

What is the Stress Modalities for my Patient ?



João V. Vitola, MD, PhD

Cardiologist and Nuclear Medicine Physician
Quanta Diagnostico Nuclear
Curitiba - Brazil



DISCLOSURES

Honorarium – Research and Conferences in Nuclear Cardiology

BMS, CVT, Astellas, Pgx Health/Forest laboratories, Lantheus Medical Imaging
International Atomic Energy Agency

Royalties – Publications in Nuclear Cardiology

Springer-Verlag-*Nuclear Cardiology and Correlative Imaging: a teaching file*, NY, 2004

Lippincott Williams & Wilkins, - *Nuclear Medicine teaching File*, 2009

Topics to cover

Goal of stressing

hyperemia/testing coronary reserve

Decide on type of stress

Discordant ECG changes and Perfusion

Bayes theorem - impact on test result

Advantages, drawbacks and efficacy of different options

Mechanisms of action / Interfering factors: medications and diet

Protocols: a practical approach

IAEA documents and recommendations from 2012 (website)

Before Choosing a Stress Modality

1- Collect data – medical history

Understand who your patient is

Estimate pre test probability – symptoms + risk factors

ACCURACY OF A TEST DEPENDS ON DISEASE PREVALENCE

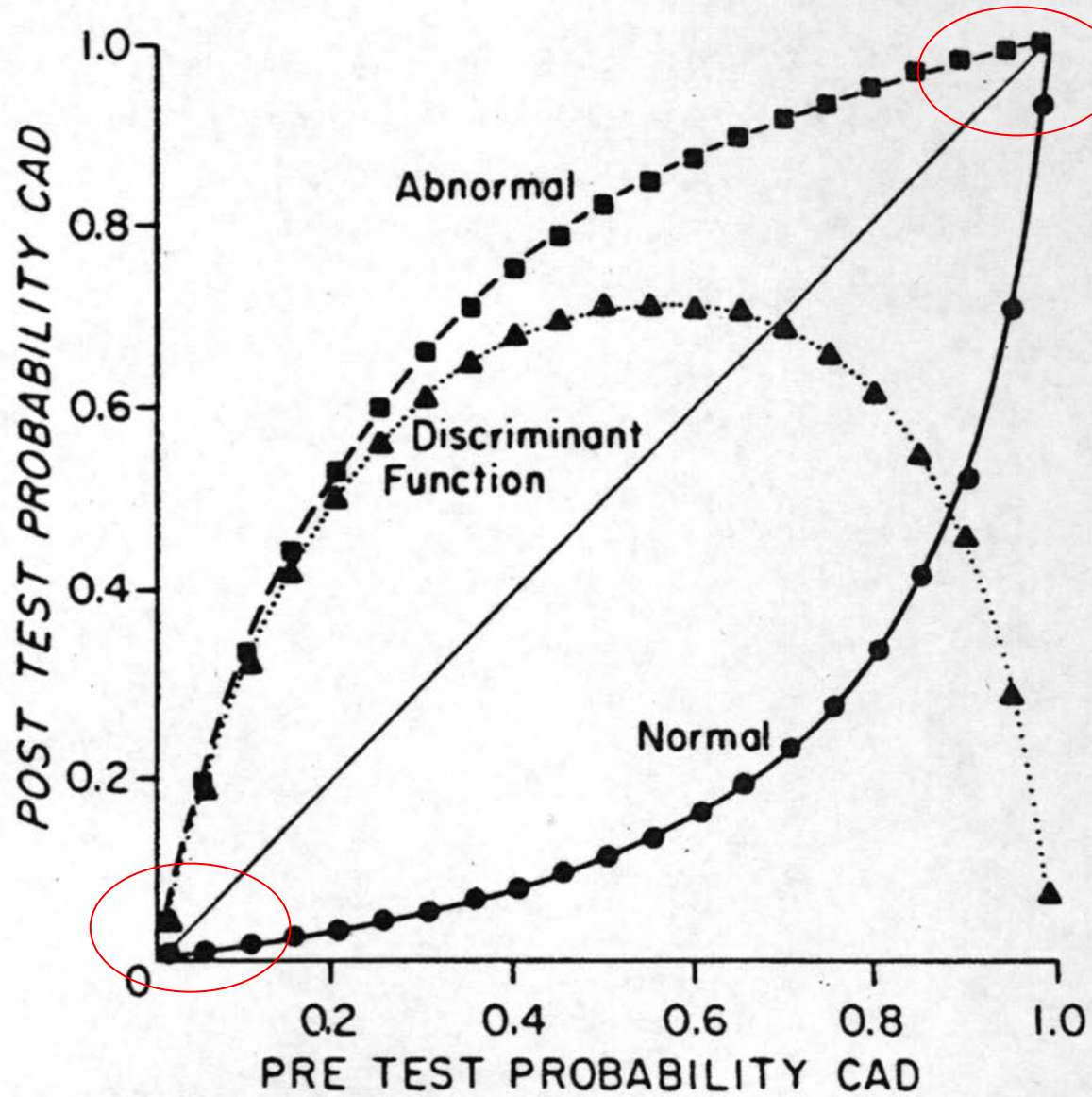
False positive ECGs
Consider artifacts on SPECT

Actual Disease Prevalence (%)	Predictive Value of a Positive Test (%)	Predictive Value of a Negative Test (%)
1	16.1	99.9
2	27.9	99.9
5	50.0	99.7
10	67.9	99.4
20	82.6	98.7
50	95.0	95.0
75	98.3	83.7
100	100.0	—

Consider false negative
ECG LAHB
Balanced disease on SPECT

Vecchio TH, NEJM 274:1171

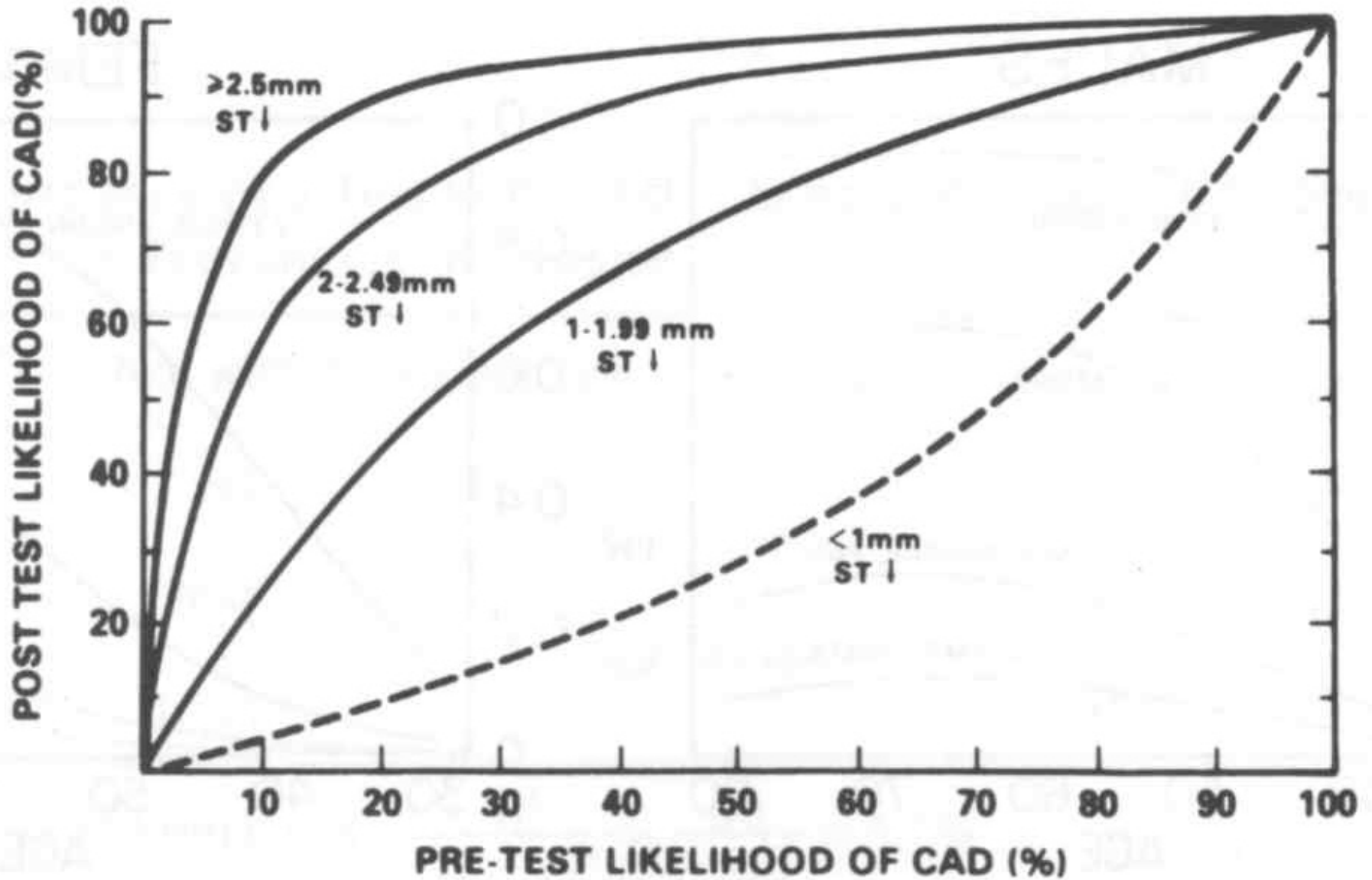
BAYES THEOREM



**ACCURACY OF A TEST DEPENDS ON DISEASE PREVALENCE
AND ALSO YOUR DEFINITION OF ABNORMALITY
(i. e. 1 mm ST depression or very mild perfusion defect)**

Actual Disease Prevalence (%)	Predictive Value of a Positive Test (%)	Predictive Value of a Negative Test (%)
1	16.1	99.9
2	27.9	99.9
5	50.0	99.7
10	67.9	99.4
20	82.6	98.7
50	95.0	95.0
75	98.3	83.7
100	100.0	—

ST depression magnitude and Predictive Value



1- Collect data – medical history

Estimation of pre test probability –symptoms, risk factors

Interview needed to better define ideal stress protocols

Needed to define which question clinician want to answer

Diagnosis ? Prognosis ?

Culprit artery ?

Viability? Function ?

2- Stress data

Estimate functional capacity

Some Diagnostic and Prognostic info

Duke Score

New pre test probability before imaging

Define ideal for post stress imaging 15' vs 30' vs 60'

3- Imaging analysis

Consider info from history and stress test for image interpretation
(more sensitive or specific reading)

4 –Final report (1+2+ 3)

Protocols

Most Common

Exercise (“ max”)

Bruce, Ellestad, Modified Bruce, Kattus, Naughton

→ **Combined (exercise + vasodilator: DipEx)**

Dipyridamole (Adenosine)

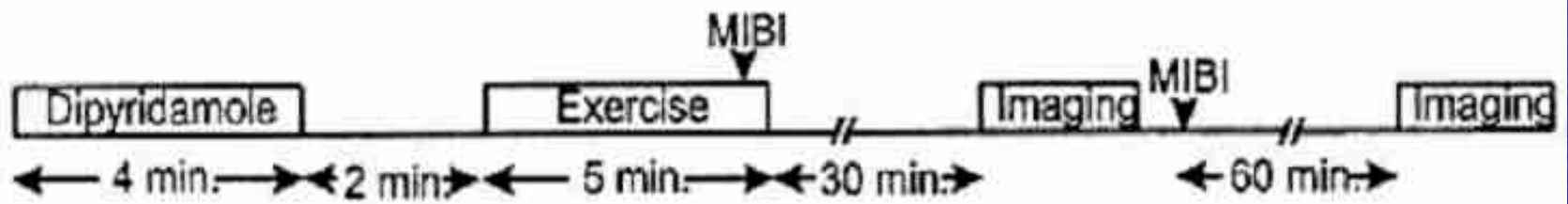
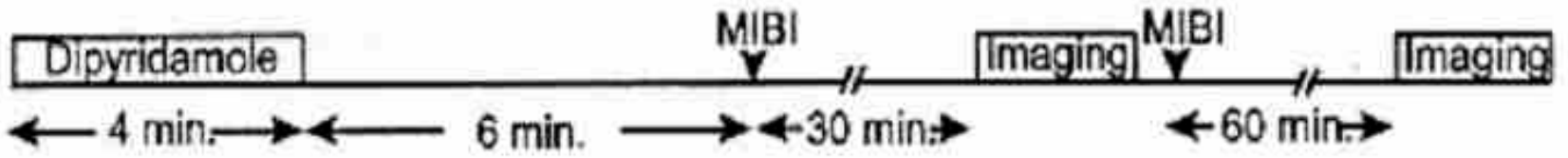
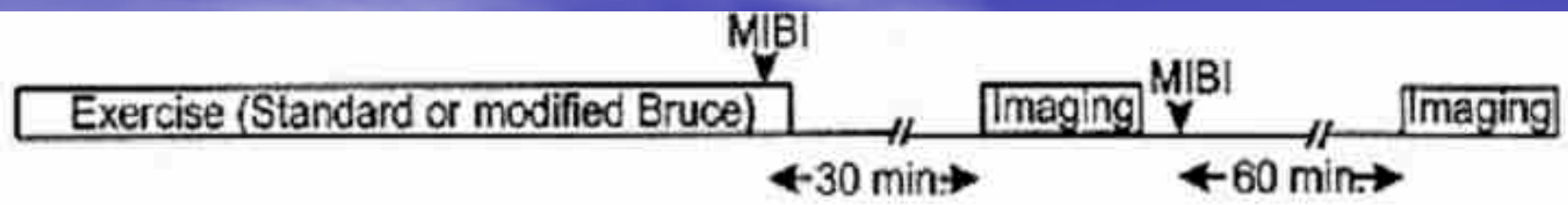
Less Common

