PHARMACOLOGICAL "STRESS" TESTING

Southwestern Chapter - SNMMI

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DISCLOSURE

Dr. Moore is a member of the Speakers Bureau and a Consultant for Astellas Pharma US.

This talk is NOT sponsored by Astellas.

Off-Label (Not FDA-approved) applications will be discussed.

Topics To Be Discussed

- Why Myocardial Perfusion Imaging?
- Why Pharmacological Stress?
- Pharmacologic Stress agents
  - Vasodilators
  - Inotropes
- Physiology and Protocols
- Diagnosis and Prognosis
- Side Effects and Adverse Reactions
- Clinical Test Selection

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FACT: In many surveys, the most common nuclear medicine test in the United States is myocardial perfusion imaging (MPI).

- Why Do We Do Radionuclide Myocardial Perfusion Imaging?

Radionuclide Applications in Coronary Artery Disease

- Diagnosis of CAD
- Severity/Extent/Location of CAD
- Effects of CAD
  - Ischemia/Scarring/Viability
  - Mechanical Function
  - Ventricular Volume
  - Electrical Function
- Prognosis of CAD
- Effects of Intervention
- Molecular Effects

Appropriate Clinical Indications for MPI

- Suspected coronary artery disease in patients with abnormal resting ECG
- Possible coronary artery disease in asymptomatic patients with positive exercise ECG
- Possible coronary artery disease in symptomatic patients with normal exercise ECG
- Possible coronary artery disease in patients unable to achieve an adequate heart-rate response on exercise ECG
- Possible coronary artery disease in patients with likely uninterpretable exercise ECG
- Evaluations of myocardial viability for revascularization
- Follow-up of interventions in symptomatic patients
- Follow-up long-term after intervention

Diagnosis and Prognosis
Where is the patient on the spectrum of myocardial ischemia?

- Normal
- Vasodilator-Induced Flow Redistribution without cellular ischemia
- Stress-Induced Ischemia
- Chronic Ischemia (Hibernation)
- Infarction (Scarring)

Myocardial Perfusion Imaging

- FACT: The treadmill/ECG test has been the standard screening test of choice for CAD for over 50 years.
- Why is the MPI study needed?
  - False negative treadmill/ECG test

    Inadequate sensitivity of treadmill/ECG test
  - False positive treadmill/ECG test
  - Incomplete information from treadmill/ECG

    test alone (location, extent, viability, prognosis)
  - Limited value of treadmill/ECG test when inadequate stress is achieved
  - The portion of patients undergoing CAD screening who perform adequate stress is decreasing.

MPI: Diagnosis

Effect of Maximum Heart Rate on Test Sensitivity

%MPHR:	50-64	65-74	75-85	≥85
N:	17	32	38	47
MPI Sens:	72**	88	91	85
TMT Sens:	14*	31*	42*	59

*P<0.05

** P<0.01

MPI: Prognostic Indicators

- Myocardial
  - Defect size and number
  - Defect reversibility
- Functional
  - Ejection fraction
- Non-myocardial
  - Lung uptake
  - “Transient Ischemic Dilatation” of LV

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Why Do We Do MPI with Pharmacological Stress?

- Pharmacological stress is widely available and may be performed with TL-201, Tc-99m, and PET* radiopharmaceuticals on any standard tomographic nuclear medicine imaging system.
- “Stress testing should be performed with dynamic exercise stress whenever possible.”
- BUT guidelines indicate that MPI is appropriate in a number of clinical situations when treadmill/ECG testing is not likely to be adequately predictive.
- The proportion of patients at risk for CAD who are capable of reaching adequate exercise parameters is decreasing.
- While the total number of MPI studies is declining, the percentage of MPI studies that is performed with pharmacologic stress is increasing.

