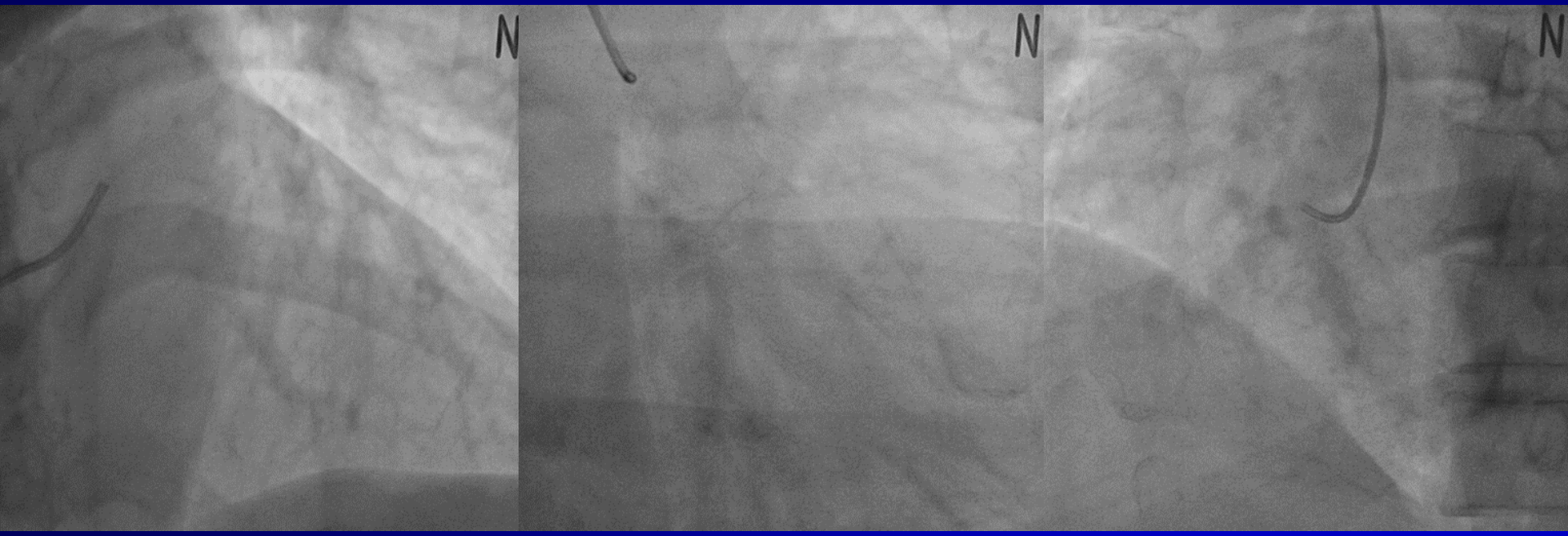
- Microvascular dysfunction was associated with a 3.3-fold increase in the risk of cardiac death at 12 years (36.9%) compared with subjects having a normal endothelial function.

van de Hoef TP, et al. Circ Cardiovasc Interv 2013;6:329–35

F/45, exertional chest pain and dyspnea for 2 years



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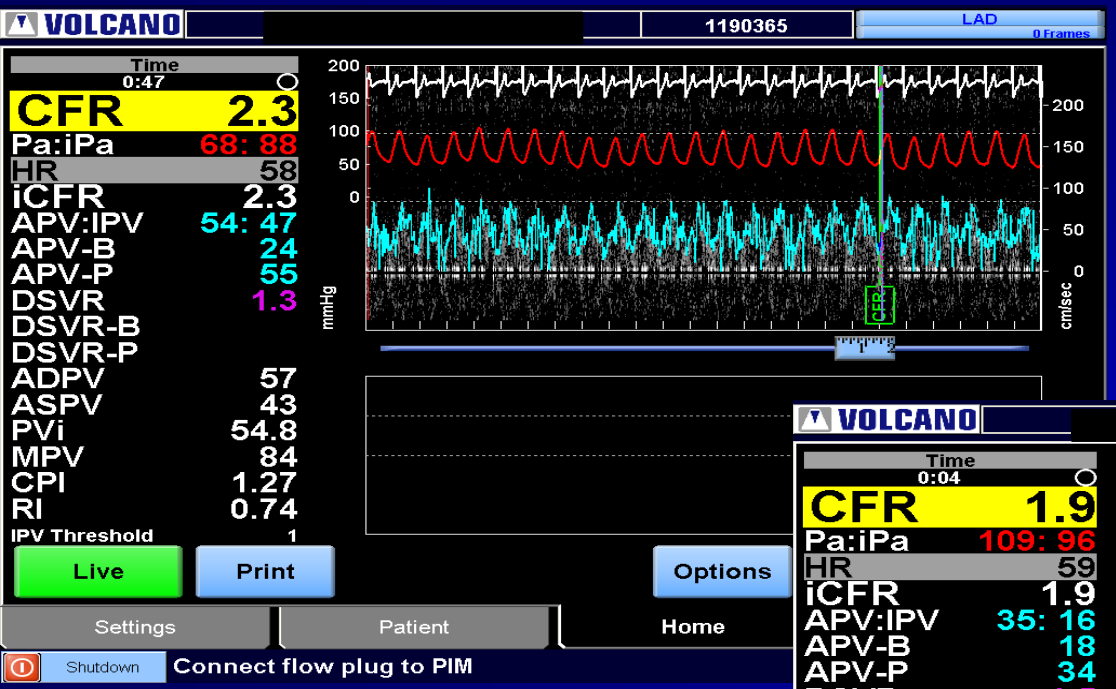
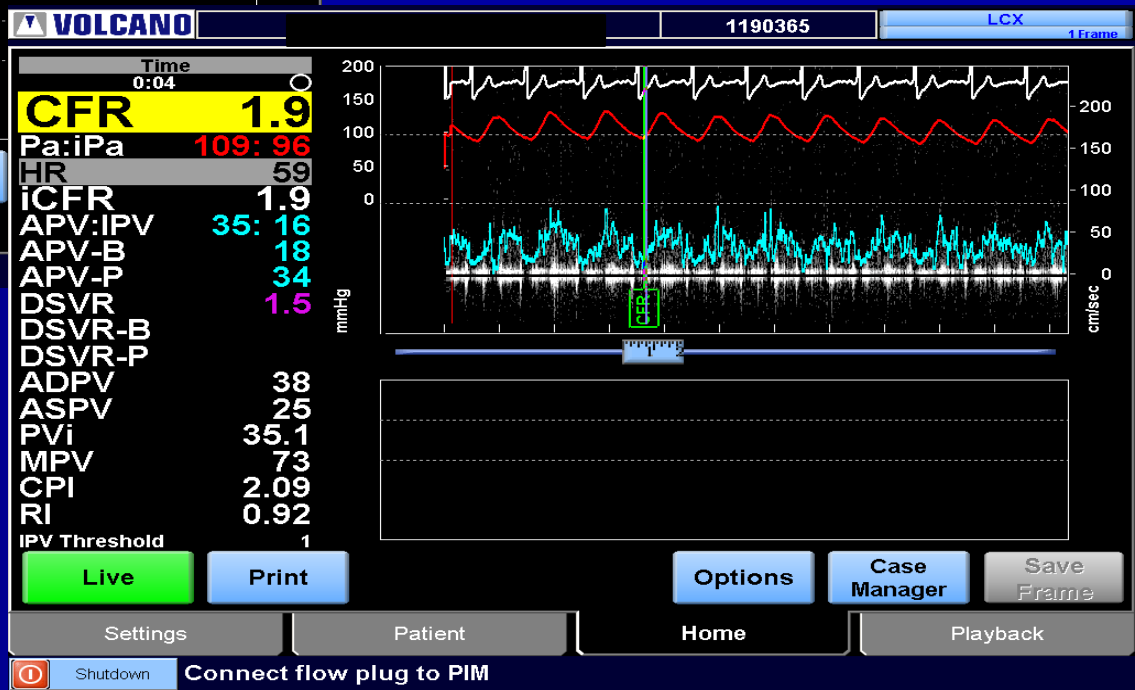
CFR measured by Flow Wire





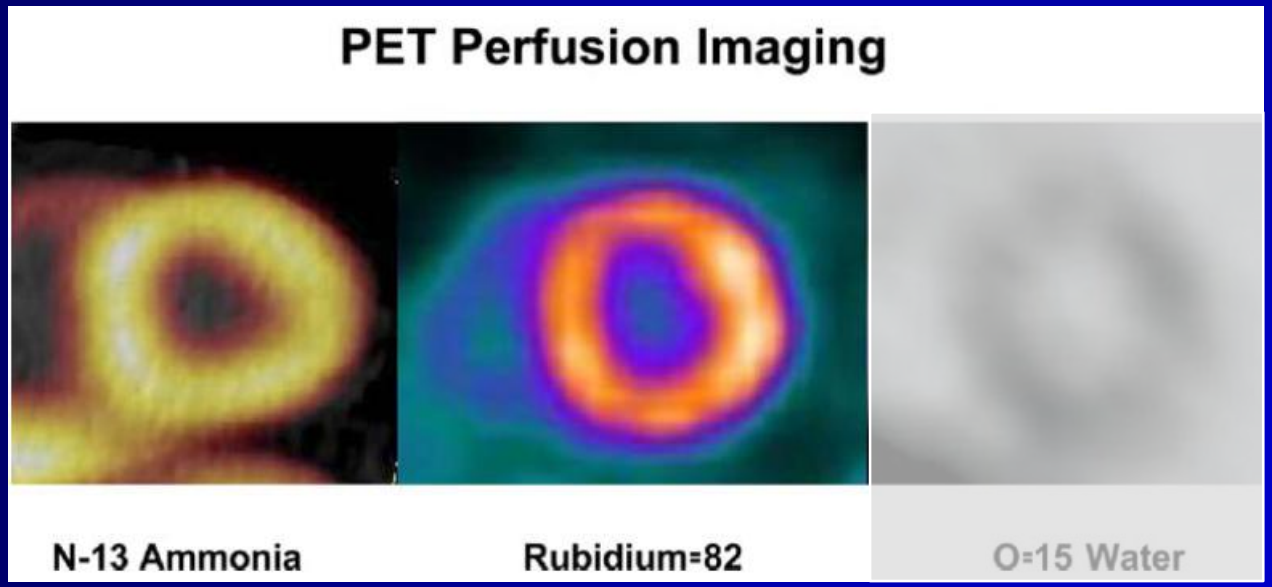
Non-Invasive Methods to Assess the Microvascular Function

- Exercise stress test, exercise treadmill test (ETT): low accuracy, in-sensitive
- Traditional stress imaging; stress imaging techniques (stress echocardiography, nuclear perfusion stress testing) remain insensitive in diagnosing CMD.
  - Standard noninvasive imaging (stress echo and myocardial perfusion SPECT) is often normal in CMD.