Dobutamine

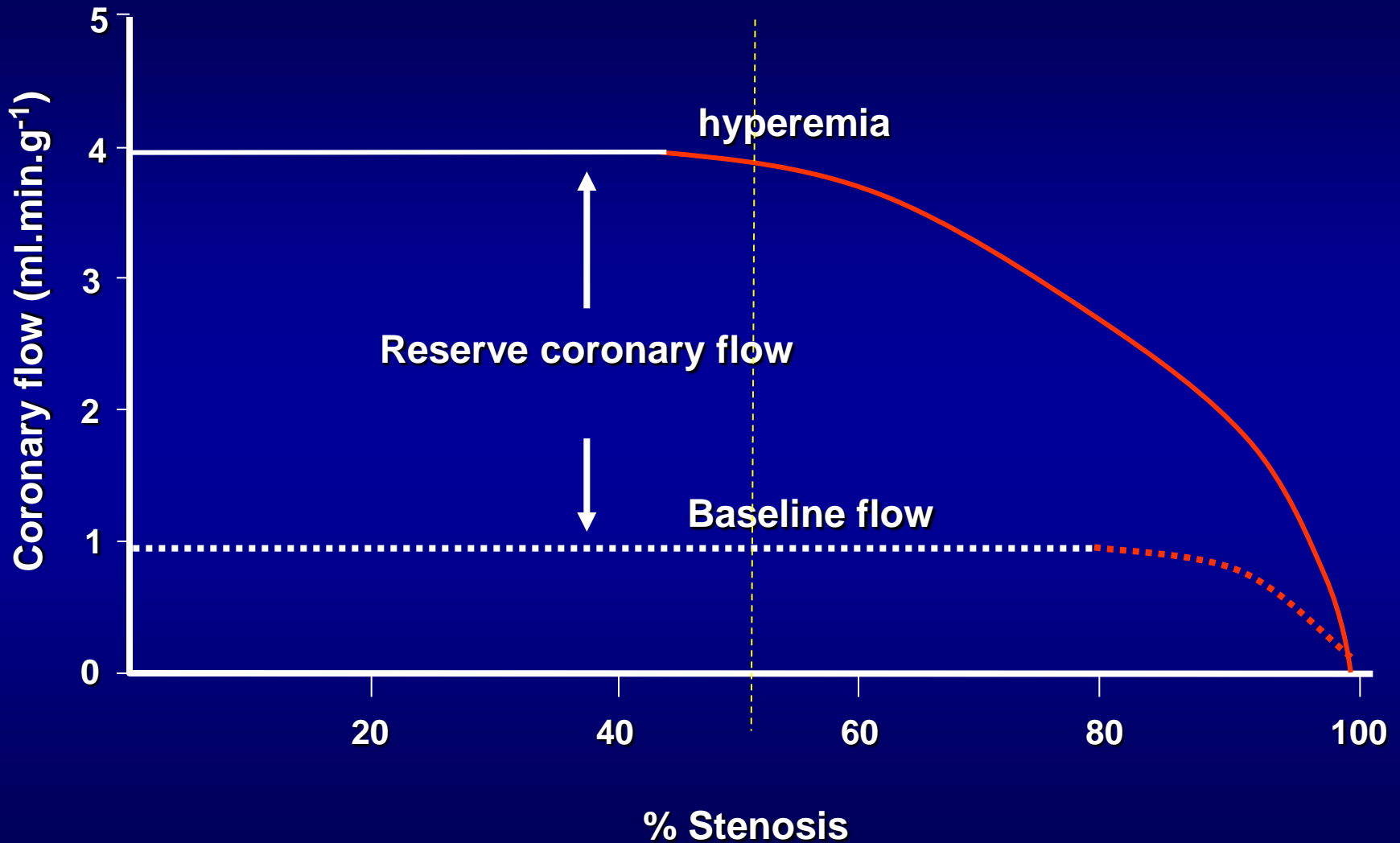
A2a - agonists

→ **Regadenoson**

→ **Apadenoson**

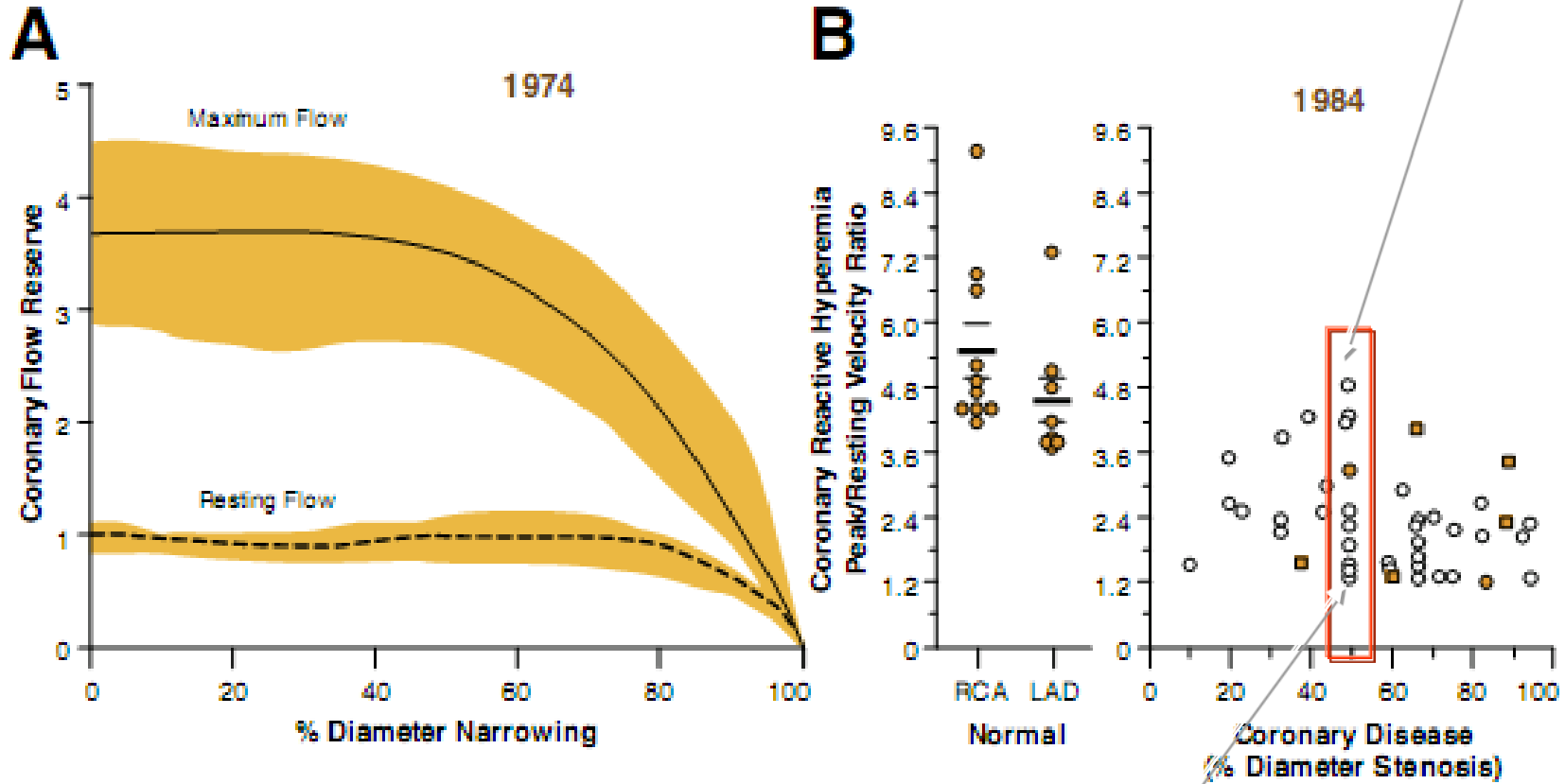


Testing Coronary Reserve



Not all 50% lesions affect reserve the same
Reasons for anatomy vs Physiology discordances

50% and normal reserve



Does Coronary Flow Trump Coronary Anatomy?

K. Lance Gould

J. Am. Coll. Cardiol. Img. 2009;2:1009-1023

doi:10.1016/j.jcmg.2009.06.004

50% and critical lesion

Not all 50% lesions affect reserve the same
Reasons for anatomy vs Physiology discordances

Not “significant”

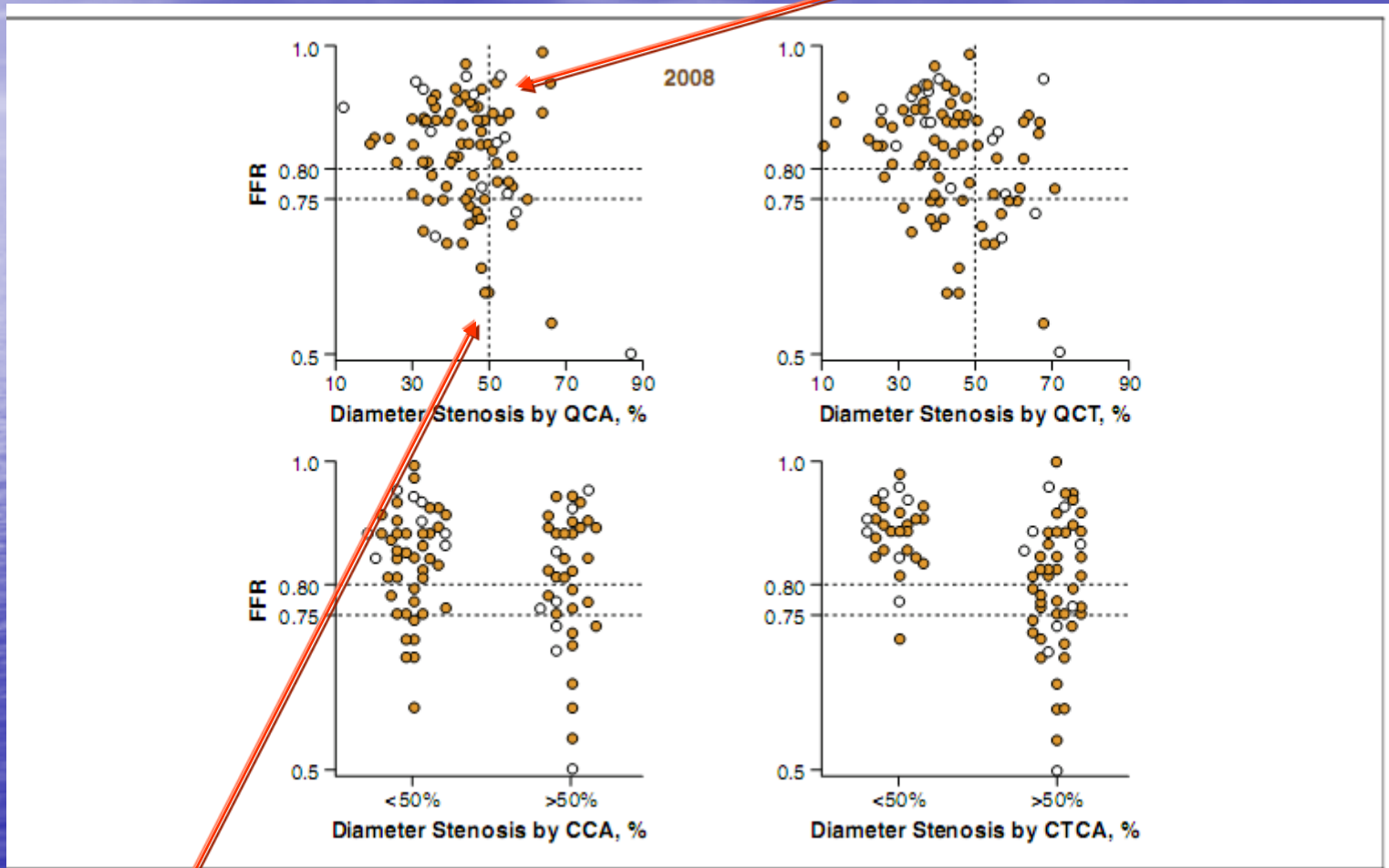


Figure 3. Coronary Function Versus Stenosis Anatomy

Critical

MPI - SPECT

Evaluates the Impact of CAD on Coronary Reserve
(also the presence of adequate collateral flow)

Principles:

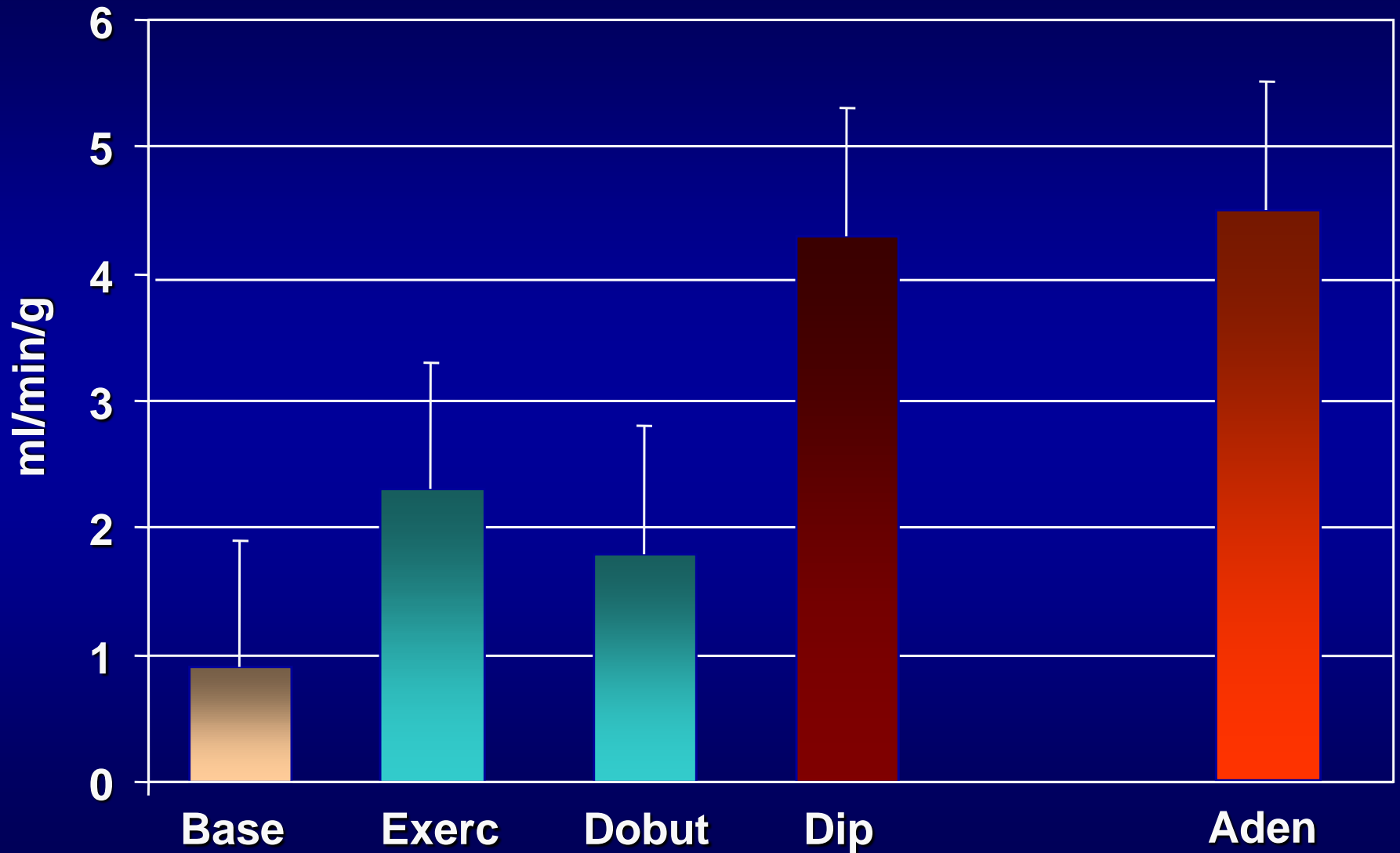
1- Stress is Applied to:

Promote a disparity in flow between a stenotic vessel
and a “normal” vessel

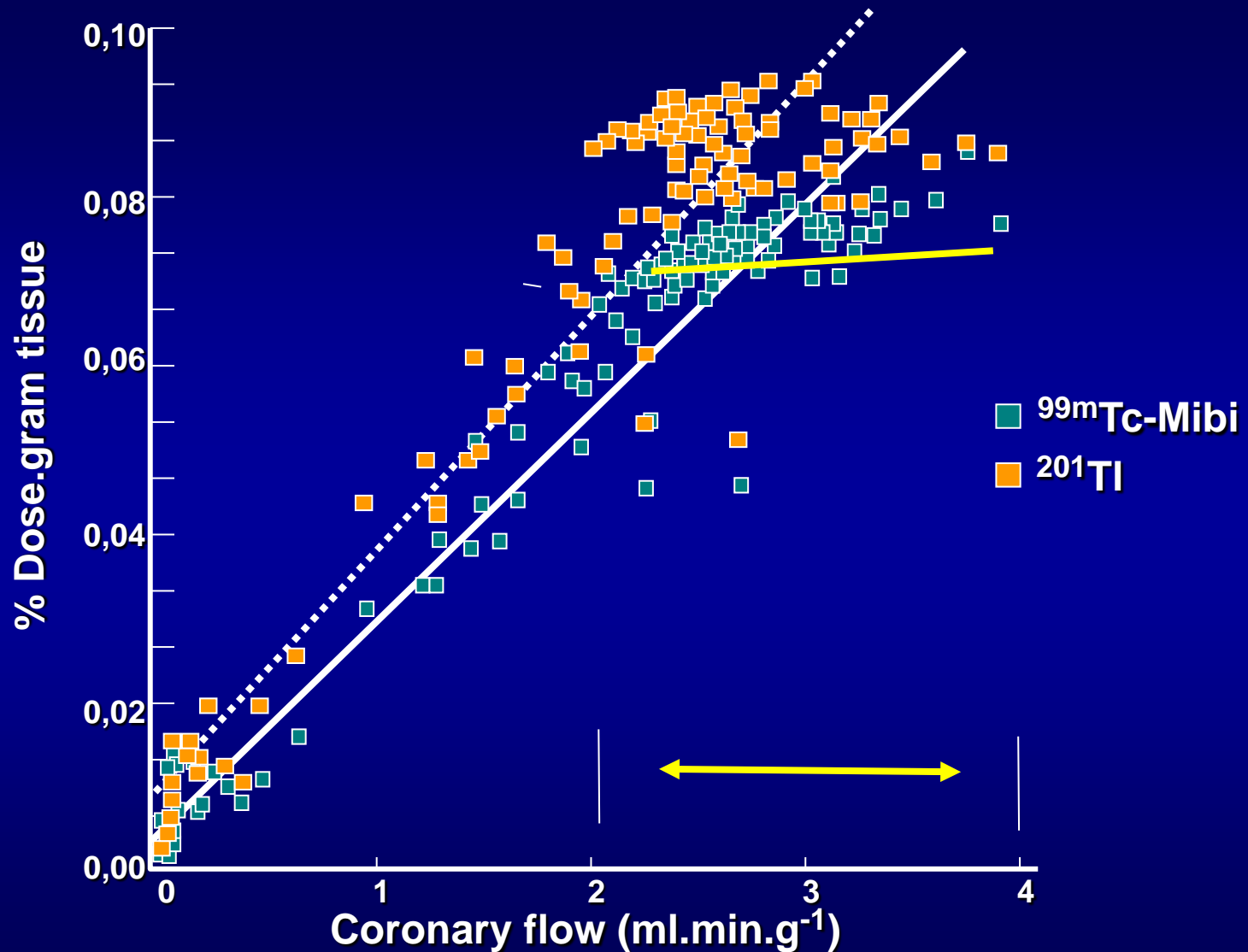
2- Radioactive Tracers :

Distribute proportional to flow up to a limit
(plateau of extraction)

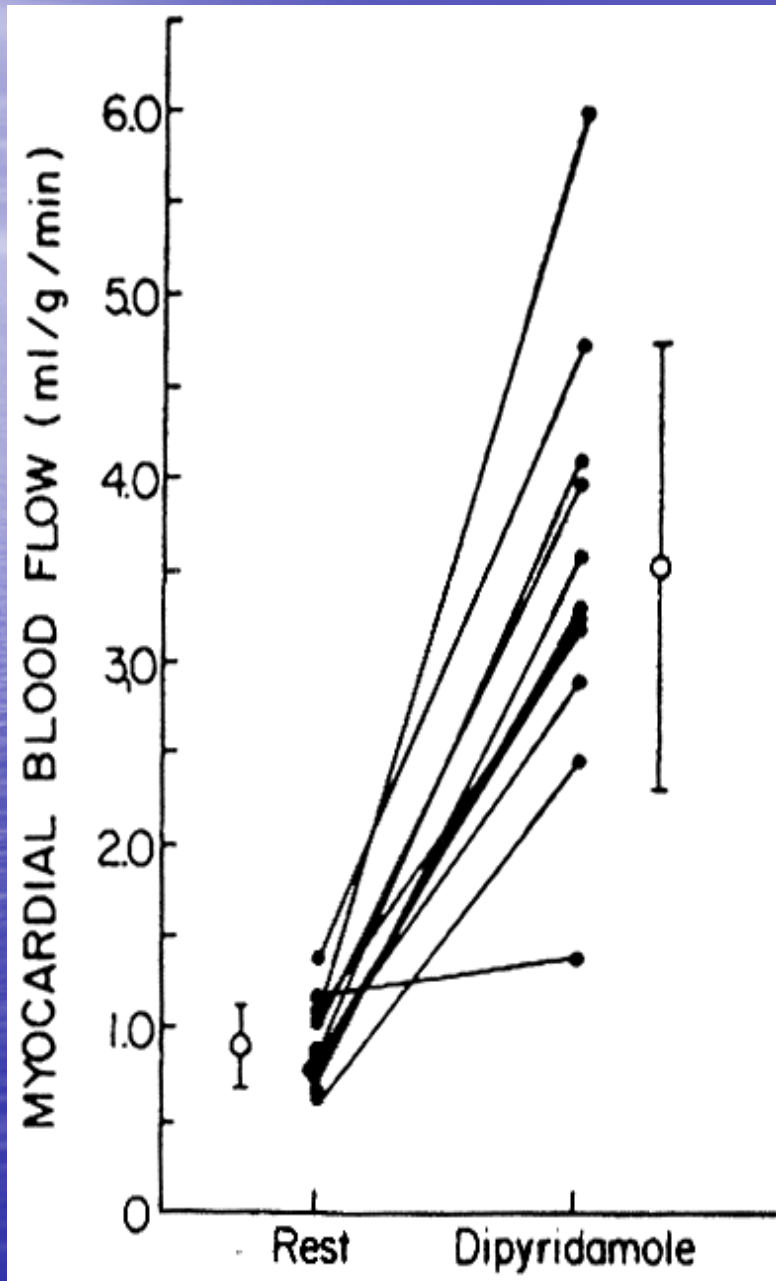
Modalities and Hyperemic Flow – observe SD



Does Higher Flow Means higher sensitivity ? effects of myocardial extraction plateau



All patients respond the same ? Why a wide SD ?

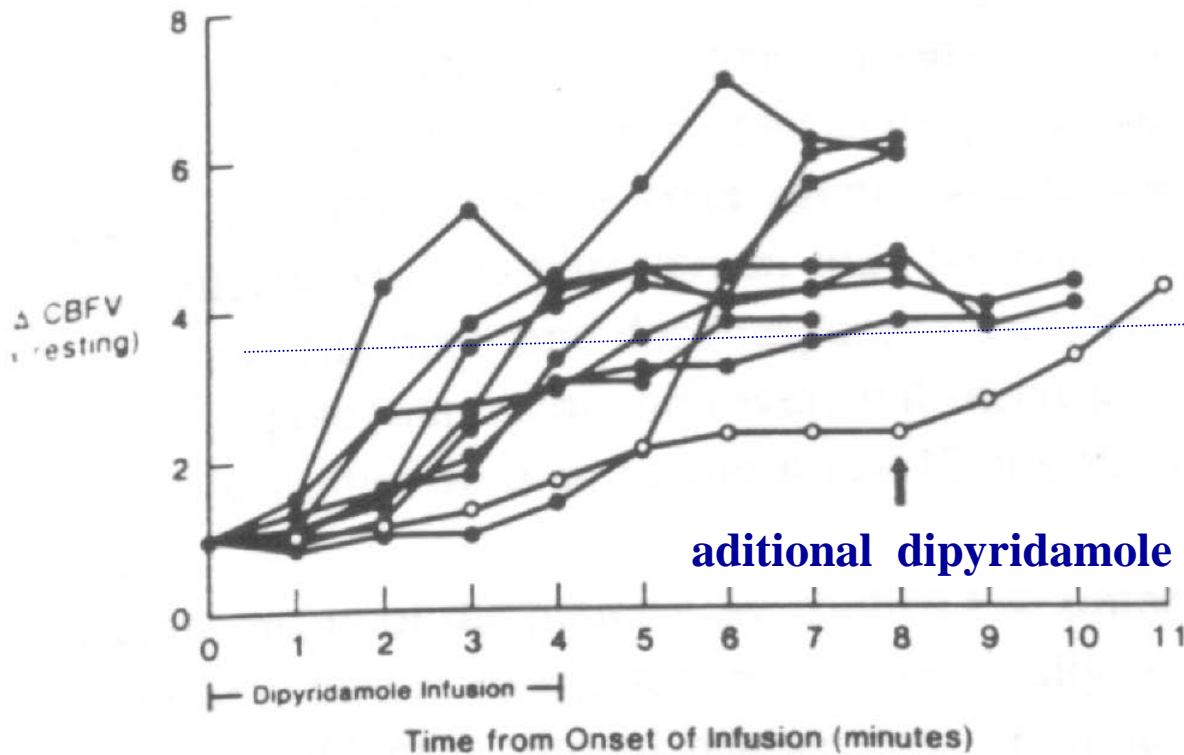


Normal Volunteers
MBF - H₂¹⁵O - PET

Dip 0.56 mg/kg

BERGMANN et al.
JACC 1989;14:639-52

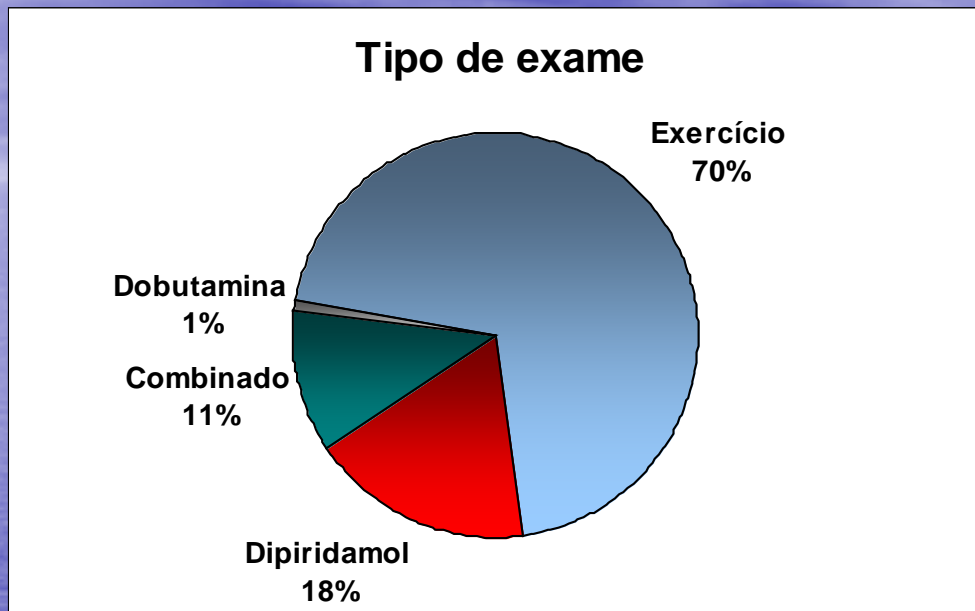
Dipyridamole dose 0.56 mg vs 0.84 mg



9/10
0.56 mg CVR > 3.8

1/10
0.56 mg CVR = 2.3

Exercise Favored as a Stress Modality

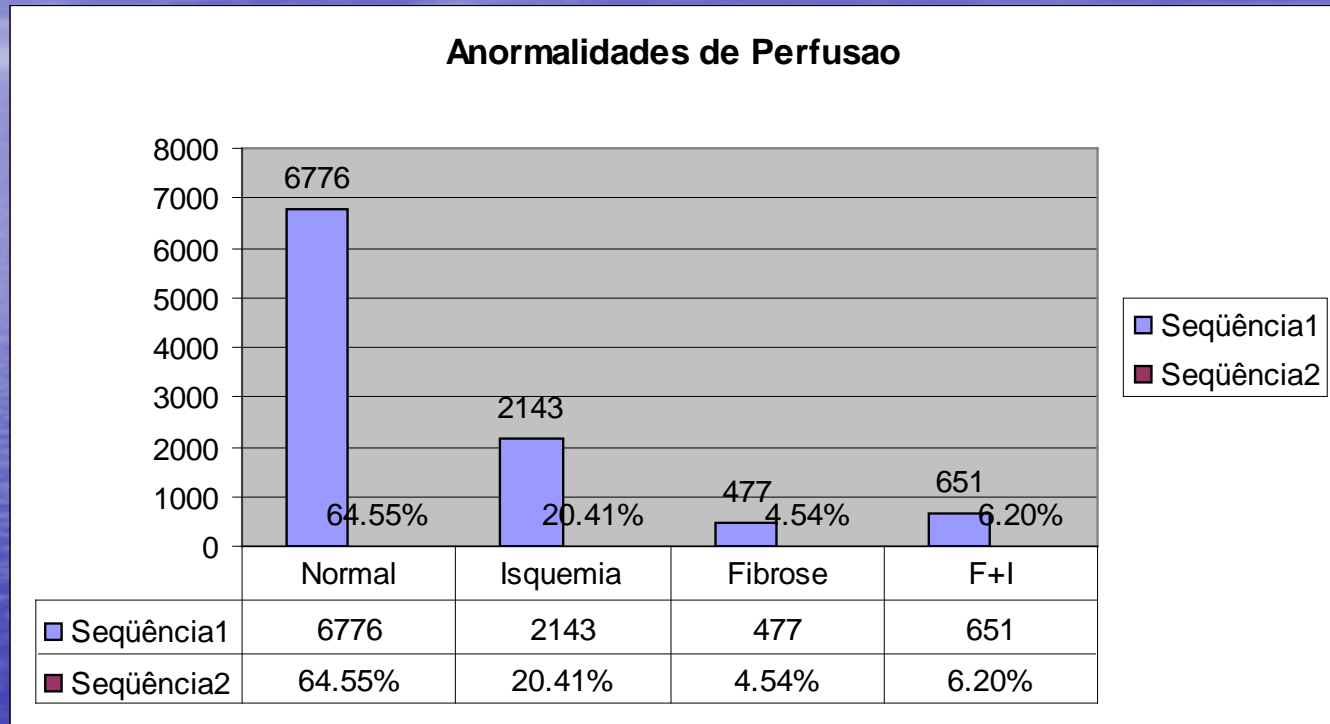


Stress	Freqüência	Percentual
Exercício	7421	70,0%
Dipiridamol	1891	17,8%
Combinado	1184	11,2%
Dobutamina	99	0,9%
Total	10595	100,0%