LIMITATIONS TO PERFORMING MAXIMAL EXERCISE STRESS

- Cerebrovascular disease
- Spinal injuries
- Amputations
- Musculoskeletal or orthopedic problems
- Peripheral arterial disease
- Lung disease
- Poor physical conditioning
- Lack of motivation
- Limiting noncardiac symptoms
- Medications

Detection of Myocardial Ischemia

Ischemia vs. Redistribution of Flow

Exercise

Chronotropic Stress

Inotropic Stress

dobutamine

Vasodilators

dipyridamole

adenosine

regadenoson

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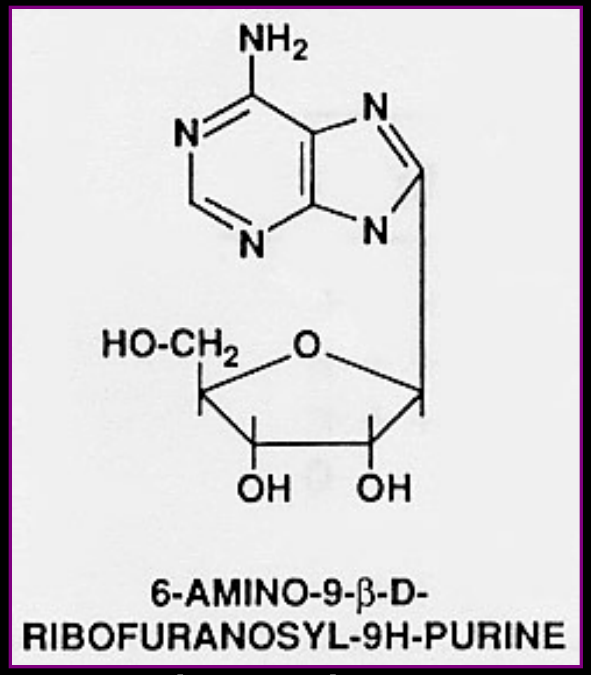
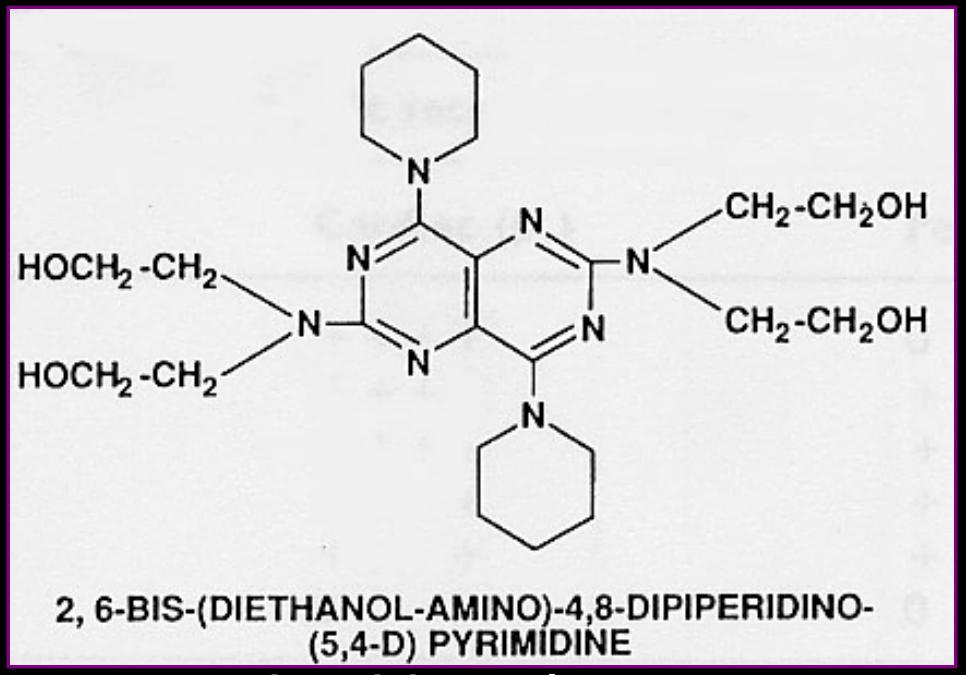