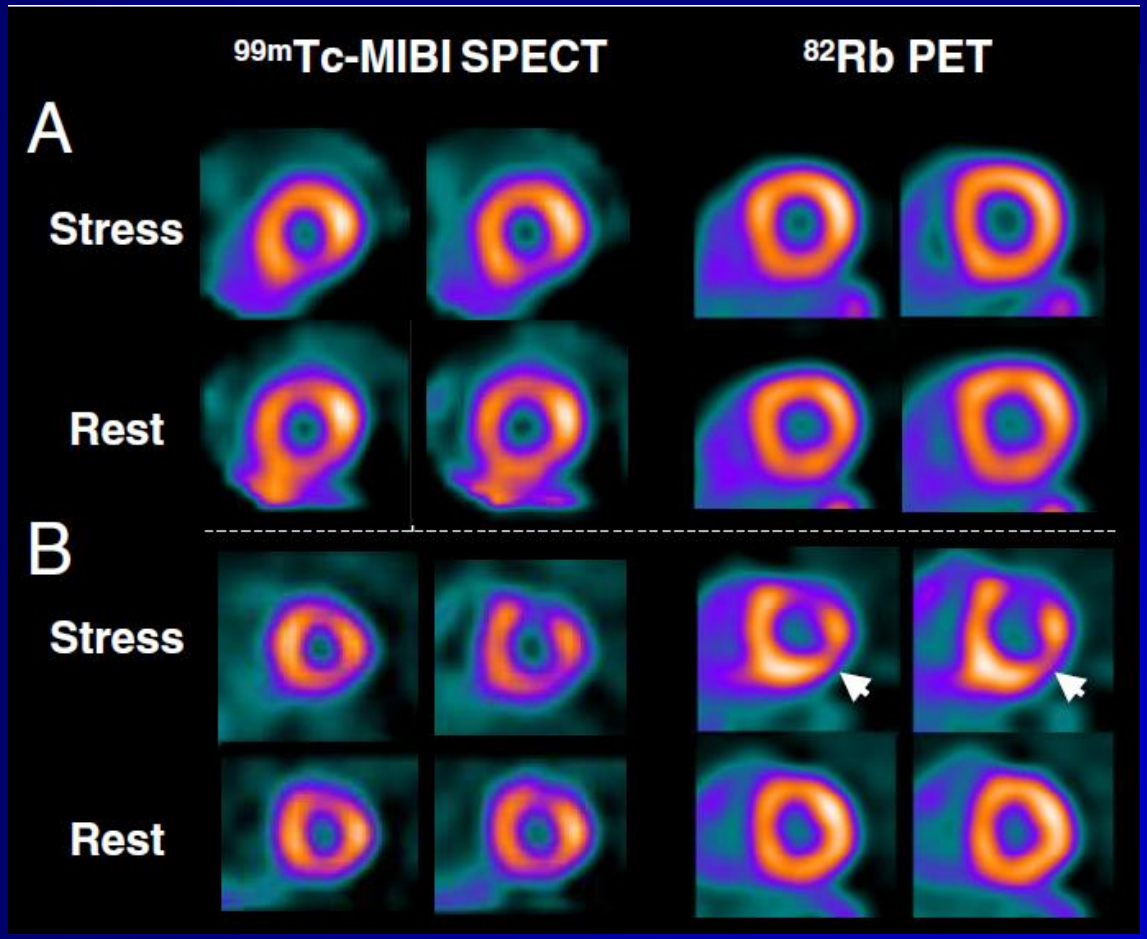
Camici PG et al. Circulation 992;86:179-86

Non-Invasive Assessment of Coronary Microcirculation

- PET (positron emission tomography) scan:
  - Most established non-invasive technique form the assessment of CBF, regional MBF and reserve



Why PET?
- Comparison of PET and SPECT Perfusion Imaging



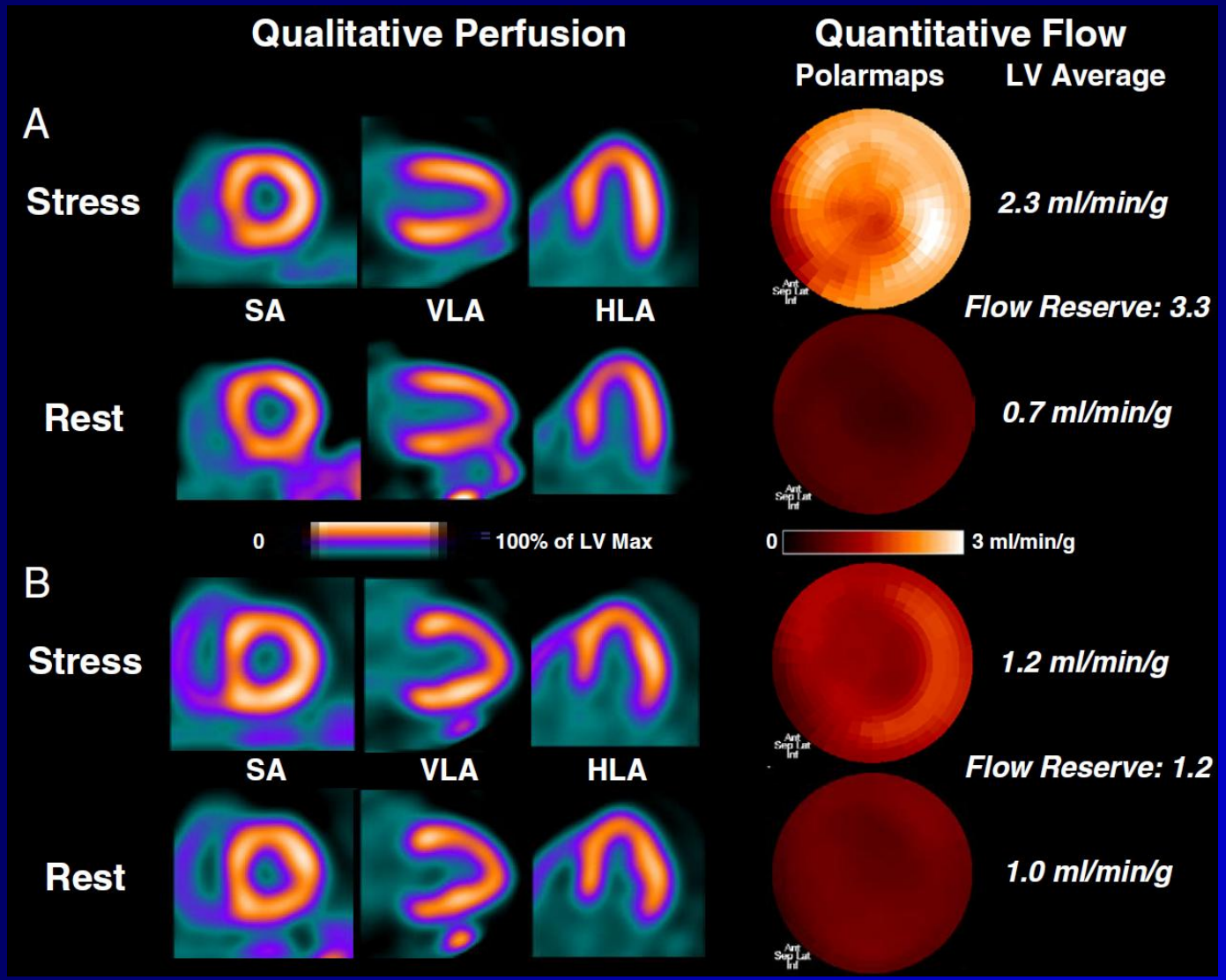
Diagnostic Accuracy of PET Myocardial Perfusion Imaging

Sensitivity (%)	Specificity (%)	No. Patients	Agent	Author
95	100	50	NH_3, ^{82}Rb	Gould et al[224]
94	95	193	^{82}Rb	Demer et al[225]
93	78	202	^{82}Rb	Go et al[226]
97	100	45	NH_3	Schelbert et al[227]
93	100	49	NH_3	Yonekura et al[228]
98	93	146	^{82}Rb	Williams et al[229]
84	88	81	^{82}Rb	Stewart et al[230]
95	95	25	NH_3	Tamaki et al[231]
93	92	791		Average

Author	Tracer	Accuracy (%)	Sensitivity (%)	Specificity (%)
Go et al[232] (n = 132)	Rb-82	92	95	82
	T1-201	78	79	76
Stewart et al[233] (n = 81)	Rb-82	85	87	82
	T1-201	78	87	52
Tamaki et al[234] (n = 51)	NH3	98	98	100
	T1-201	98	96	100
Total (n = 264)	PET	91	93	82
	SPECT	81	85	67

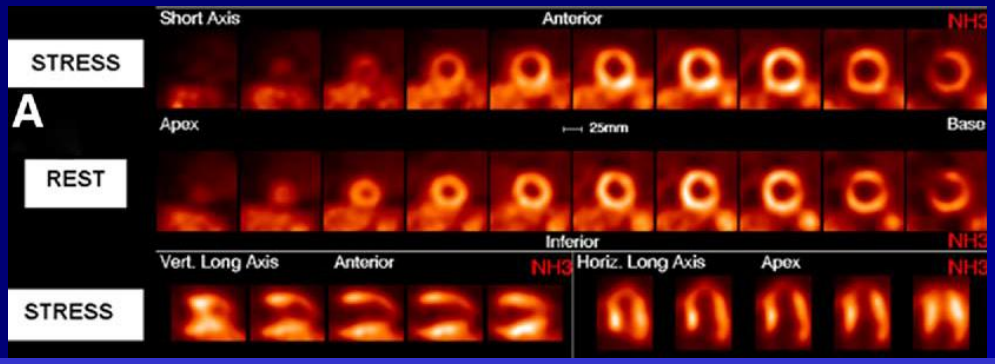
Josef M. Nucl Med 2005;35:17-36

Flow Quantification by PET

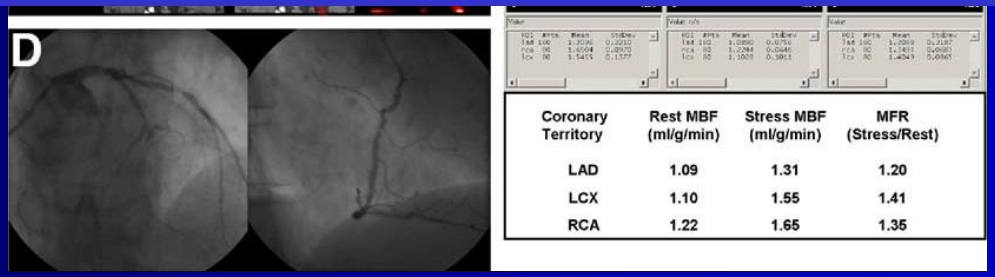


Bengel FM et al. J Am Coll Cardiol 2009;54:1-15

Myocardial Blood Flow And Reserve by PET



- **Provides insight into early and subclinical abnormalities in coronary arterial vascular function and/or structure, non-invasively**
- **Predict Prognosis**

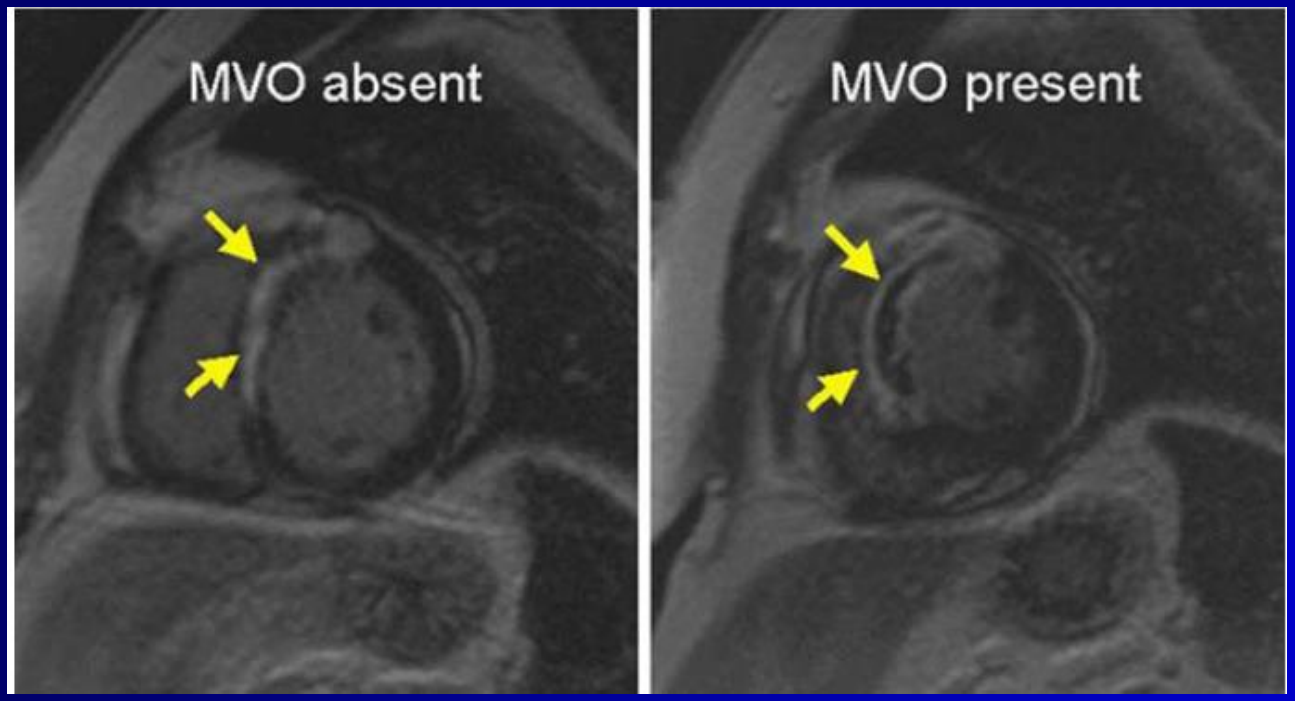


Coronary Territory	Rest MBF (ml/g/min)	Stress MBF (ml/g/min)	MFR (Stress/Rest)
LAD	1.09	1.31	1.20
LCX	1.10	1.55	1.41
RCA	1.22	1.65	1.35