81%

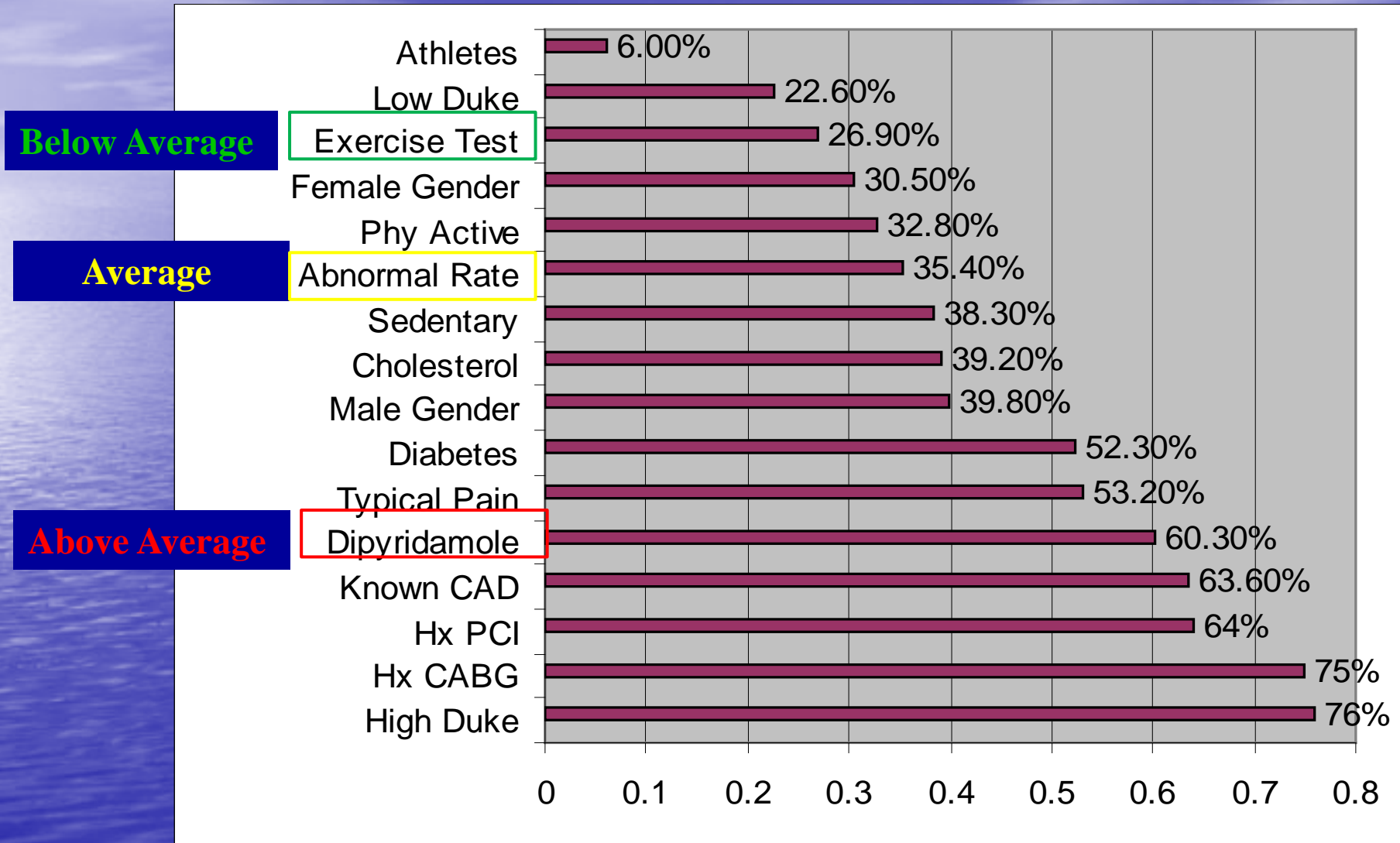
Patterns of Perfusion Abnormality

Your abnormal rate will tell you about the prevalence of disease in the population referred

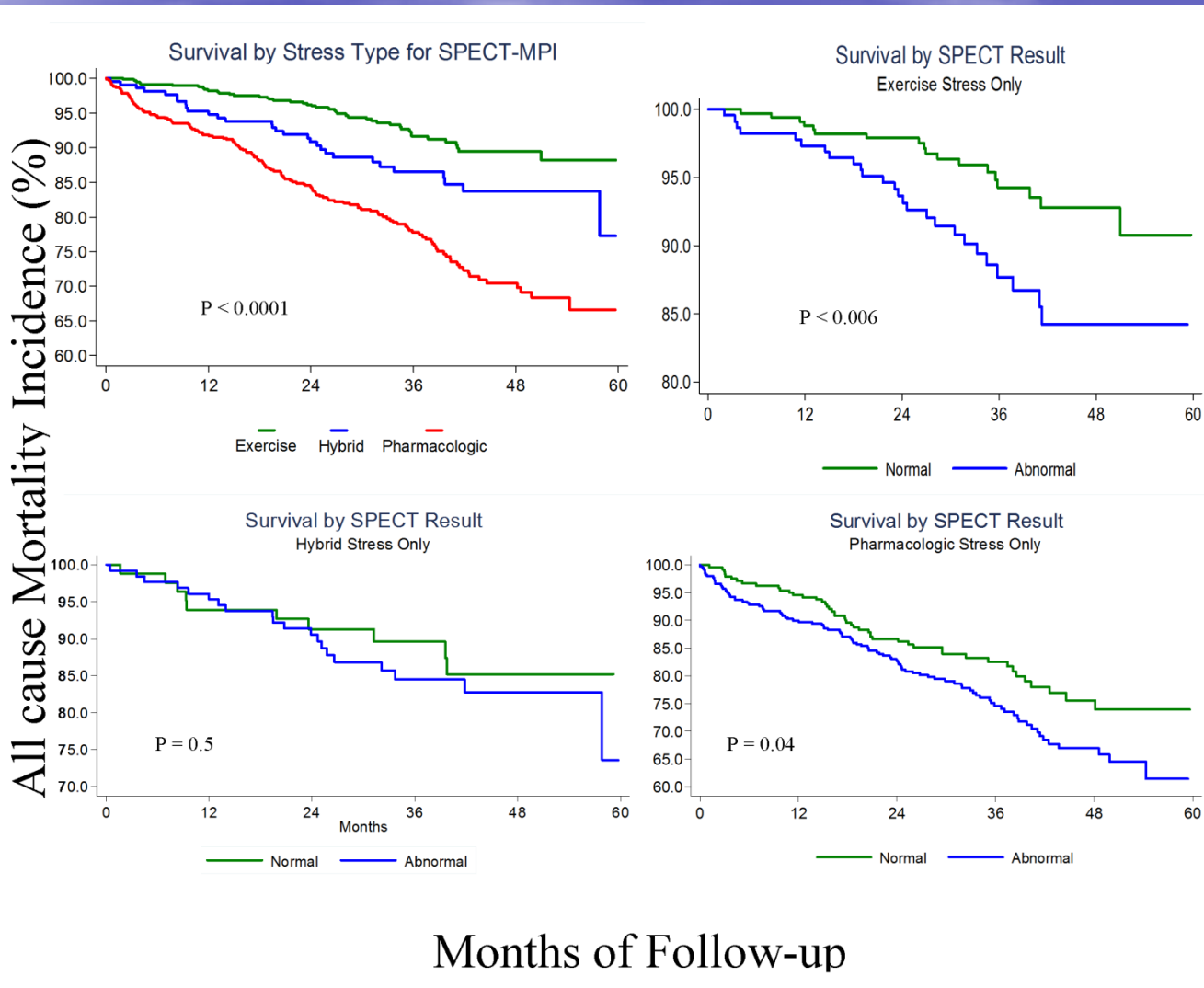


Average Abnormal Rate 35.4%

Frequency of Abnormal SPECT – relation to stress modality



Mortality in a higher risk subset (>75 yo) according to stress modality Exercise vs Pharmacologic stress (n=1358)



MECHANISMS OF ACTION

The goal is hyperemia

- **Exercise**

- Increase Oxygen Demand

- **Adenosine**

- A_2 , AMPc, decrease intracellular calcium, relax SMC
- decrease R_2 resistance

- **Dipyridamole**

- inhibits adenosine deaminase and adenosine reuptake
- increase endogenous adenosine

- **Dobutamine**

- B_1 , contractility, HR
- Increase Oxygen Demand

Main Meds Interfering

B-blocker 4

Ca blocker 2 d

Nitrates 1 d

Main Meds Interfering

Caffeine 12 hrs

Xanthines/Theophylline

EXERCISE

- Preferred modality
- Hemodynamic data - BP, HR
- Adicional info
 - **DUKE SCORE**: + mins - 5 x ST - 4 x angina
 - Ex time (mins)
 - ST (mm)
 - Angina (0 - 2)

DUKE TREADMILL SCORE

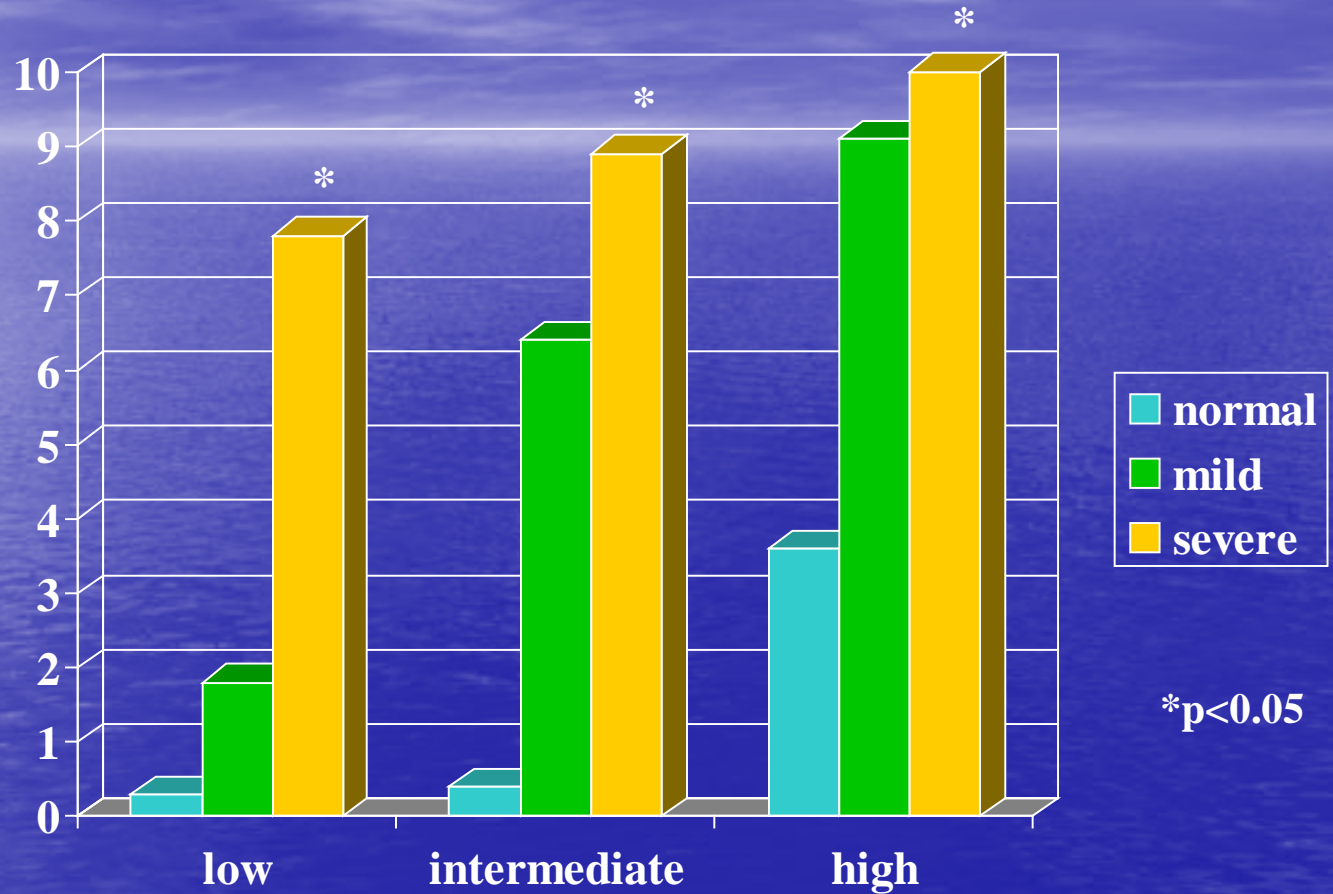
- **Calculation** : + mins - 5 x ST - 4 x angina

<u>Risk</u>	<u>Score</u>	<u>Mortality/year</u>
• Low	≥ 5	0.25%
• Interm	4.... -10	1.25%
• High	≤ -11	5.25%

Use DUKE to:

- 1- Estimate if nuclear is needed after a treadmill test
- 2- Use the exercise and perfusion data combined to guide management

TMT AND SPECT FINDINGS FAVOR EXERCISE !