6-AMINO-9-β-D-RIBOFURANOSYL-9H-PURINE

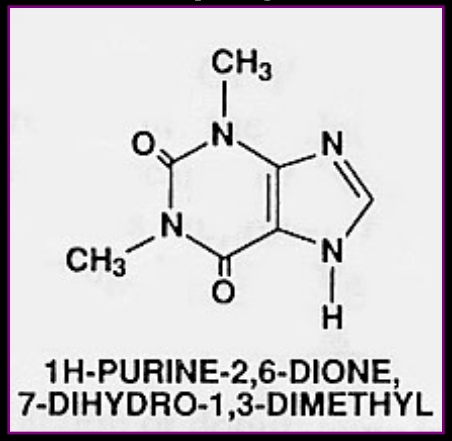
Adenosine



2, 6-BIS-(DIETHANOL-AMINO)-4,8-DIPIPERIDINO-(5,4-D) PYRIMIDINE

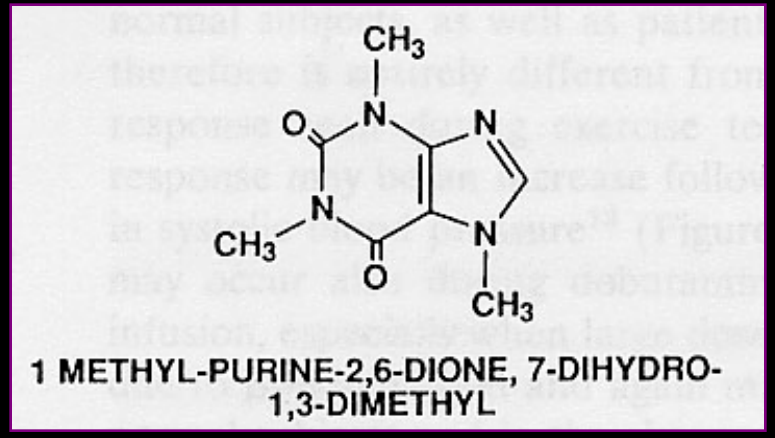
Dipyridamole (24 hours)

Theophylline (12-24 hours)



1H-PURINE-2,6-DIONE, 7-DIHYDRO-1,3-DIMETHYL

Caffeine (6-12 hours)



1 METHYL-PURINE-2,6-DIONE, 7-DIHYDRO-1,3-DIMETHYL

Verani MS. *Am Heart J* 122, 1991.

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Comparison of ^{201}TI chloride, ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin

Retention	Mibi>Tetr>Thal
First pass extraction	Thal>Mibi & Tetr
Uptake @ peak flow	Thal>Mibi>Tetr
Liver activity	Thal<Tetr<Mibi
Gated Images /LVgram	Tetr & Mibi>Thal