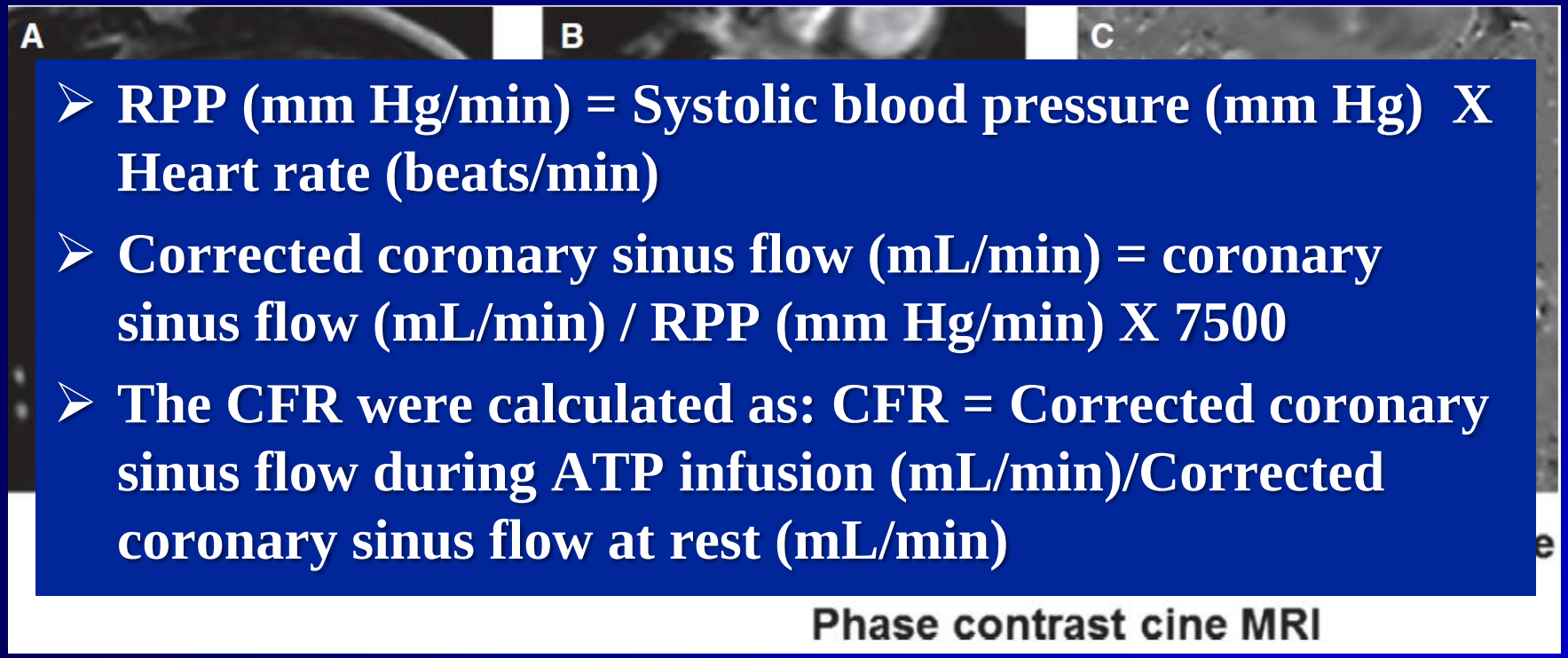
Shindler TH et al. J Am Coll Cardiol 2010;3:623-40

Non-Invasive Assessment of Coronary Microcirculation

- MRI
  - Can also be used for quantification of myocardial blood flow



Phase-Contrast Cine MRI



- **RPP (mm Hg/min) = Systolic blood pressure (mm Hg) X Heart rate (beats/min)**
- **Corrected coronary sinus flow (mL/min) = coronary sinus flow (mL/min) / RPP (mm Hg/min) X 7500**
- **The CFR were calculated as: CFR = Corrected coronary sinus flow during ATP infusion (mL/min)/Corrected coronary sinus flow at rest (mL/min)**

Kato S et al. J Am Heart Assoc. 2016;5:e002649

Invasive Assessment of CMD

- TIMI Frame Count and TIMI Frame Count Reserve
- TIMI Myocardial Perfusion Grade
- Coronary Reactivity Test
  - Coronary blood flow reserve (CFR)
  - Index of microvascular index (IMR)
  - Hyperemic microvascular resistance index

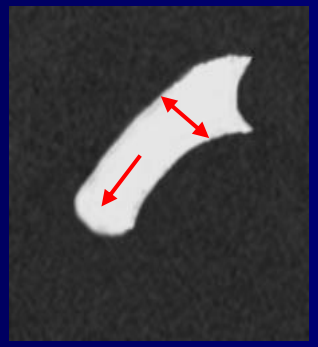
Coronary Reactivity Test

- Assessment of endotheliaum-dependent CFR by acetylcholine
- Assessment of endotheliaum-independent CFR by adenosine
- A >50% increase in CBF above baseline in response to acetylcholine and a CFR >2.5 in response to adenosine is considered normal.

Corrected TIMI Frame Count

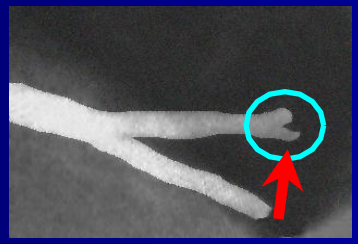
First Frame Definition

***Frame 0*: Dye Touches One or No Borders**

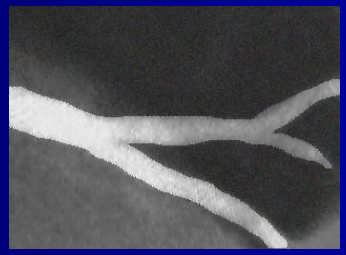


***Frame 1*: Dye Touches Both Borders & Moves Forward**

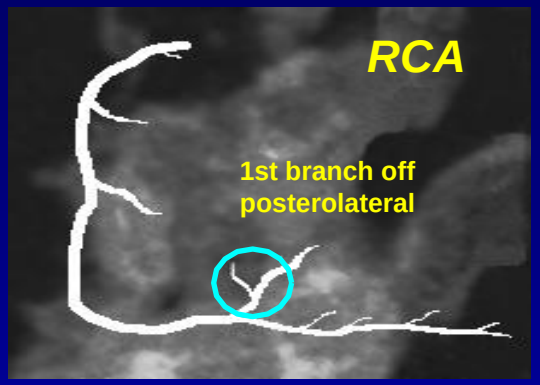
Last Frame Definition

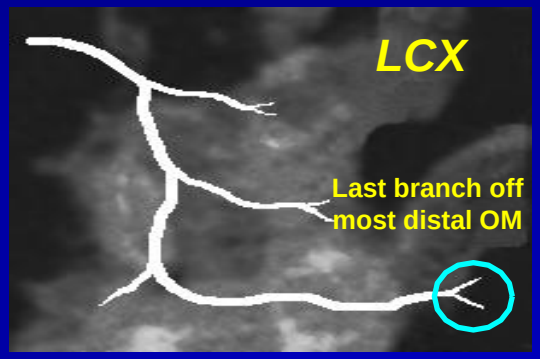


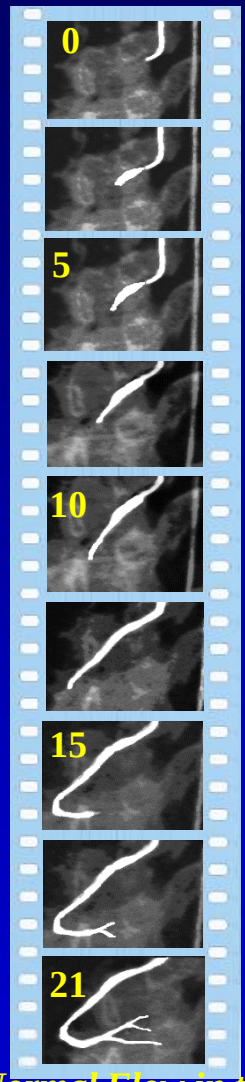
***Frame 21*: Dye First Enters Landmark**



Distal Landmark





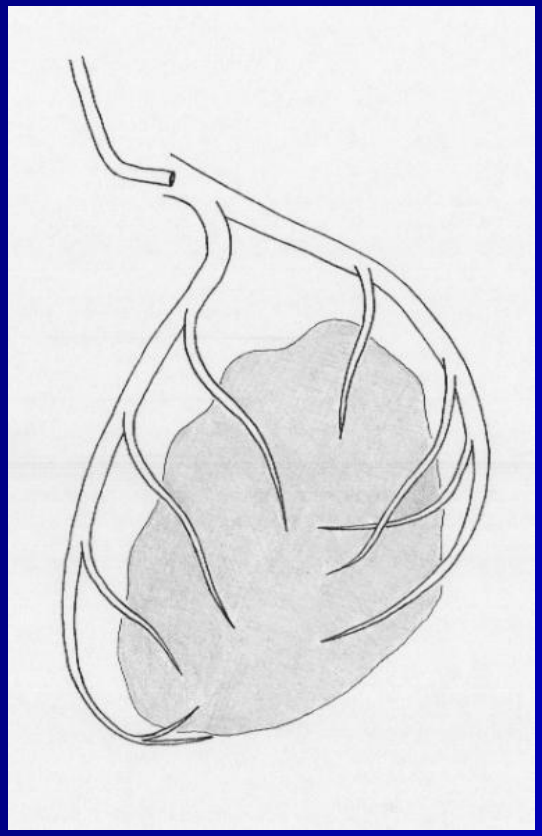


Normal Flow in the Absence of MI: 21.0 ± 3.1 Frames

Gibson CM. *Circulation* 1996; 93:879-888.

Myocardial Blush

- **Following contrast injection into the coronary arteries, there is late filling of the distal capillaries**
- **In order to visualize myocardial blush, it is important to remain on the cine pedal for an extended period**



TIMI Myocardial Perfusion Grade (TMPG)

- **TMPG 0**
  No appearance of blush or opacification of the myocardium

- **TMPG 1**
  Presence of blush but no clearance of contrast (stain is present on the next injection)

- **TMPG 2**
  Blush clears slowly – clears minimally or not at all during three cardiac cycles

- **TMPG 3**
  Blush begins to washout and is only minimally persistent after three cardiac cycles

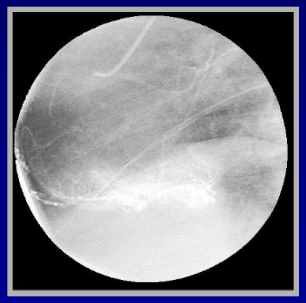
TIMI Myocardial Perfusion (TMP) Grades

TMP Grade 3

Normal ground-glass appearance of blush. Dye mildly persistent at end of washout.