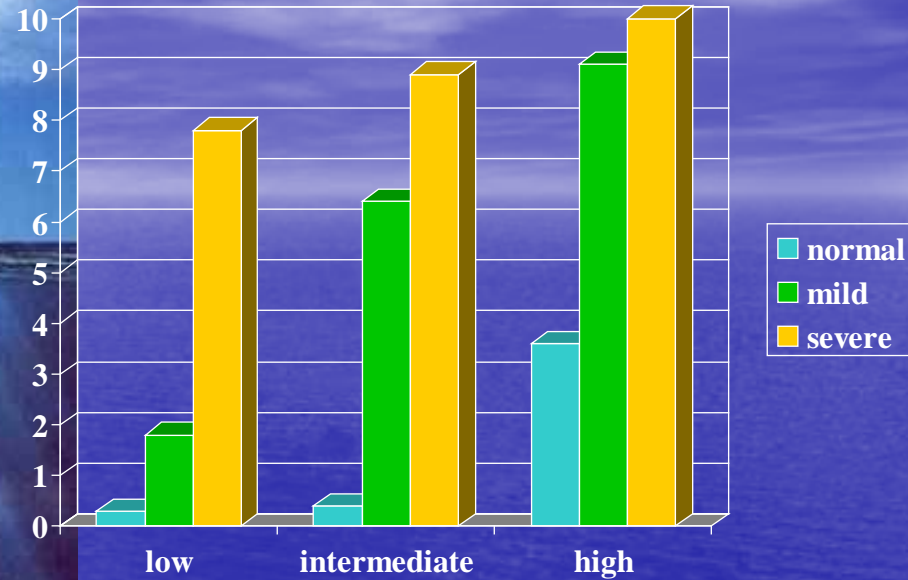


* $p < 0.05$

Duke TM Score

Hachamovitch,
Circulation 1996

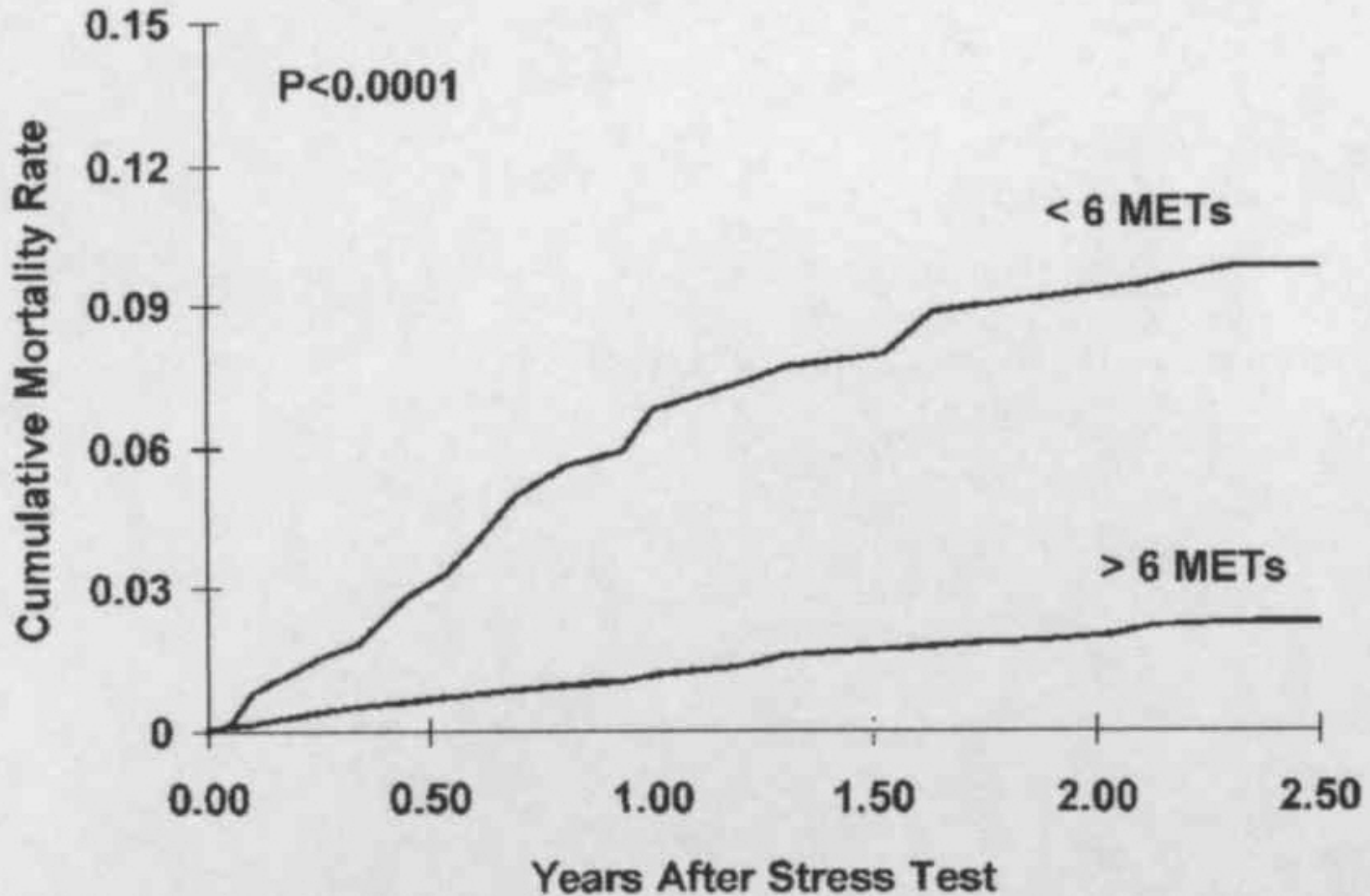
SPECT



TMT

Small perfusion defect
Strongly positive TMT
At low workload
On a high risk patient
Anatomy unknown = **Cath**

WORKLOAD AS A PREDICTOR OF DEATH



x 5

5-6 min Bruce

Snader CE et al, **JACC**, 1997;30:641-8

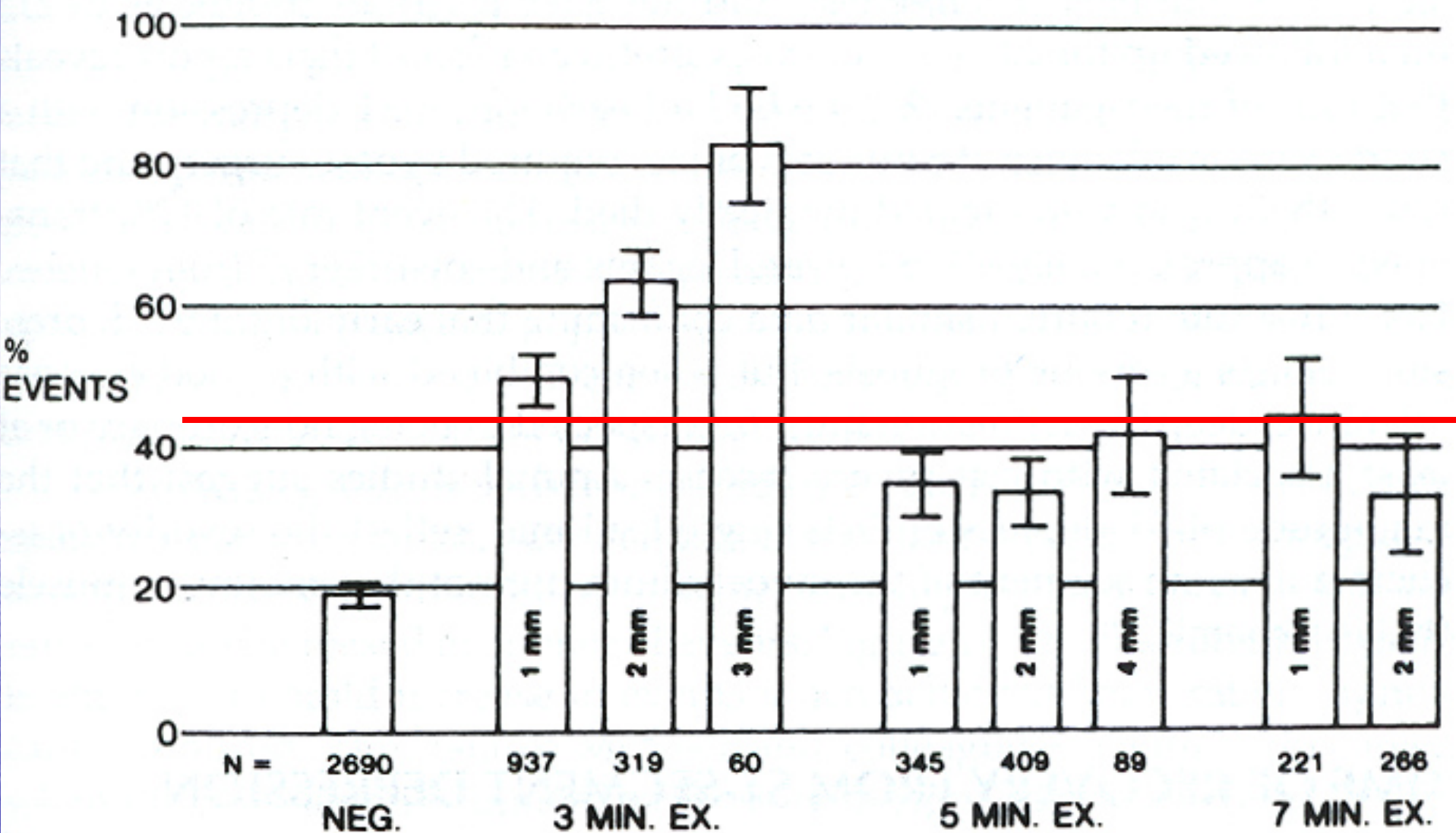
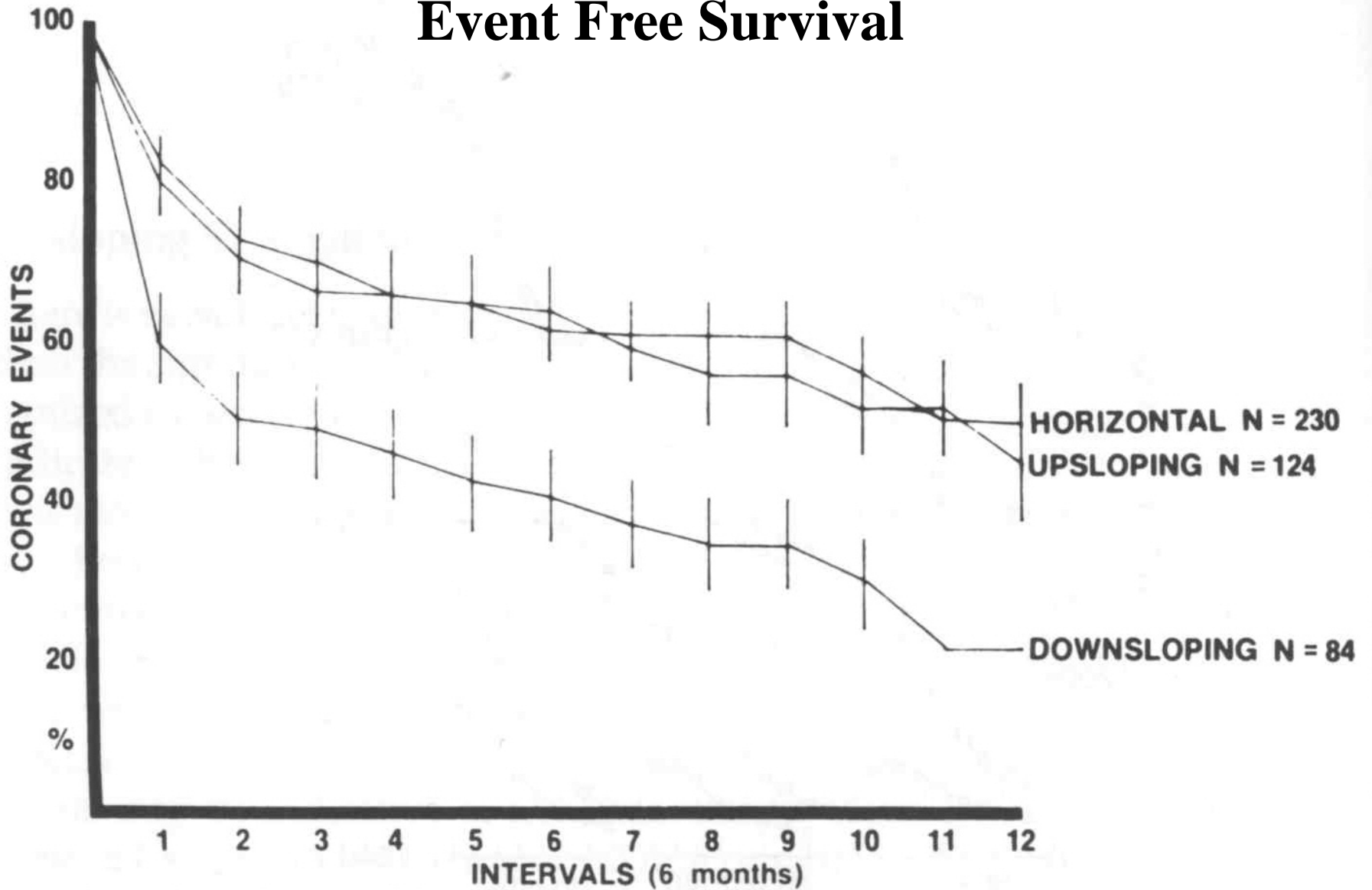
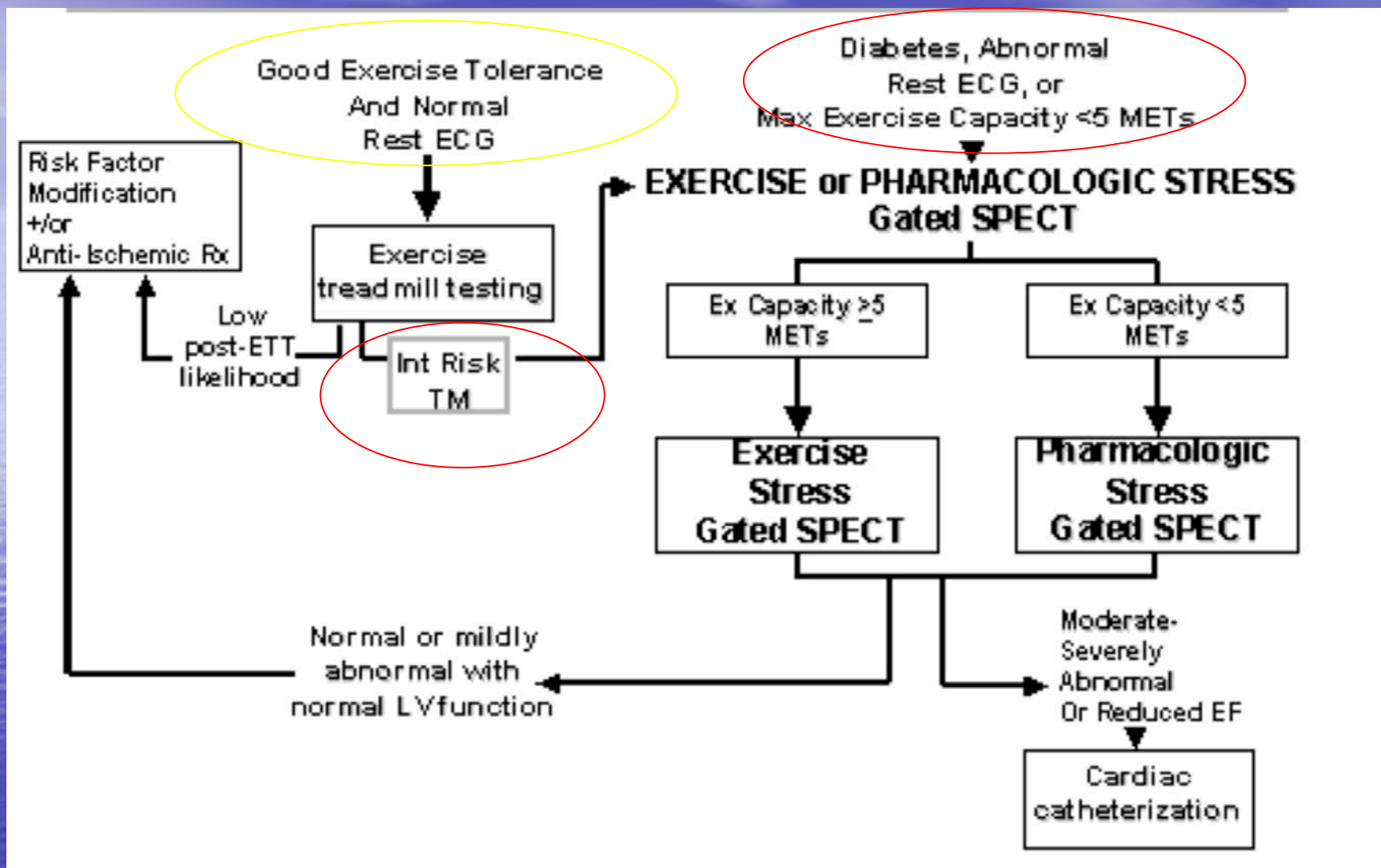