Tracer Uptake Relative to Coronary Flow

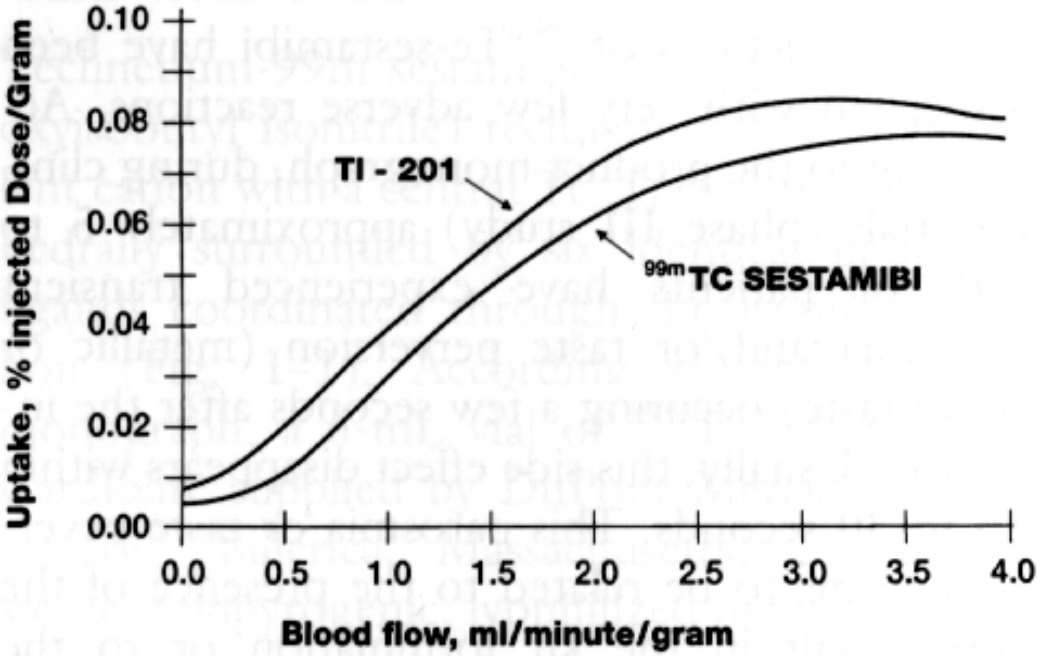


Figure 1–2. Comparative myocardial uptake of thallium-201 and ^{99m}Tc-sestamibi versus coronary blood flow. There is a good correlation for the physiologic ranges of blood flows. However, there is an overestimation of blood flow at low flow rates and underestimation at high flow rates (both extremities of the curves).

Pharmacologic/Exercise Stress in Nuclear Perfusion Studies

- Heterogeneous augmentation of coronary blood flow
- Regional differences in tracer concentration
- Increase in coronary blood flow is mediated by one of two mechanisms:
  - Direct vasodilation (flow reserve)
  - Cardiac positive inotropic agents - secondary vasodilation from increase in myocardial oxygen demand (flow reserve and myocardial ischemia)