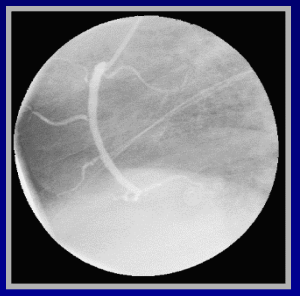
TMP Grade 2

Dye strongly persistent at end of washout. Gone by next injection

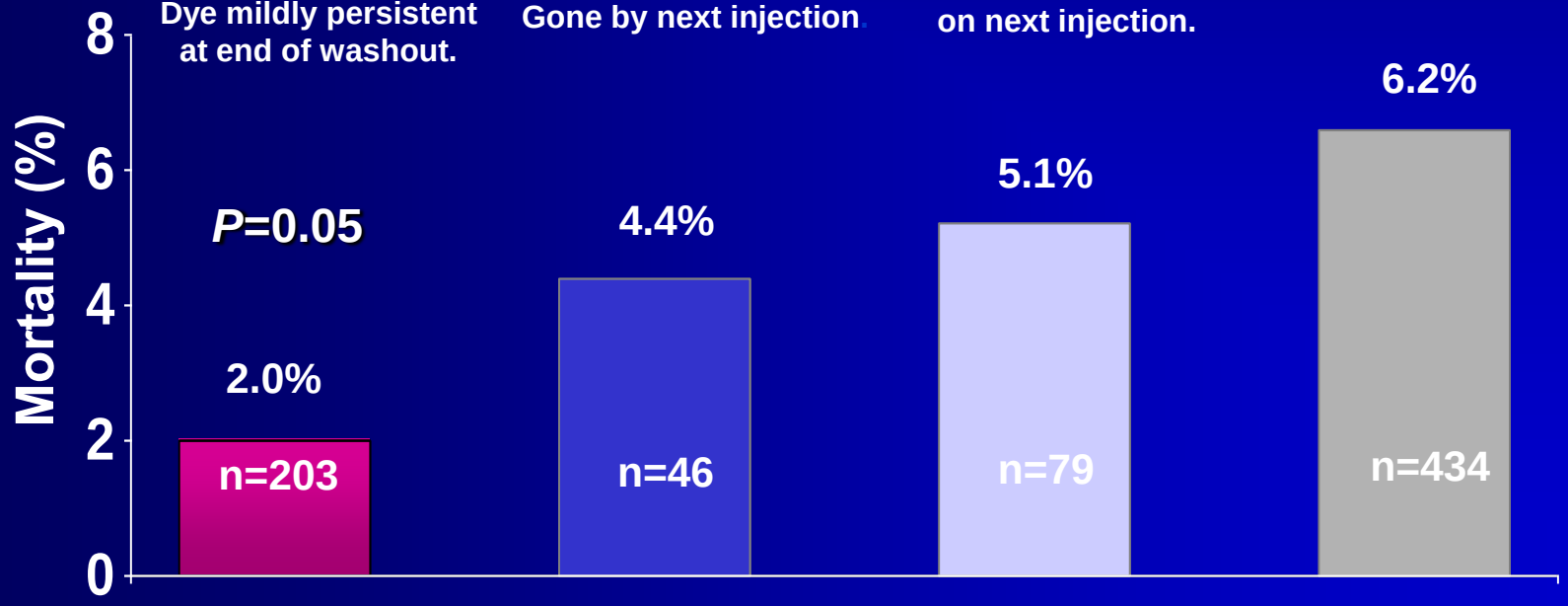


TMP Grade 1

Stain present. Blush persists on next injection.



TMP Grade 0
No or minimal blush.



Gibson CM, et al. *Circulation.* 2000;101:125-130

TMPG

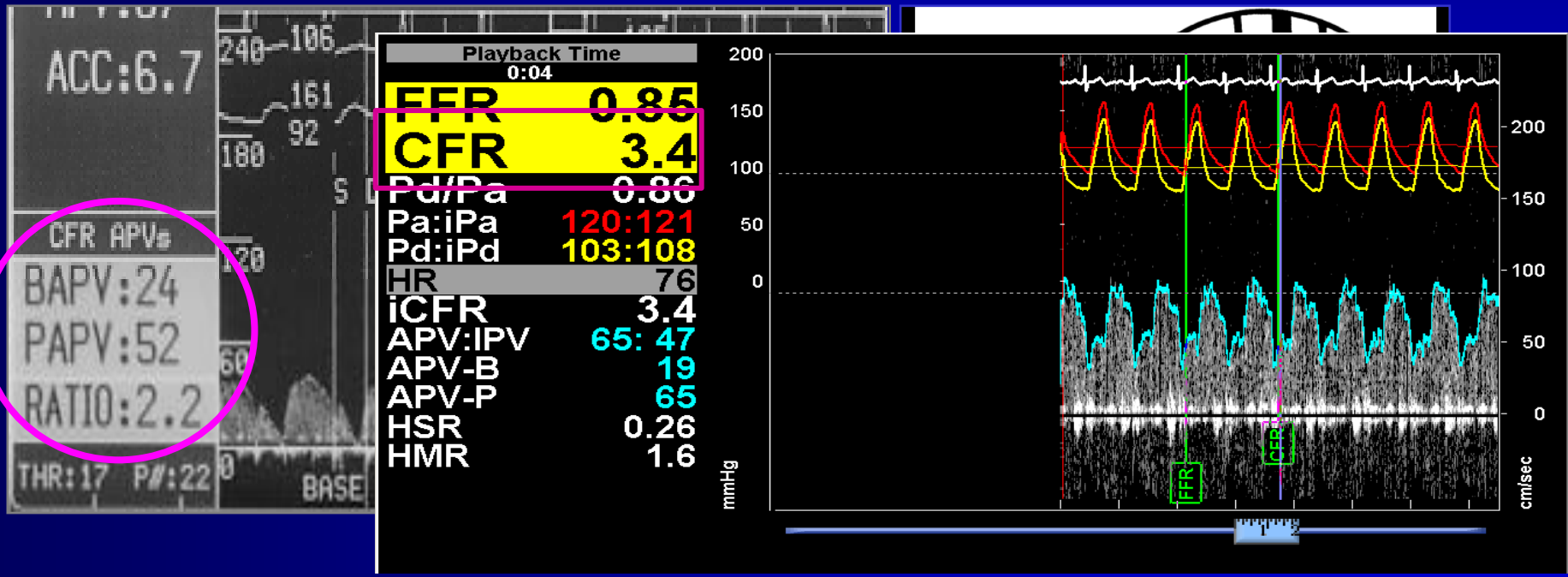
- **Simple, however, several limitations**
  - ✓ **Inter- and intraobserver variability**
  - ✓ **Semi-quantitative, subjective**

		Differences			
	N	Agreement	1 Grade	2 Grades	3 Grades
Intraobserver variability	40	92.5%	7.5%	0%	0%
Interobserver variability	40	85.0%	12.5%	2.5%	0%

Stone GW, et.al. *J Am Coll Cardiol* 2002;39:591

CFR by Intracoronary Doppler

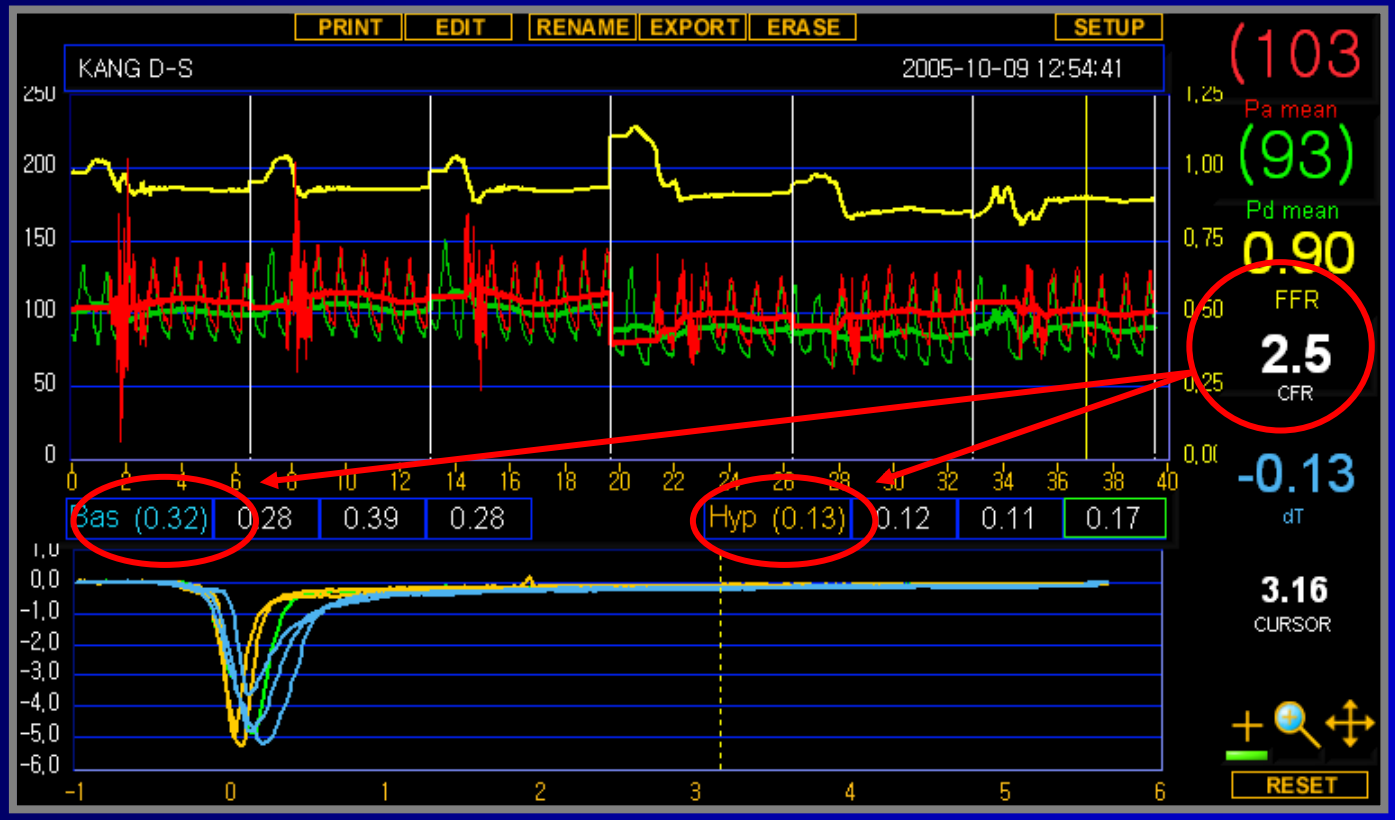
- **CFR** $_{doppler}$
  - = hAPV/2 X CSA / bAPV/2 x CSA
  - = hAPV / bAPV



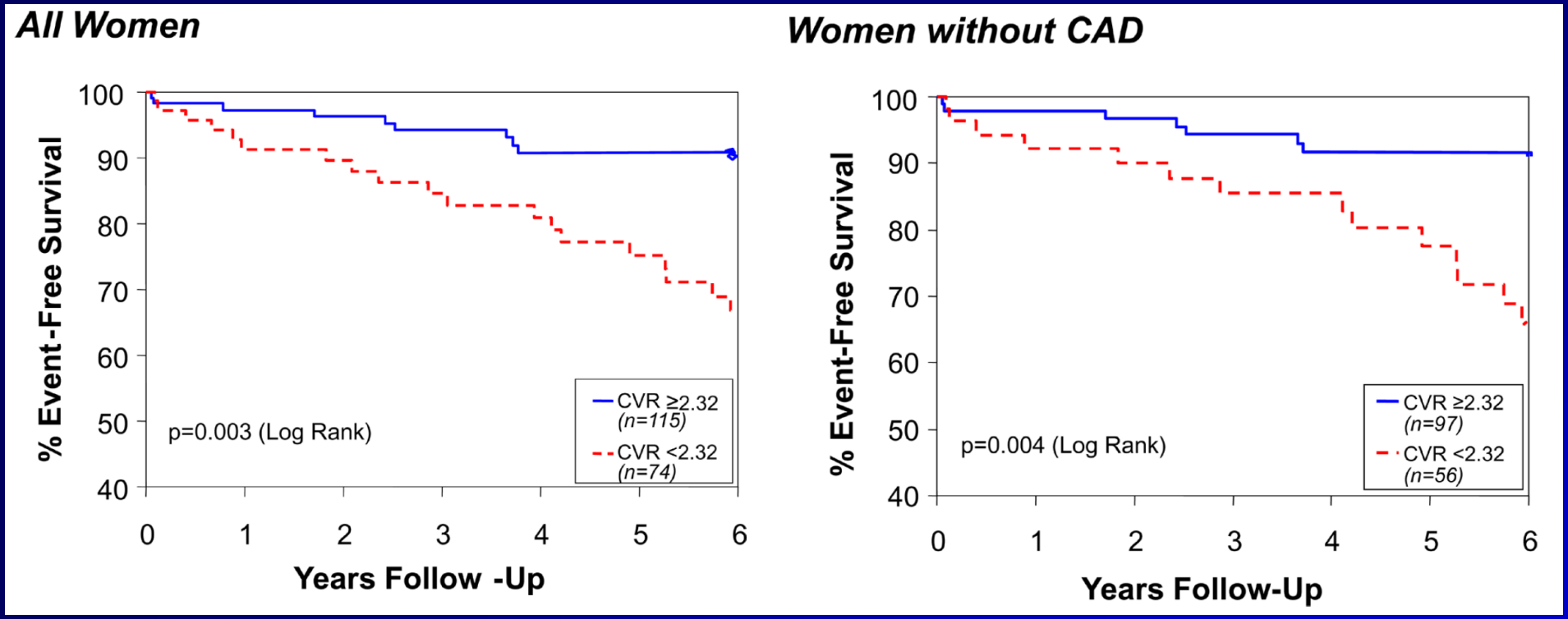
CFR by Pressure Wire (Thermodilusion Method)