FIGURE 14-15. The incidence of subsequent coronary events (progression of angina, MI, and death) increases with the magnitude of the ST-segment depression only when analyzed at a light workload (3 minutes of exercise = 4 METS; time span = 6 years).

Event Free Survival





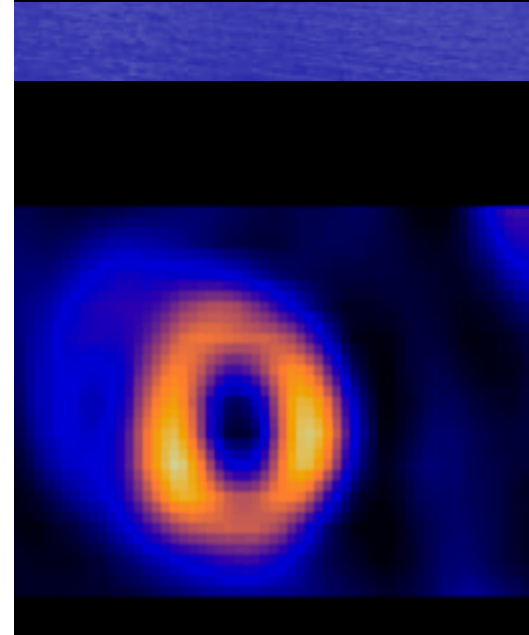
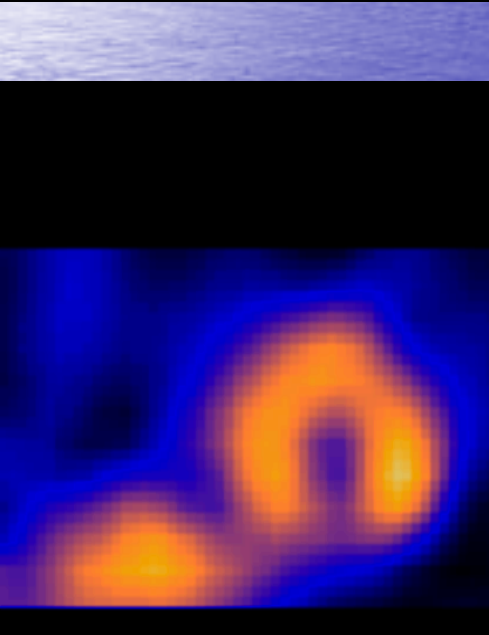
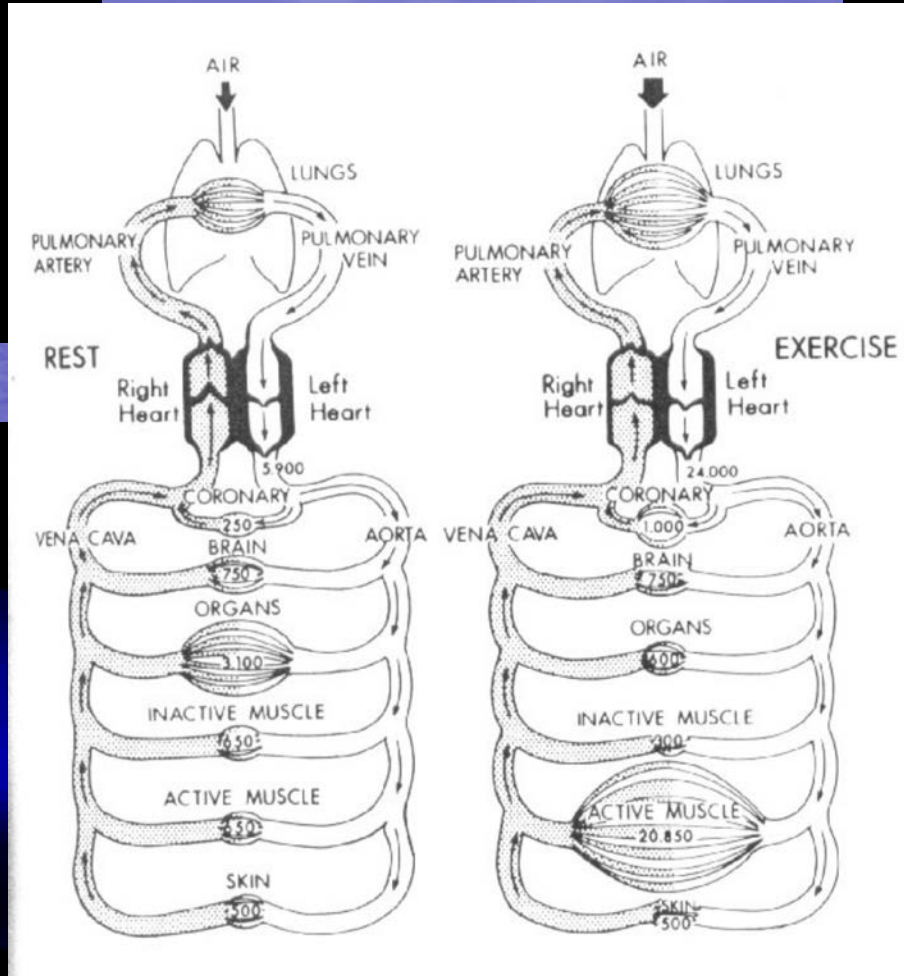
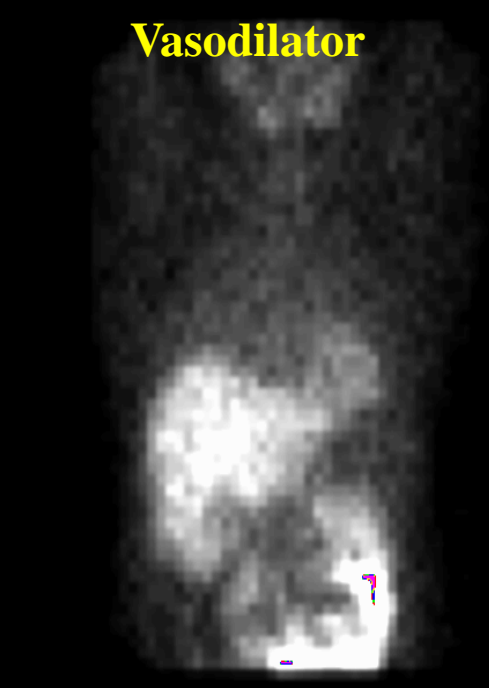
Vasodilator

Exercise

IMAGE QUALITY

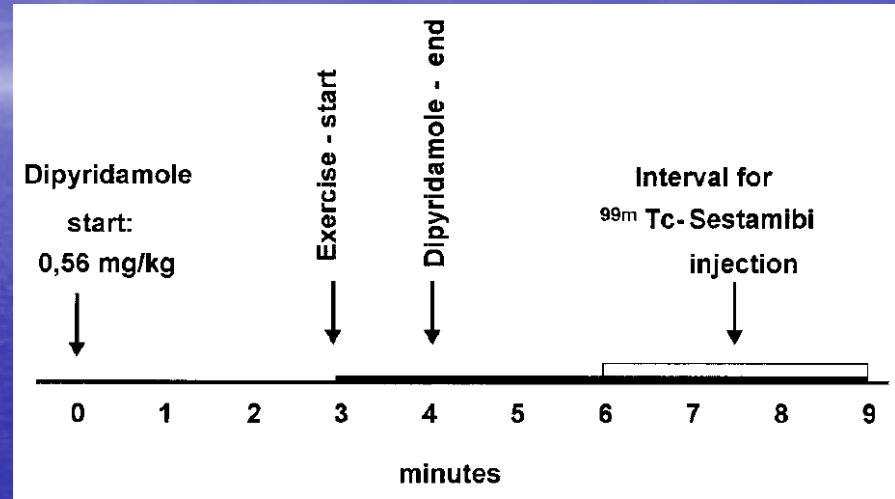
Exercise vs Vasodilator

BLOOD FLOW distribution



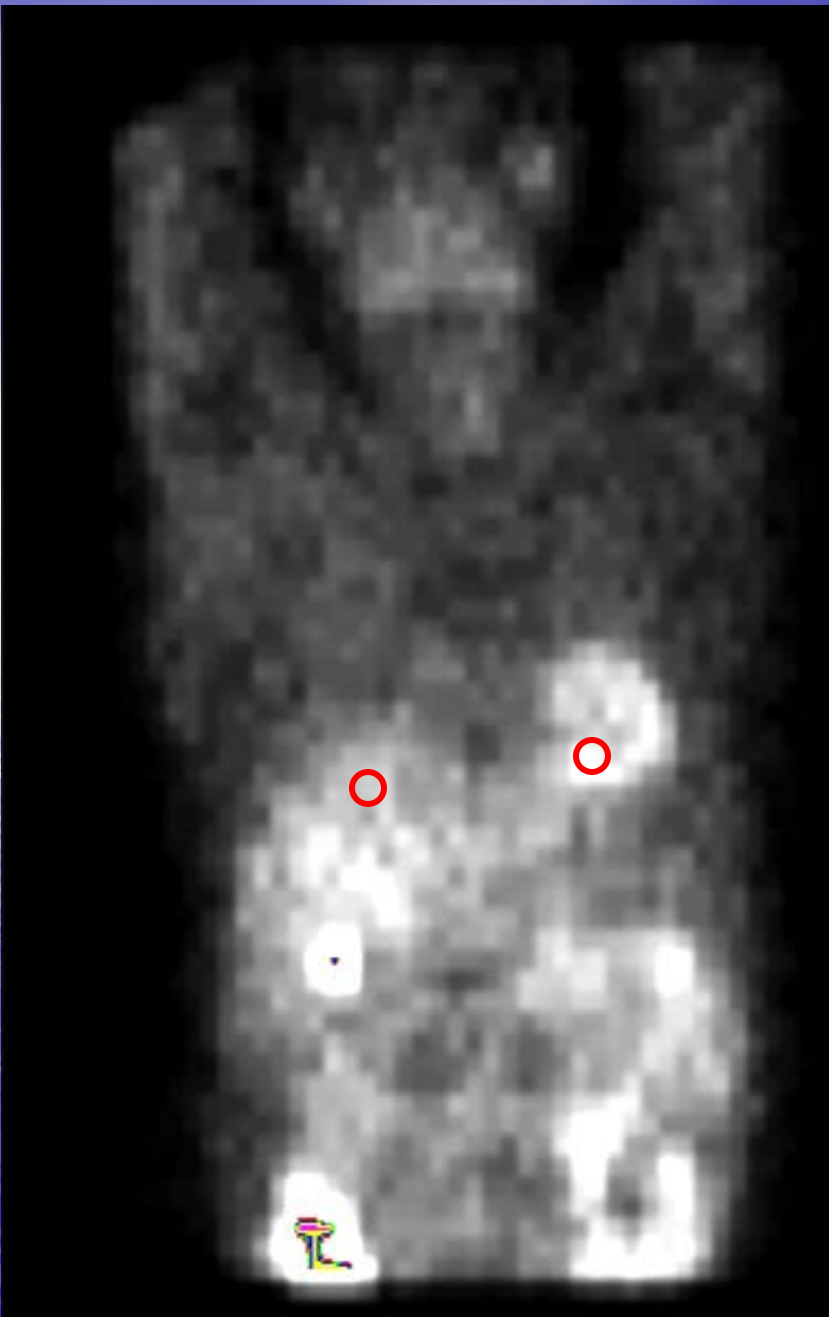
Combined protocol : Vasodilator + low level exercise

DipEx since 1998



Exercise supplementation to dipyridamole prevents hypotension, improves electrocardiogram sensitivity, and increases heart-to-liver activity ratio on Tc-99m sestamibi imaging

João V. Vitola, MD, PhD,^{a,b,c,d} José C. Brambatti, MD,^a Fábio Caligaris, MD,^b Carlos R. Lesse, MD,^a Paulo R. Nogueira, MD,^a Adriana I. Joaquim, MD,^{a,b,c} Mario Loyo, MD,^{a,b,c} Fernando V. Salis, MD, PhD,^{a,b,c} Eleuses V. Paiva, MD,^{a,b,c} William A. Chalela, MD, PhD,^d and J. Claudio Meneghetti, MD, PhD^d



↑ **heart/ liver**

Dip

1.3 ± 0.3

(46%)

Exercise

1.9 ± 0.5*

Taillefer et al

Dip

1.3 ± 0.5

(23%)

Exer + Dip

1.6 ± 0.6*

Vitola et al

***p<0.05**

Increased Sensitivity of MPI DipEx

(n=54)