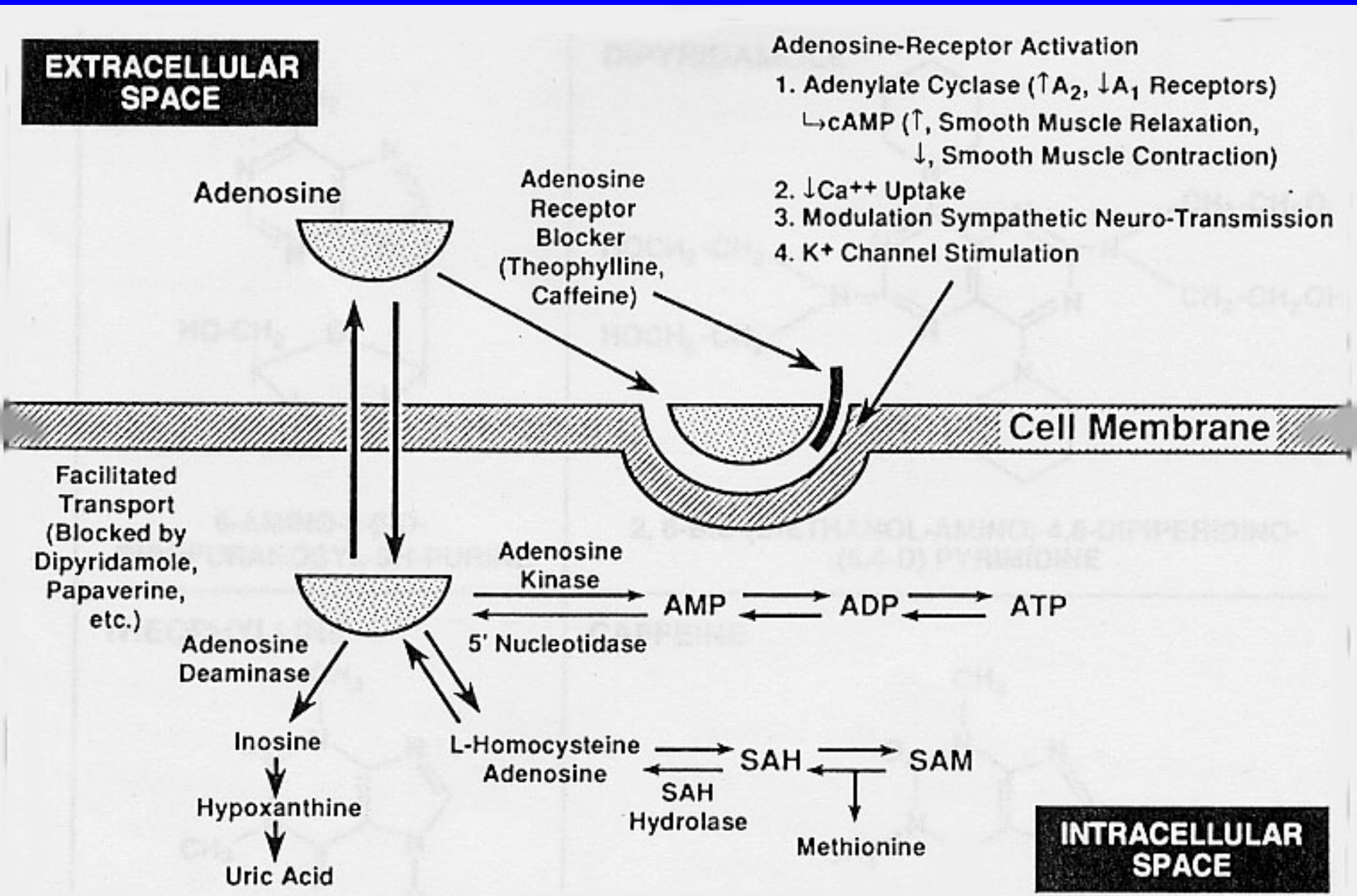
Vasodilator Physiology

All act directly or indirectly via effects on ADENOSINE RECEPTORS.

Type	Primary Location	Primary Effect
A_1	cardiac	delay AV conduction
A2a	cor. vessels	cor. vasodilation
A2b	peripheral vessels	periph. vasodilation
A3	pulm. bronchioles	bronchoconstriction

Adenosine Mode of Action

- Naturally endogenously produced with 11 sec blood clearance halftime due to cellular reuptake
- Binds to multiple types of cell surface adenosine receptors in multiple tissues
- A_{2a} receptor activation has multiple metabolic effects, including vasodilatation by relaxation of smooth muscle
- Pharmacologic intravenous doses create rapid dilatation, but excess is rapidly cleared and effect of bolus rapidly clears
- Aminophylline reverses effect via competition for receptor binding sites
- Onset is rapid compared dipyridamole and dobutamine and duration of action is short