- **CFR thermo**

  = mean bTMN / mean hTMN

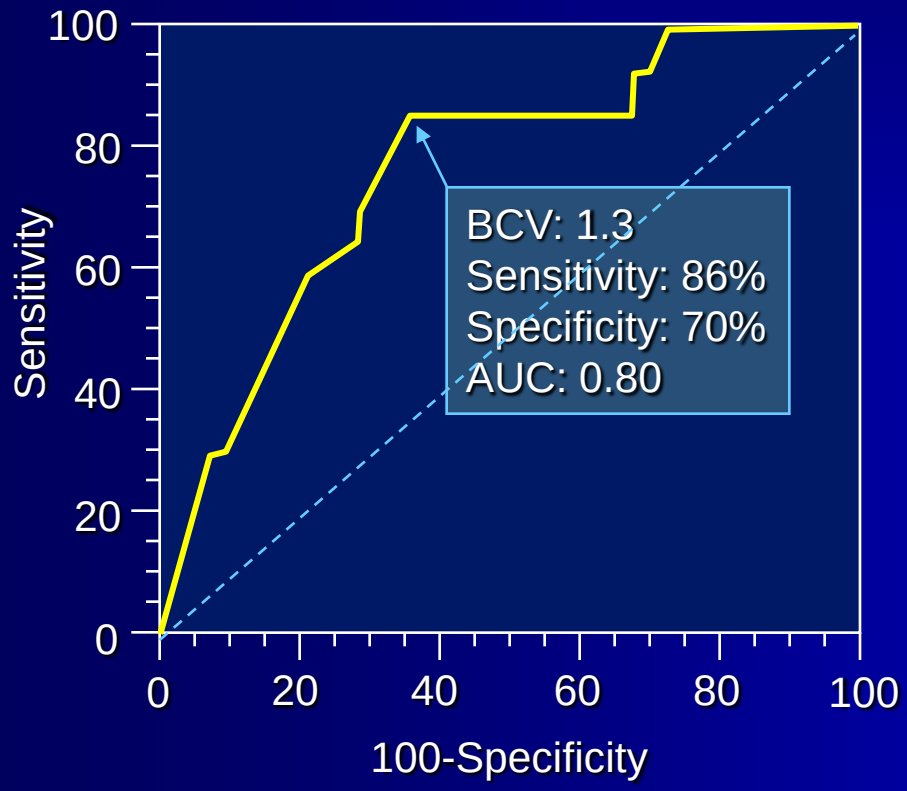


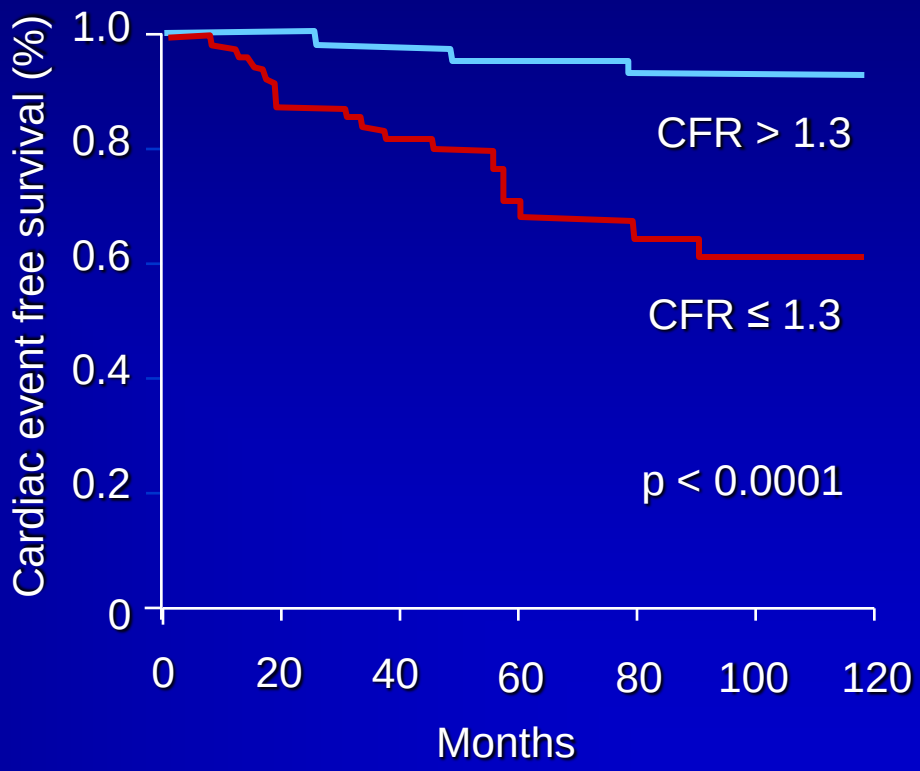
CMD in Women Without or Non-Obstructive CAD



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

CFR After Primary PCI for AMI in Predicting Long-Term MACE





Takahashi T, et al. Am J Cardiol 2007;100:806

Advantages and Limitations of CFR

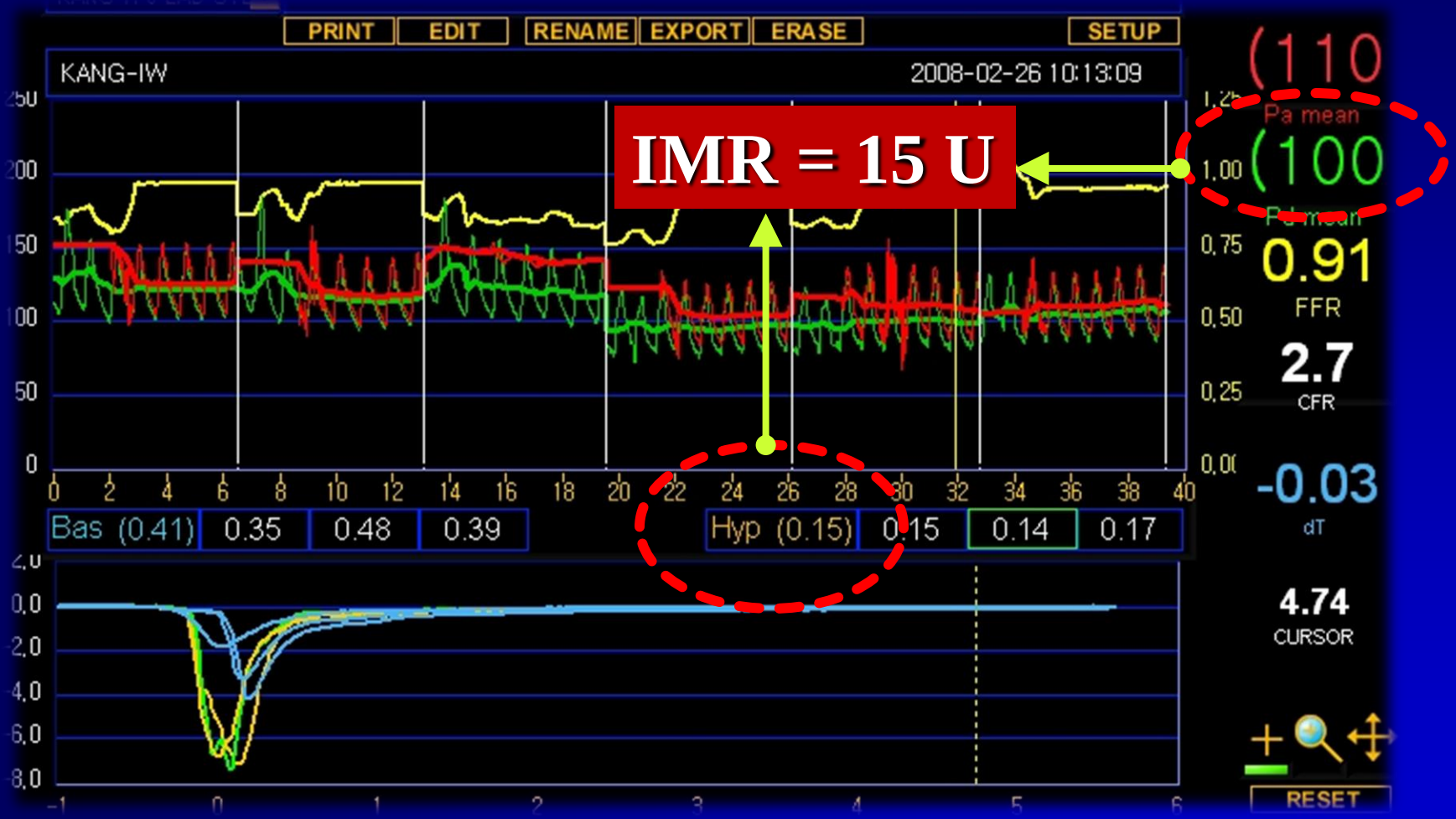
- Advantages
  - ✓Concrete Data for microvascular angina
  - ✓Abnormal value between 2.0-2.5
- Another factors affecting CFR
  - ✓LVH, LVEDP, HR, Age, Hemodynamic conditions

IMR
(Index of Microvascular Resistance)