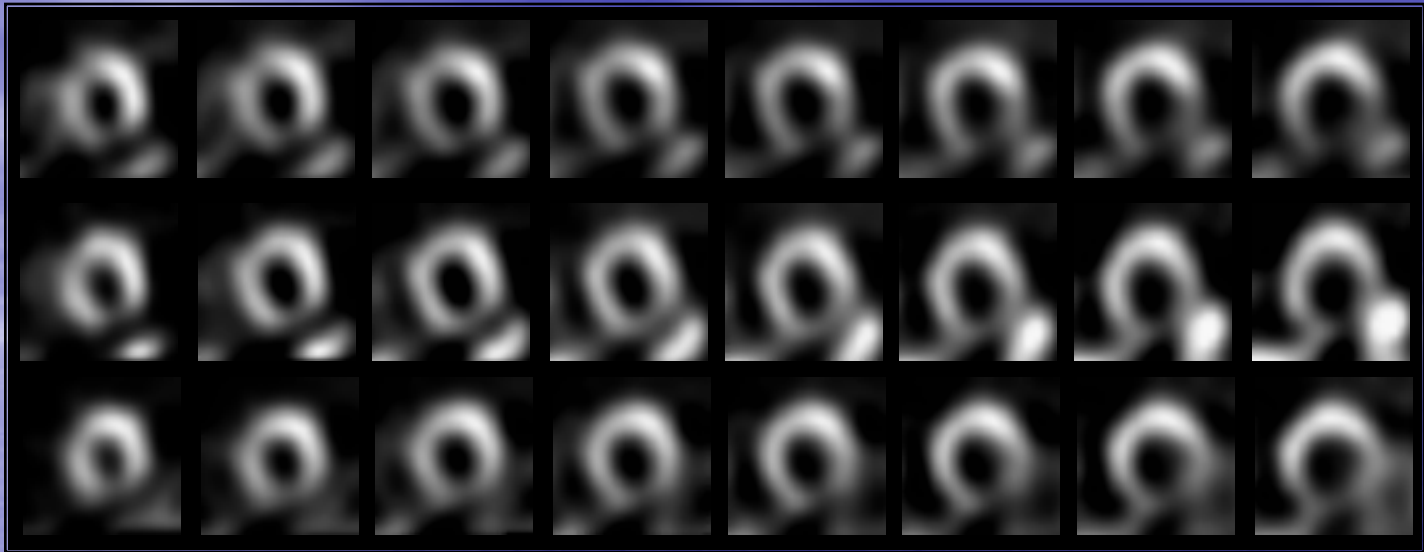
	Dip	DipEx
Isch Patients	30	39*
Isch Segts/pt (multivessel)	1.3 ± 1.5	2.5 ± 2.2*
Extent (% polar map)	16.8 ± 12.9	26.4 ± 18.5*
Lung Uptake	5	16*
TID	4	10*

Tc-99m-sestamibi

Ad-Ex

Ad

Rest



Short Axis

Horizontal Long Axis

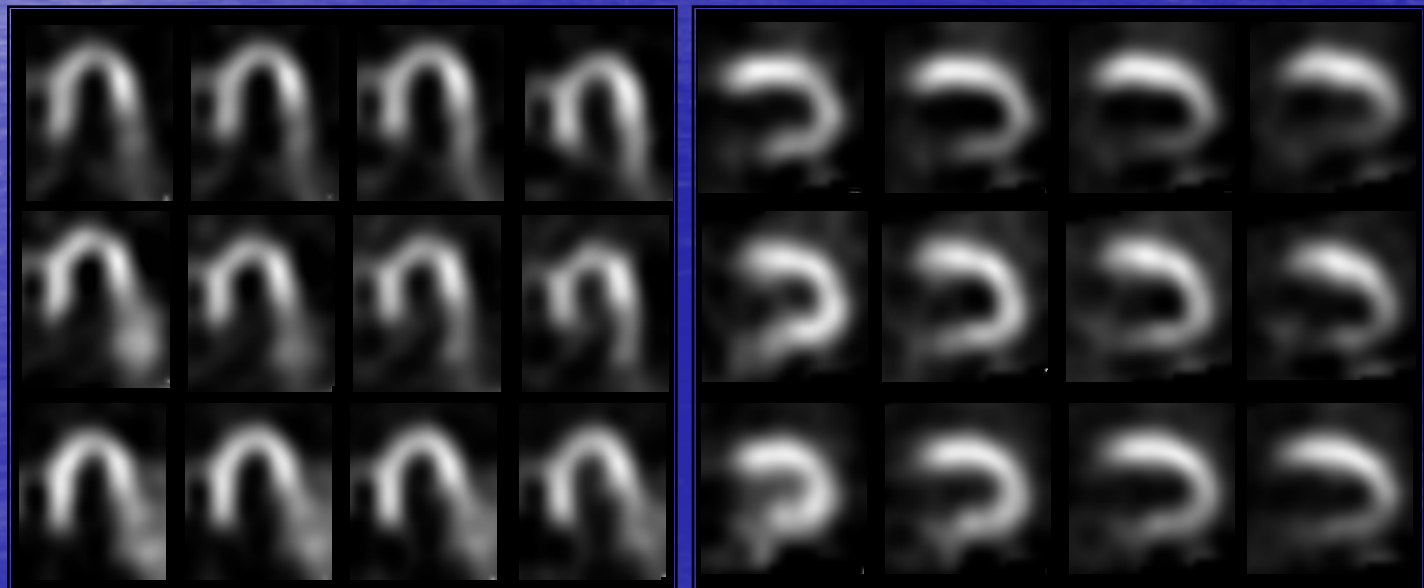
Vertical Long Axis

Ad-EX

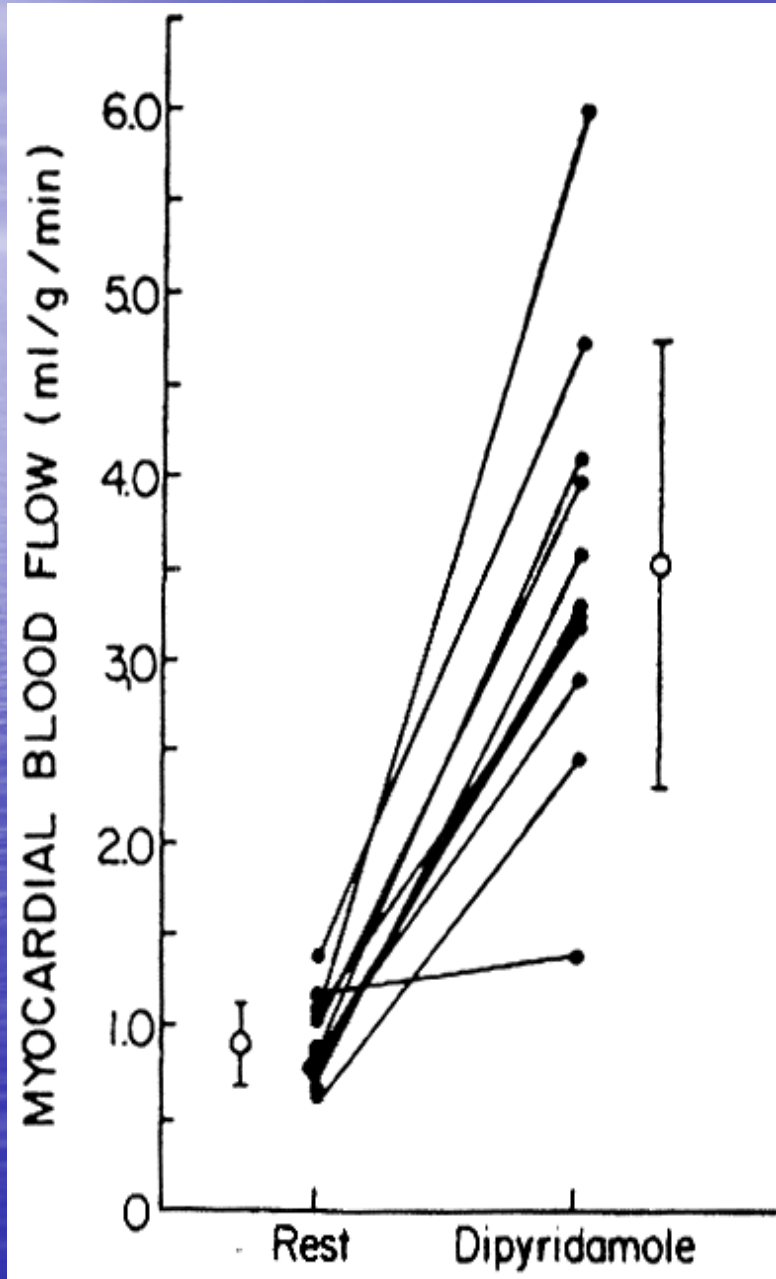
Ad

Rest

CF



All patients respond the same ? Why a wide SD ?



Normal Volunteers
MBF - H₂¹⁵O - PET

Dip 0.56 mg/kg

BERGMANN et al.
JACC 1989;14:639-52

VASODILATORS

Indication

- Incapacity to exercise (consider adding **low workload exercise**)
- LBBB, PM (vasodilator alone)
- On Medications

Limitations compared to exercise

- Side effects
- Sensitivity of the ECG ($< 6\%$)
- Information from exercise not available
- Liver uptake – inferior artifacts
- Non-responders

DOBUTAMINE

Indication

- Incapacity to exercise
- COPD

Protocol

- 10 / 20 / 30 / 40 microgramas/kg/min (push to max HR) ↑

ATROPINE (0.5 + 0.5 + 0.5 + 0.5)*

***careful Glaucoma and BPH**

DOBUTAMINE

Limitations

- HR response variable
- BP response variable
- Hyperemia variable
- Arrhythmias/other side effects
- Fragile patient (Elderly COPD)
- VT (4%)

Side effect	Adenosine	Dipyridamole	Dobutamine
Any	81%	47%	75%
Flushing	37%	43%	14%
Dyspnea	35%	3%	14%
Chest Pain	35%	20%	31%
ST depression	6%	8%	30%
GI discomfort	15%	6%	-
Headache	14%	12%	14%
AV Block	8%	0%	0%
Arrythmia	3%	5%	50%

General Contraindications

AMI within 24 horas

ACS

Uncontrolled CHF

Specific Contraindications

Adenosine/Dipyridamole

Hypotension

COPD (steroids/hospit)

AV Block > 1

Dobutamine

Hipertension

Frequent Ventr Ectopy

Uncontrolled AF/Flutter

Obstruction LV outflow

Aortic Aneurysm

Selective A_{2A} Adenosine Receptor Agonists

Potential for “ on the fly ” protocol – Bolus injection

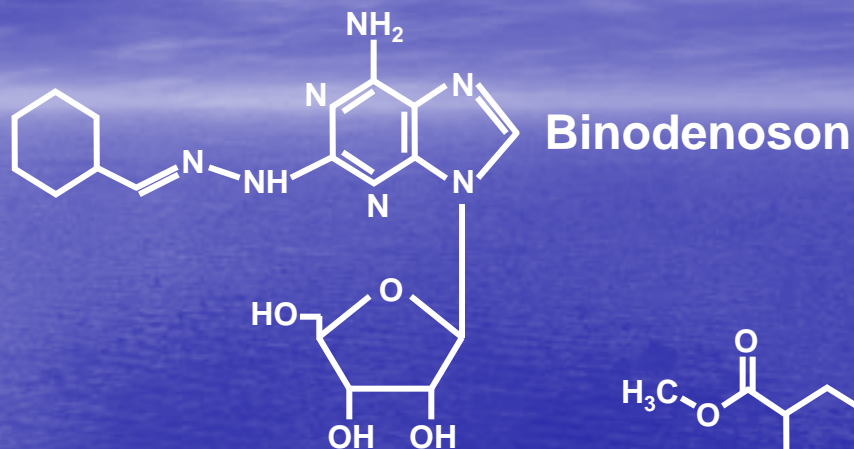


- 30 secs from peak hyperemia
- Pts on meds
- Depressed chronotropic response

Selective A_{2A} Adenosine Receptor Agonists



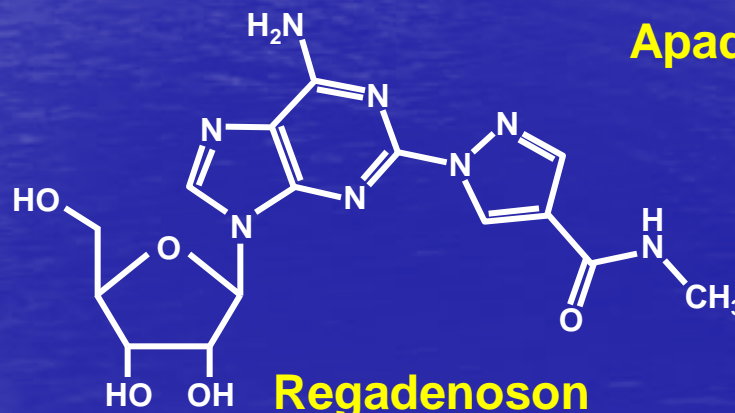
Adenosine



Binodenoson



Apadenoson



Regadenoson

Zablocki J et al. *Nucleosides Nucleotides Nucleic Acids*. 2001;20:343-360.

Gao Z et al. *J Pharmacol Exp Ther*. 2001;298:209-218.