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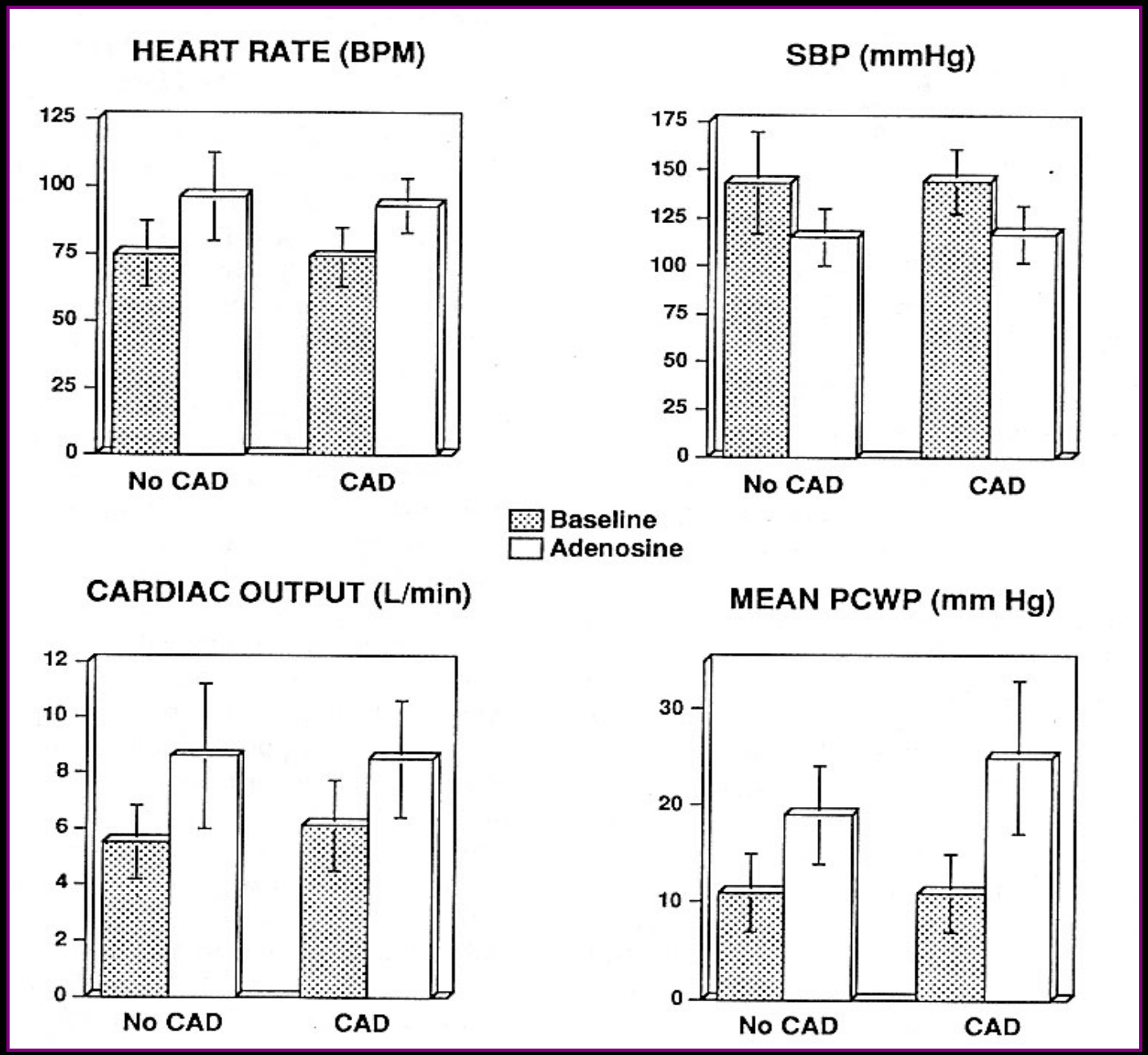


Ogilby et al. Circulation 86;887-95,1992

Dipyridamole Mode of Action

- Binds to adenosine receptors (RBCs and vascular endothelium et al.)
- Prevents adenosine uptake across cell membrane
- Secondarily raises endogenously-produced adenosine levels by blocking uptake/metabolism
- Secondarily causes coronary vasodilatation
- Aminophylline reverses effect via competition for receptor binding sites
- Onset and duration of action are prolonged compared to other vasodilator options

Regadenoson Mode of Action

- Synthetic adenosine analog, A_{2a} receptor binding agent
- High specificity for A_{2a} receptor but limited binding affinity
- Effect depends on the premise that a bolus of drug can activate enough (though not a high percentage) of receptors to create transient vasodilatation
- Bolus injection leads to rapid onset, but low affinity leads to short effective time
- Aminophylline reverses effect via competition for receptor binding sites
- Onset is similar to adenosine injection and duration of action is short

Dobutamine Mode of Action

- Main mechanism of action for dobutamine is via b1 receptors
- Also stimulate a1 and b2 receptors
- Increase in contractility, moderate increase in heart rate, and an increase in myocardial blood flow
- Hypotension may occur especially when large doses are used
- Onset of action 1-2 minutes, peak effect in several minutes
- Half-life greater than 2 minutes
- Can be reversed by beta-blockers