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

at maximal hyperemia

Measurement of IMR

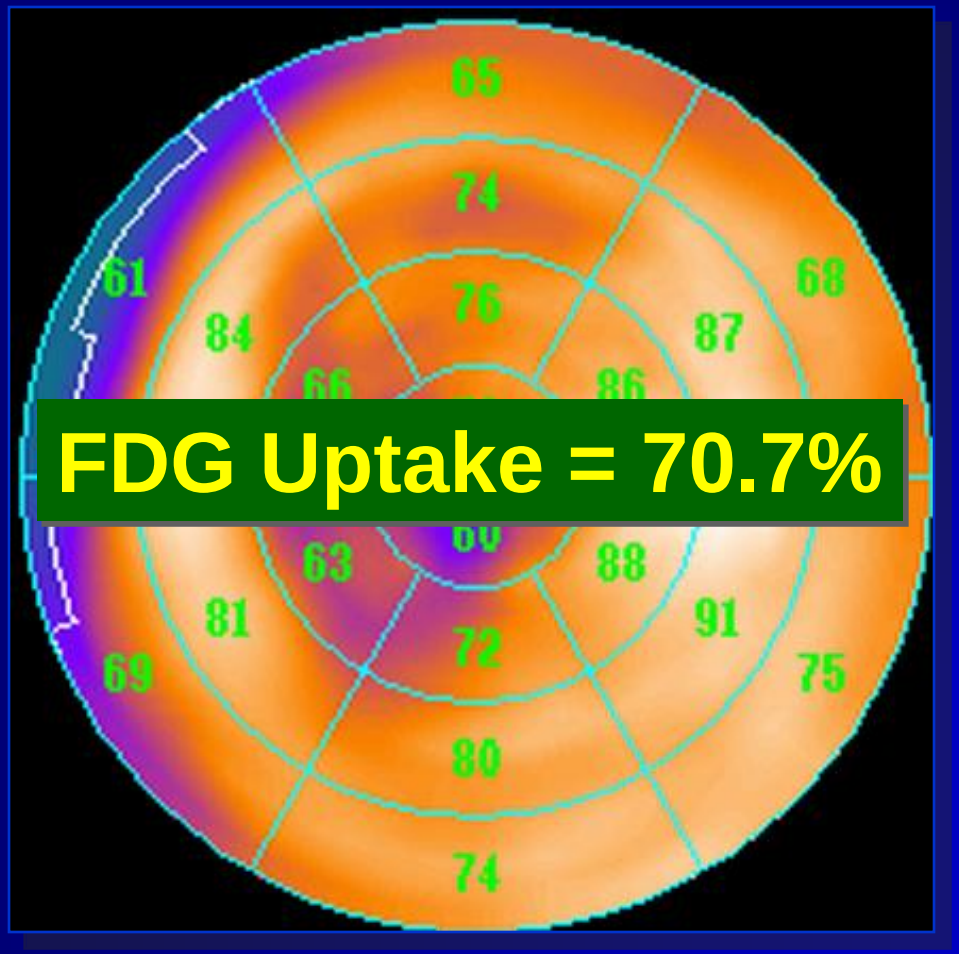


Case 1 : IMR

M/64 STEMI (ant.) **IMR : 11.7 U**

Case 1 : FDG PET

Myocardial viability with FDG PET

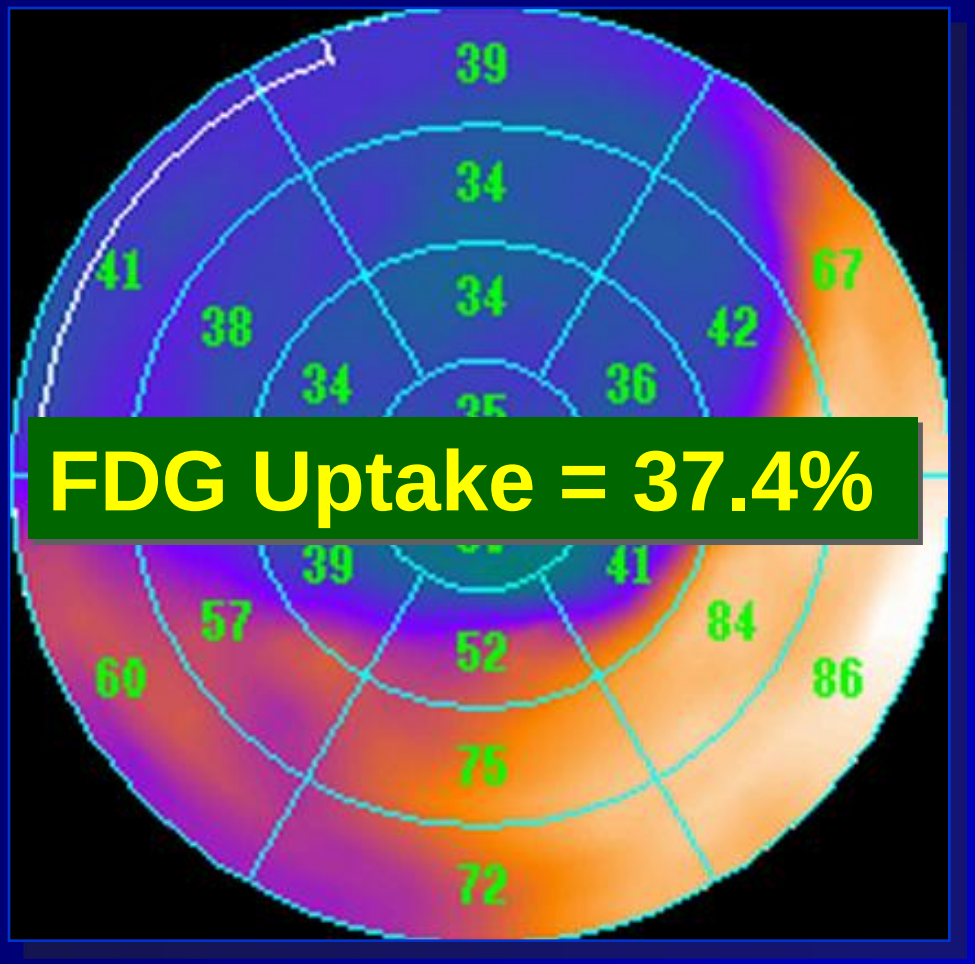


Case 2 : IMR

M/60 STEMI (ant.) **IMR : 72.3 U**

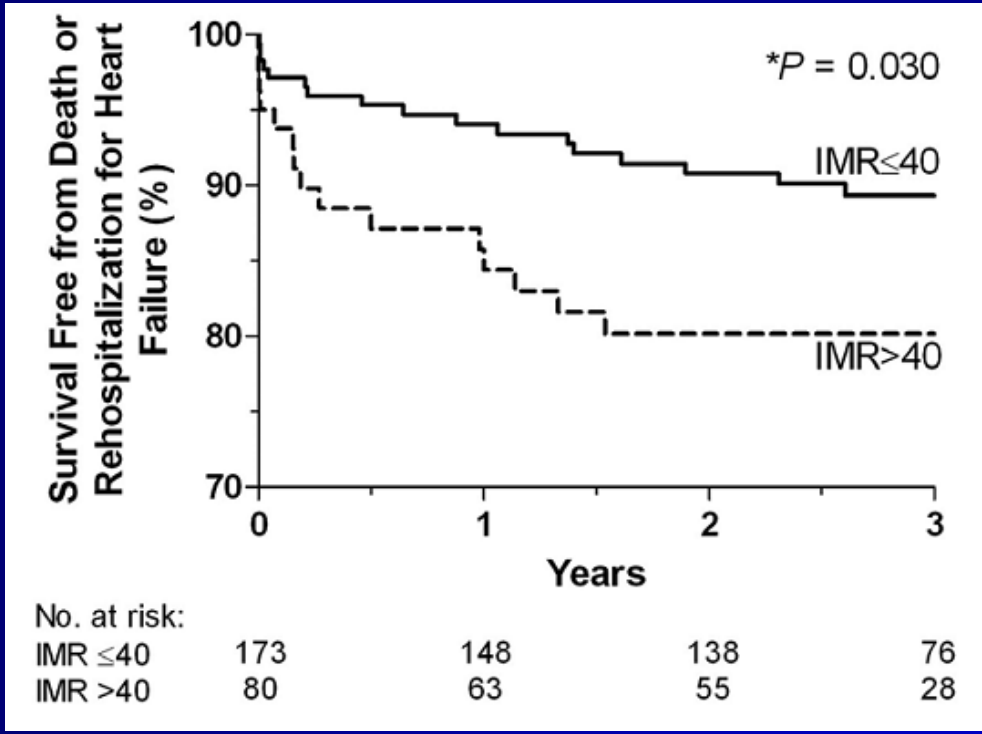
Case 2 : FDG PET

Myocardial viability with FDG PET



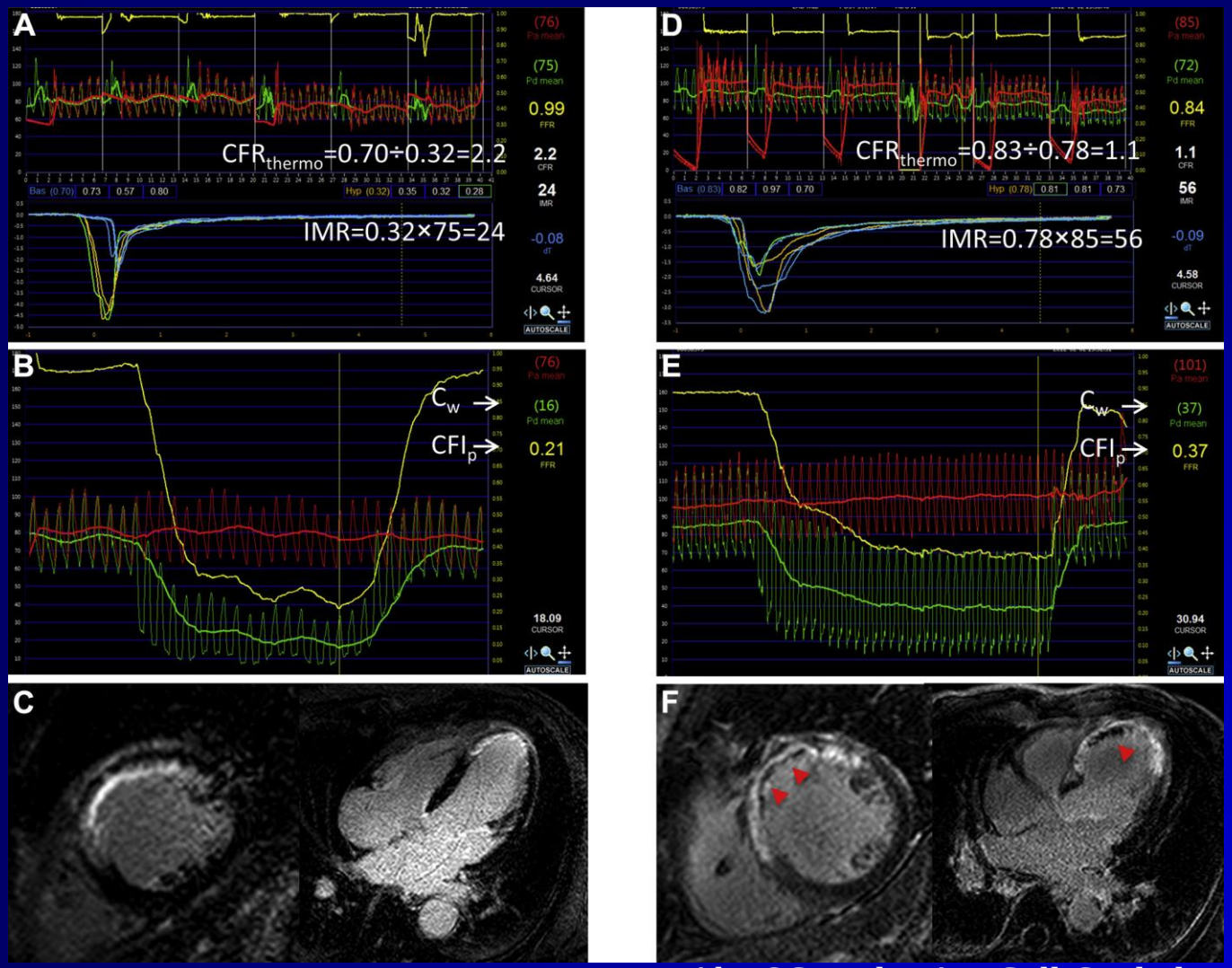
Prognostic Value of the IMR

- The Kaplan–Meier curves between IMR >40 and survival free of death or rehospitalization for heart failure.