ORIGINAL ARTICLES

Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: Results of the ADVANCE phase 3 multicenter international trial

Ami E. Iskandrian, MD, FACC,^a Timothy M. Bateman, MD, FACC,^b
Luiz Belardinelli, MD,^c Brent Blackburn, PhD,^c Manuel D. Cerqueira, MD, FACC,^d
Robert C. Hendel, MD, FACC,^e Hsiao Lieu, MD, FACC,^c
John J. Mahmarian, MD, FACC,^f Ann Olmsted, PhD,^c
S. Richard Underwood, MD, FACC,^g João Vitola, MD,^h and Whedy Wang, PhD,^c on
behalf of the ADVANCE MPI Investigators

N = 784

J Nucl Cardiol 2007; 14:645-58

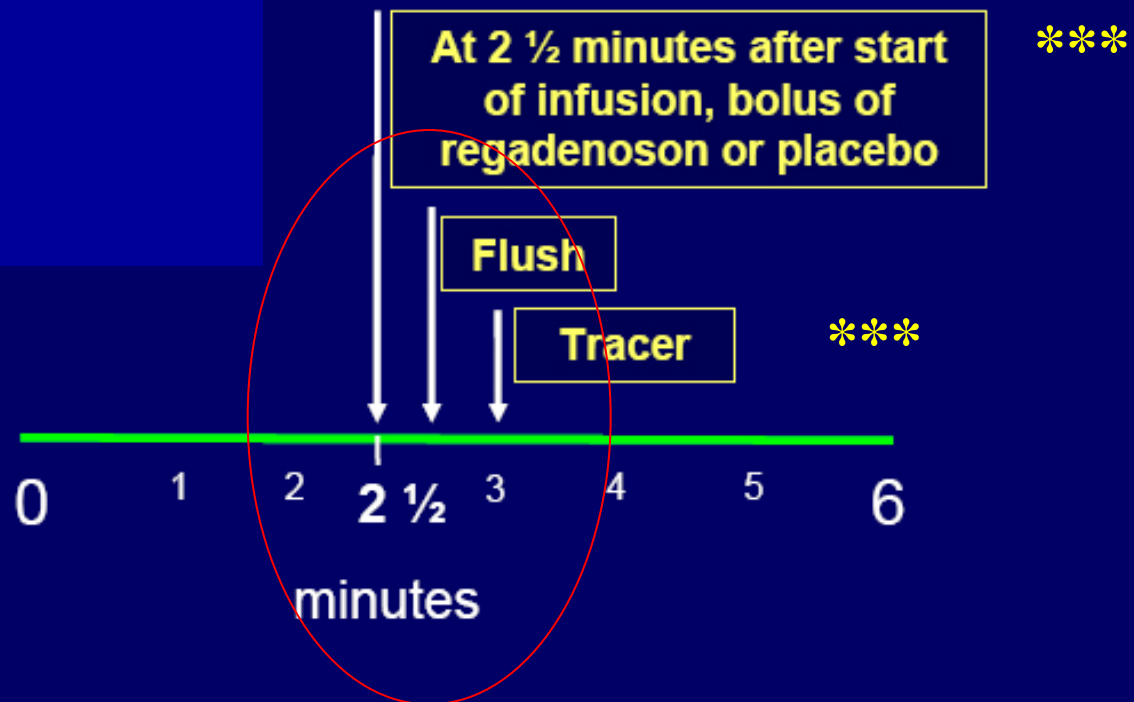
Regadenoson FDA approved in April 2008

Bolus Administration

Time to 2.4-fold above baseline: 33 sec

Speeds Stress – Potential for a 2 - 3 min Stress Test
Easier than adenosine pump

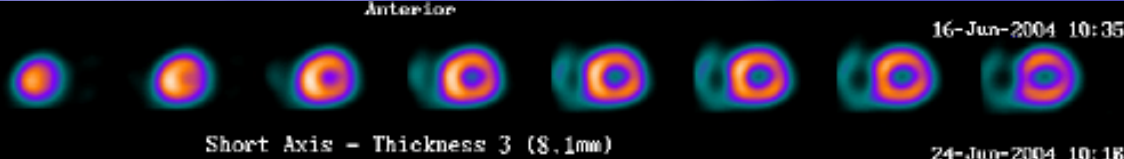
**Bolus
Arm**



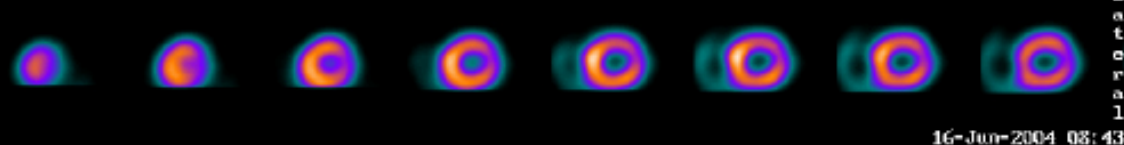
REGADENOSON = ADENOSINE

- IDENTIFY INDIVIDUALS WITH ISCHEMIA
- QUALITY OF IMAGES
- SOME POTENTIAL ADVANTAGES TO BE DISCUSSED

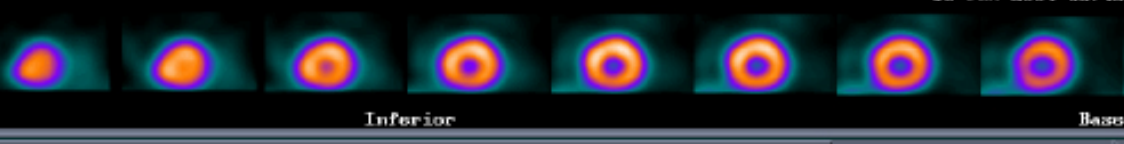
Adenosine



Regadenoson



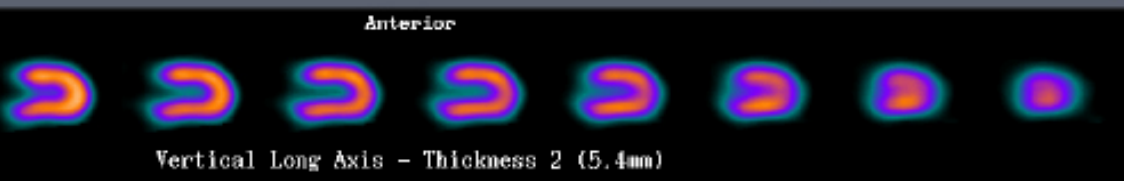
Rest



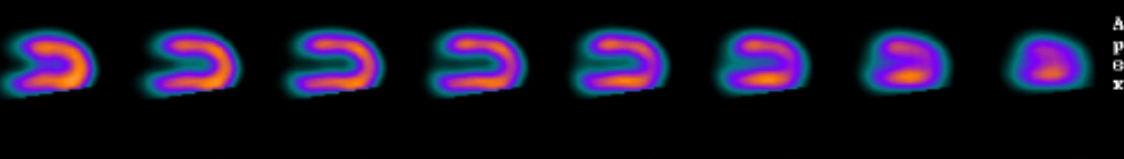
63 y.o. male with HTN, DM, CAD, CHF, and s/p CABG

Short-axis

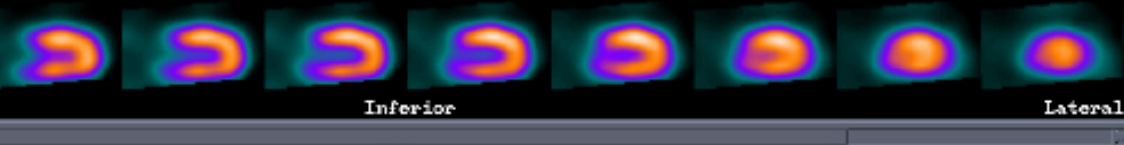
Adenosine



Regadenoson

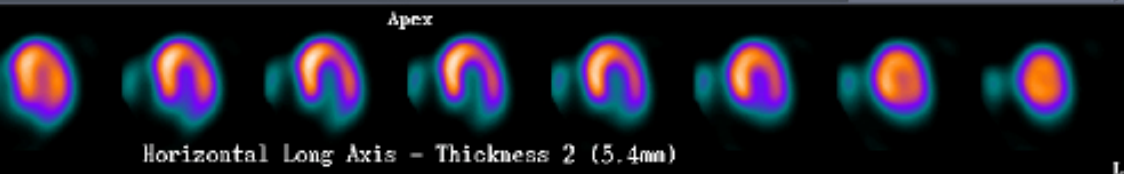


Rest

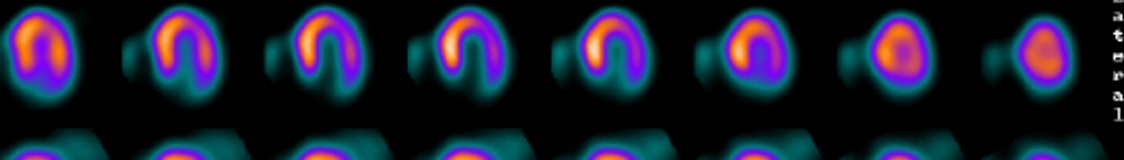


Vertical Long-axis

Adenosine



Regadenoson

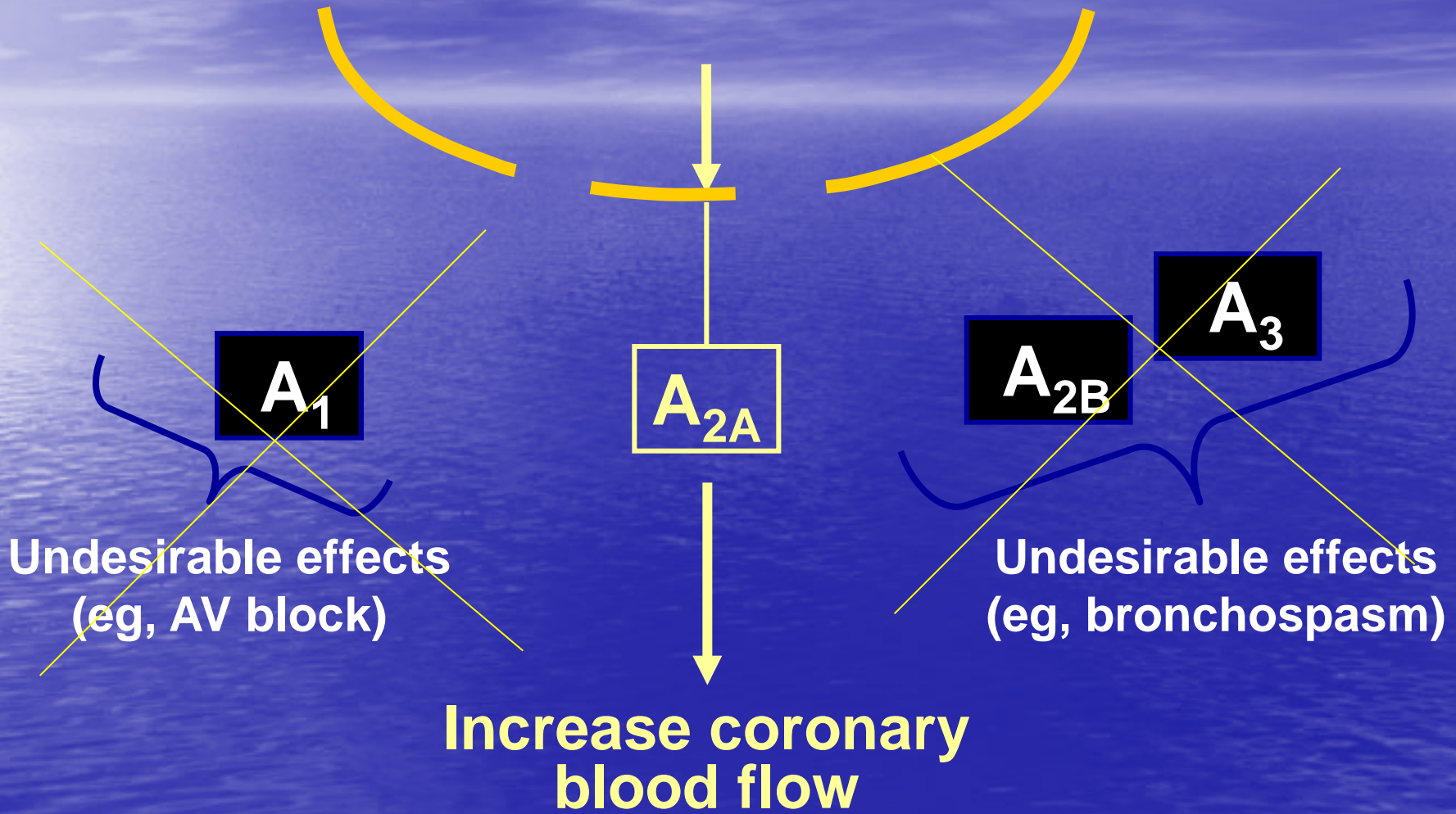


Rest



Horizontal Long-axis

Selectivity

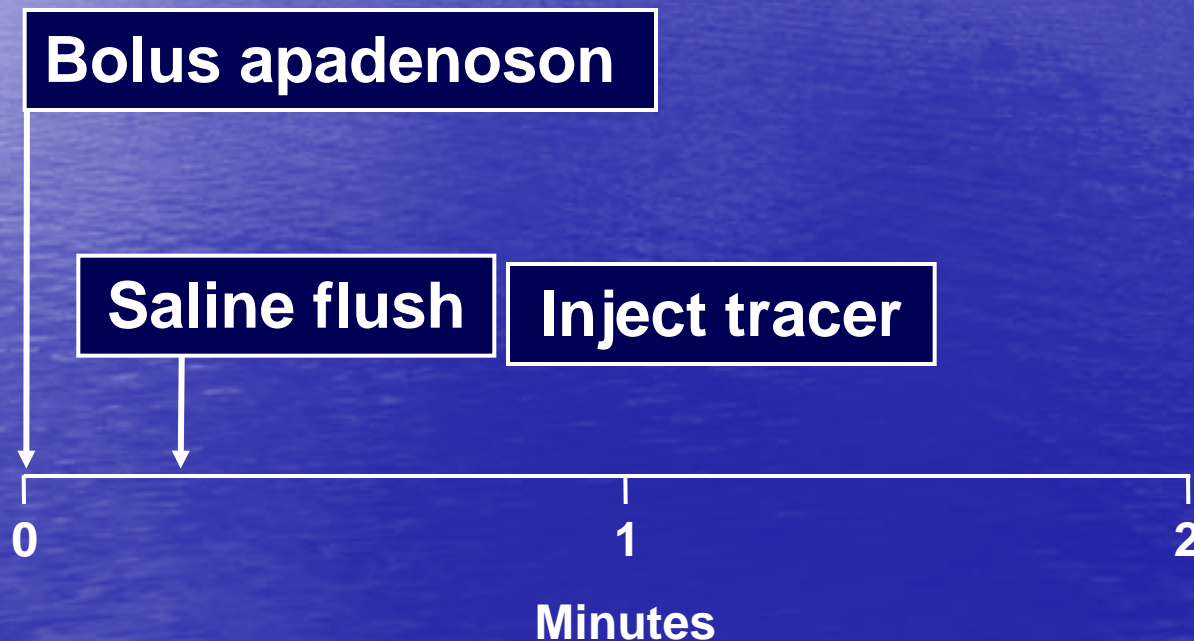


REGADENOSON

- Bolus administration
- Standard dose
- Selectivity and low to moderate receptor binding
- Special issues
 - Potential to combine with exercise

Potential Apadenoson Protocol

Fixed doses 100 μg (< 100 kg) or 150 μg (> 100 kg)



Adapted from Hendel RC et al. Abstract presented during the 2005 Annual Scientific Sessions of the American Heart Association. Dallas, Texas.

Stress testing

Conclusions

- Choose the right stress test for the right patient
- Prefer exercise
- Combined vasodilator and low level exercise :
 - Easy to do
 - Improves image quality
 - Provides additional information
- Regadenoson is similar to adenosine to detect ischemia
 - Advantage of bolus administration
 - Less side effects
 - Can be used in COPD patients
- .