Fearon W et al. Circulation. 2013;127:2436-41

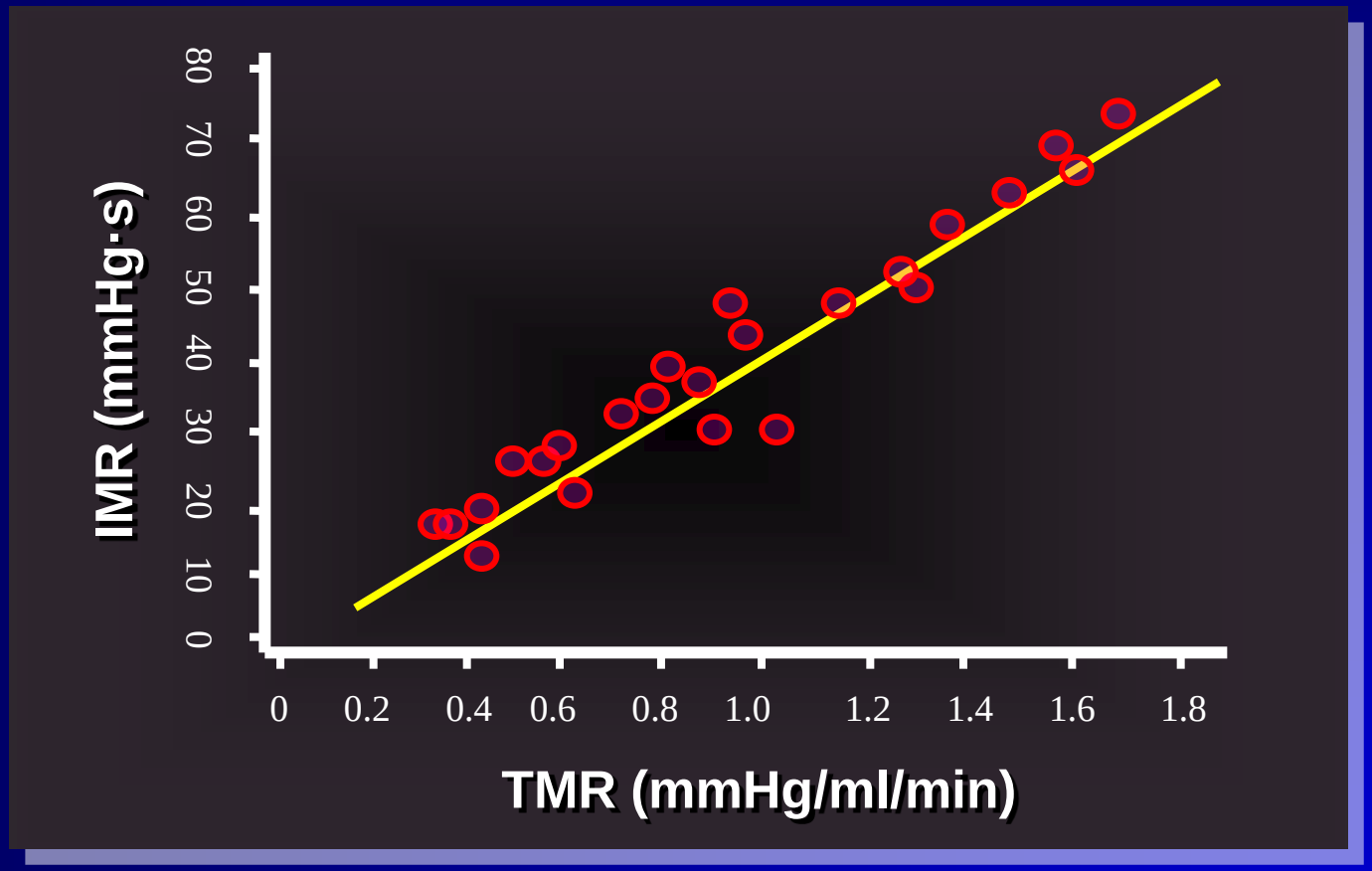
Combined Index (IMR and CFR) in AMI



Ahn SG et al. J Am Coll Cardiol Intv 2016;-:-–-

Advantage of IMR

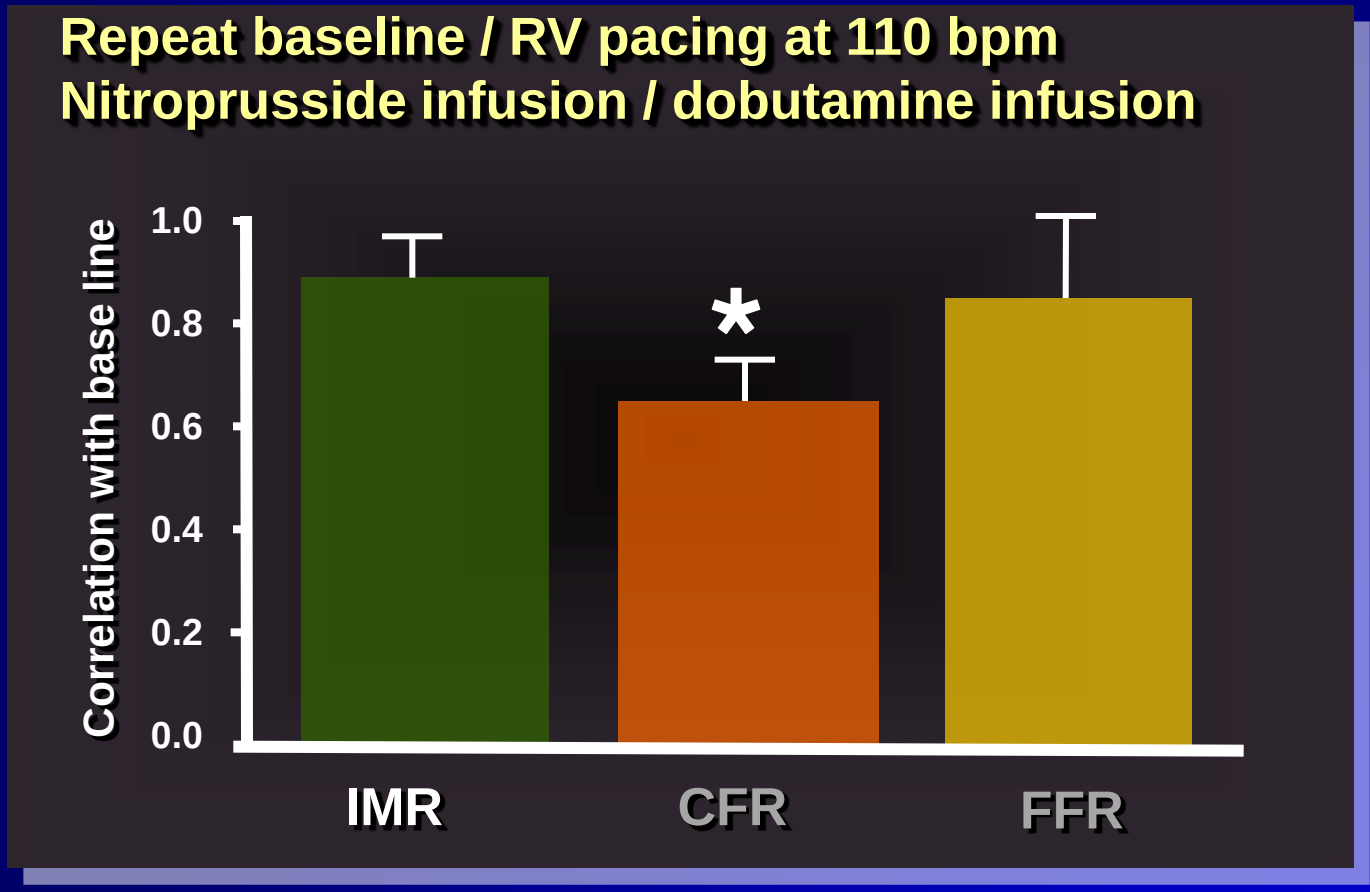
Correlation between IMR and TMR at 24 different combinations of myocardial resistance and epicardial stenosis severity



Aarnoudse et al. *Catheter Cardiovasc Interv.* 2004;62(1):56-63.

Advantage of IMR

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



Martin et al. *Circulation* 2006;113;2054-2061

Limitations of IMR

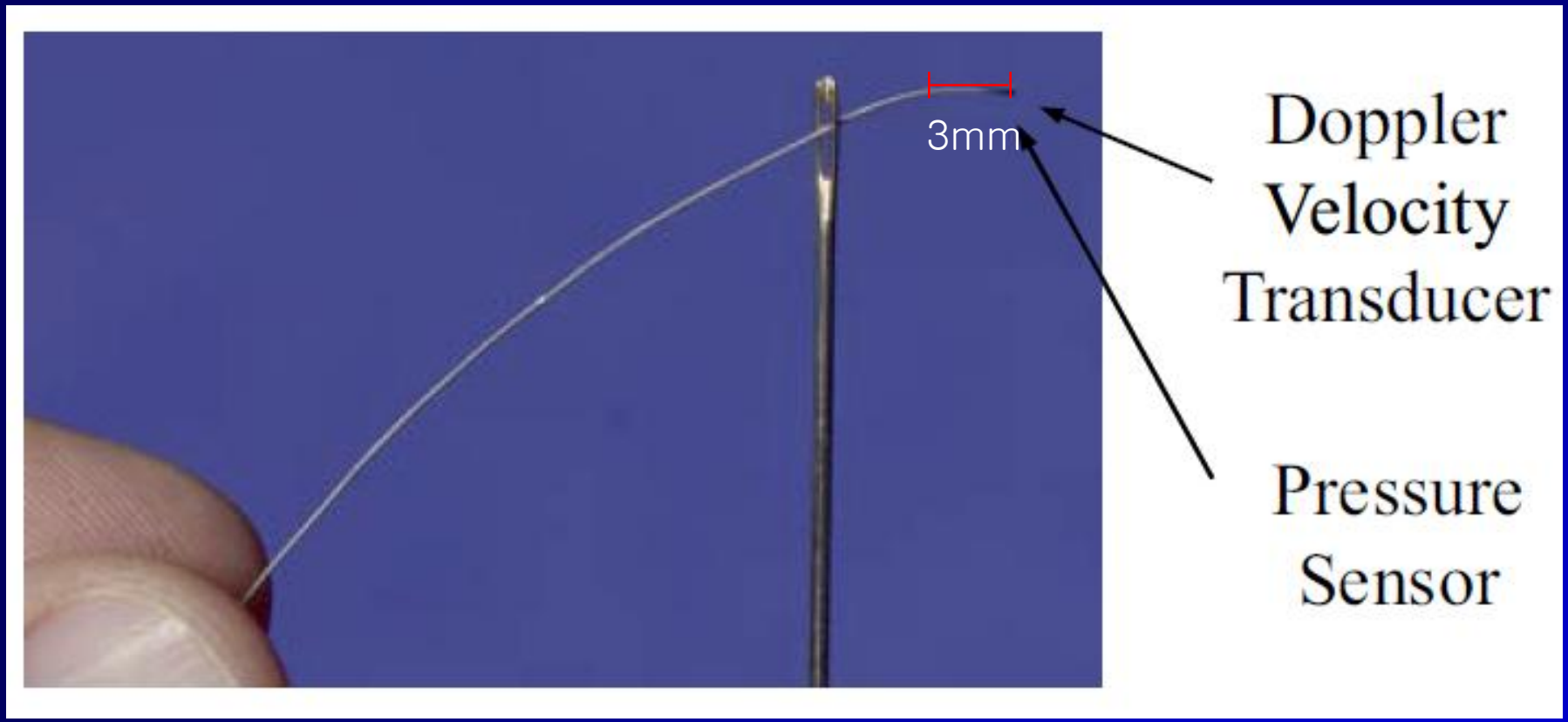
- Invasive
- Interpatient variability?
  - Sensor distance (in the distal 2/3 of the vessel)
- Normal value?
- No clinical data in patients with angina and non-obstructive CAD
- Independent of epicardial stenosis
  - Coronary wedge pressure

Hyperemic Microvascular Resistance Index (hMVRI) vs. IMR

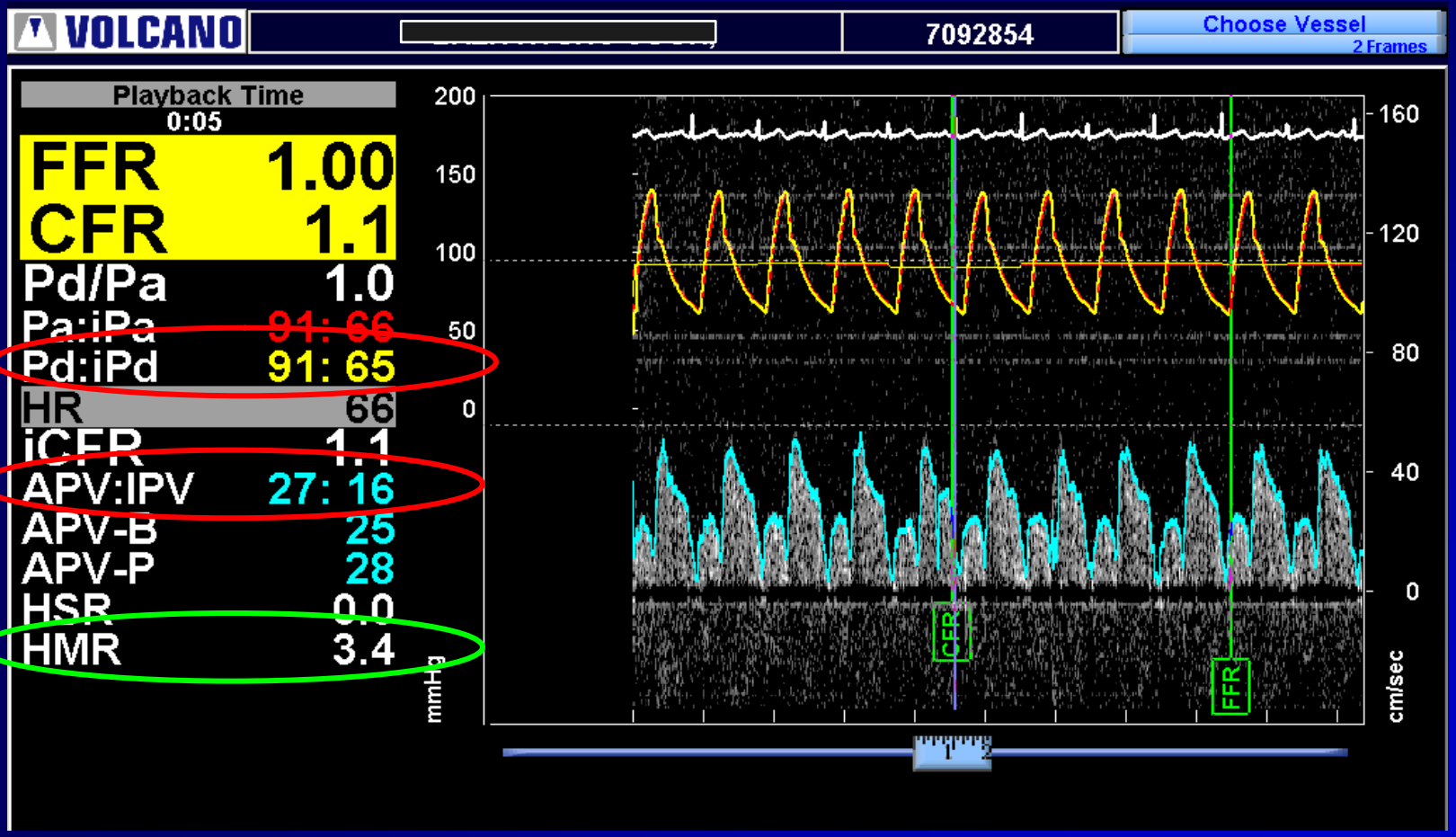
- hMVRI (mmHg·cm · sec^{-1}) = Pd/hAPV (by Combo Wire)

- IMR = Pd X Tmn (by Radi Wire)

ComboMap®: Pressure and Flow System, Soft ware Version 2.1



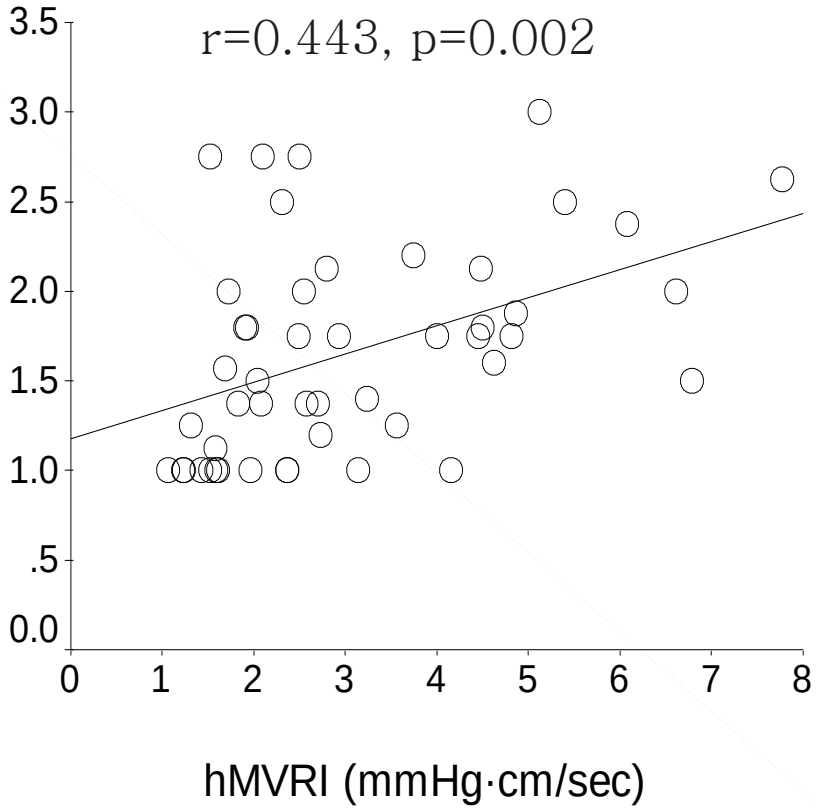
Measurement of hMVRI by Combo Wire

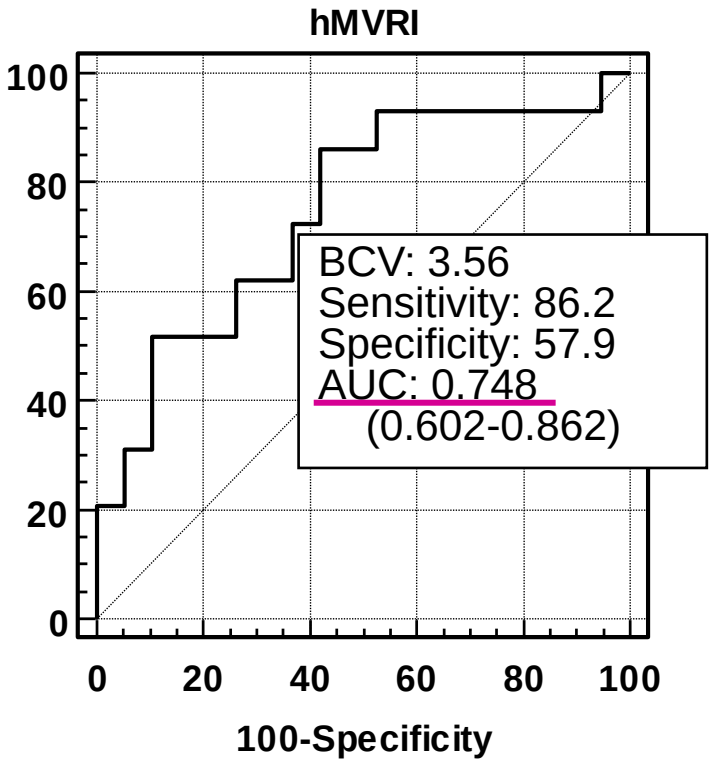


✓ **hMVRI (mmHg·cm · sec^{-1}) = Pd/hAPV**

= 91/27 = 3.37 mmHg·cm · sec^{-1}

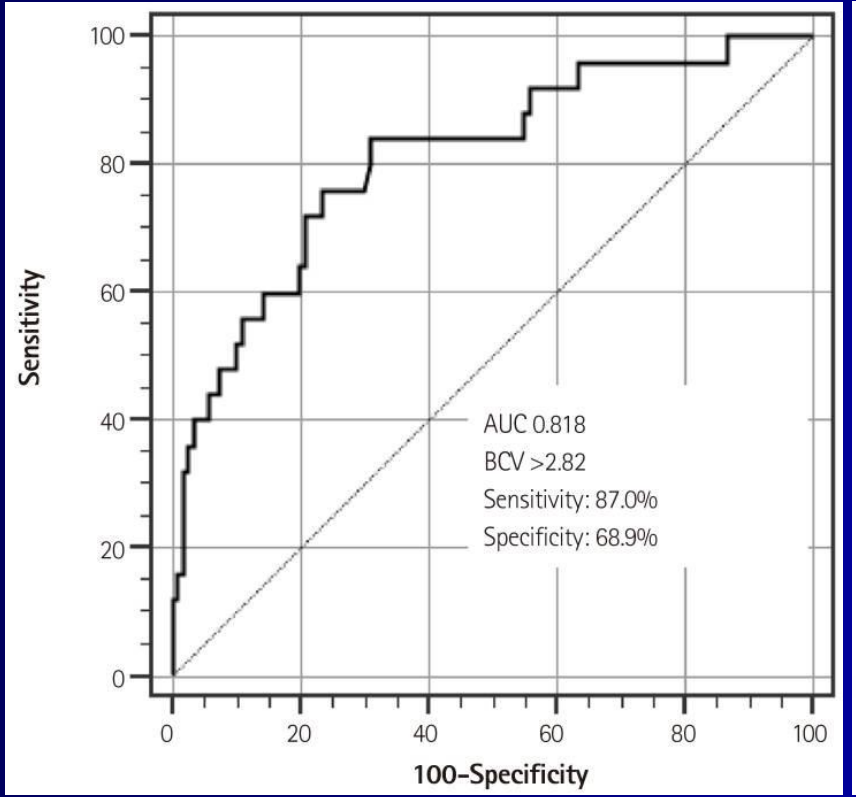
hMVRI and LV-WMA

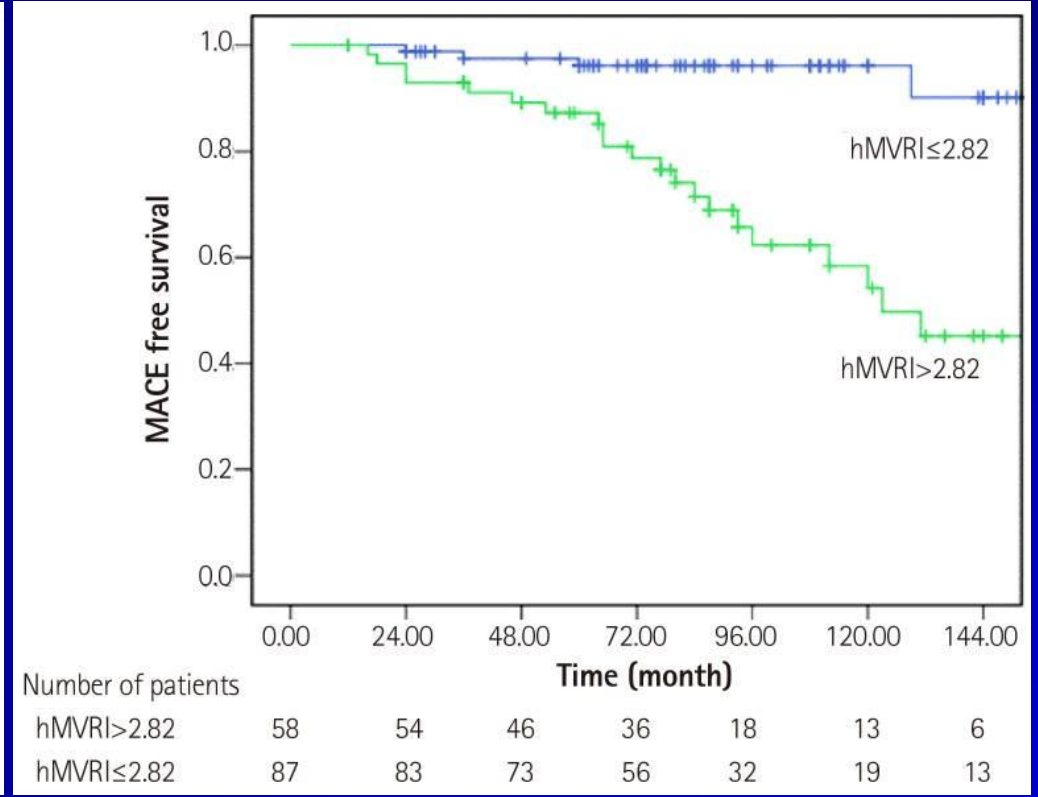




Yoon MH, *et al. Am J Cardiol* 2008;102:129

Kaplan-Meier event free survival analysis for MACE





Jin X, *et al. Korean Circ J 2015;45:194*

Why Should We Measure the Coronary Microvascular Function?

- Microvascular function is an important prognostic factor in a wide range of disease.
- In recent years, evidence has shown that CMD is a true clinical entity rather than a mystery or an academic curiosity.
- Measurement of CMD and identifying the mechanisms of angina is important to provide a rational treatment strategy and improving the quality of life and long-term prognosis.

Thank You for Your Attention