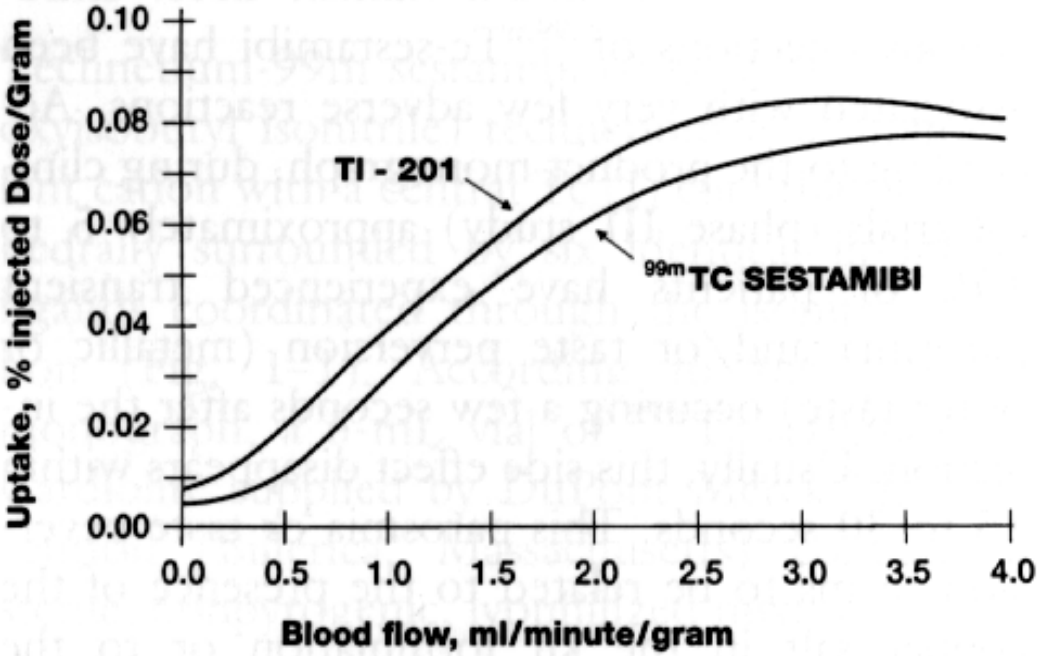
Dobutamine Effects on Radiotracer

- Theory: Dobutamine-induced Ca^{2+} influx blunts the mitochondrial membrane driving potential, diminishing uptake of the cationic molecule sestamibi
- Therefore: Thallium may be better than MIBI if you use dobutamine (conflicting data); less data for tetrofosmin
- Clinical Studies: Probably no difference in accuracy

Effects of Pharmacological Stress Agents vs. Exercise

Parameter	Exercise	Dobut.	Dipy.	Aden.	Rega.
Heart Rate	↑↑↑↑	↑↑↑	↑	↑	↑↑
Sys BP	↑↑↑↑	↑↑↑	↓	↓	↓↓
Cor. Flow	2-3	3-5	4-5	4-5	3-4
Card. Output	↑↑↑↑	↑↑↑	↑	↑	↑
O_2 Demand	↑↑↑↑	↑↑↑	~↑	~↑	~↑
Contractility	↑↑↑↑	↑↑↑	→	→	→

Tracer Uptake Relative to Coronary Flow



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Detection of Myocardial Ischemia

Imaging Principle

Separate normal from abnormal myocardium by inducing ischemia (or at least redistributing myocardial flow), then detecting the ischemia/altered flow

Detection of Myocardial Ischemia

Non- Imaging à Clinical symptoms
Vital signs (esp. BP)
EKG changes

Imaging à Δ cellular tracer uptake (MPI)
à Δ Wall Motion (Echo, MUGA)

Traditional Need for Maximal Exercise

Maximal exertion

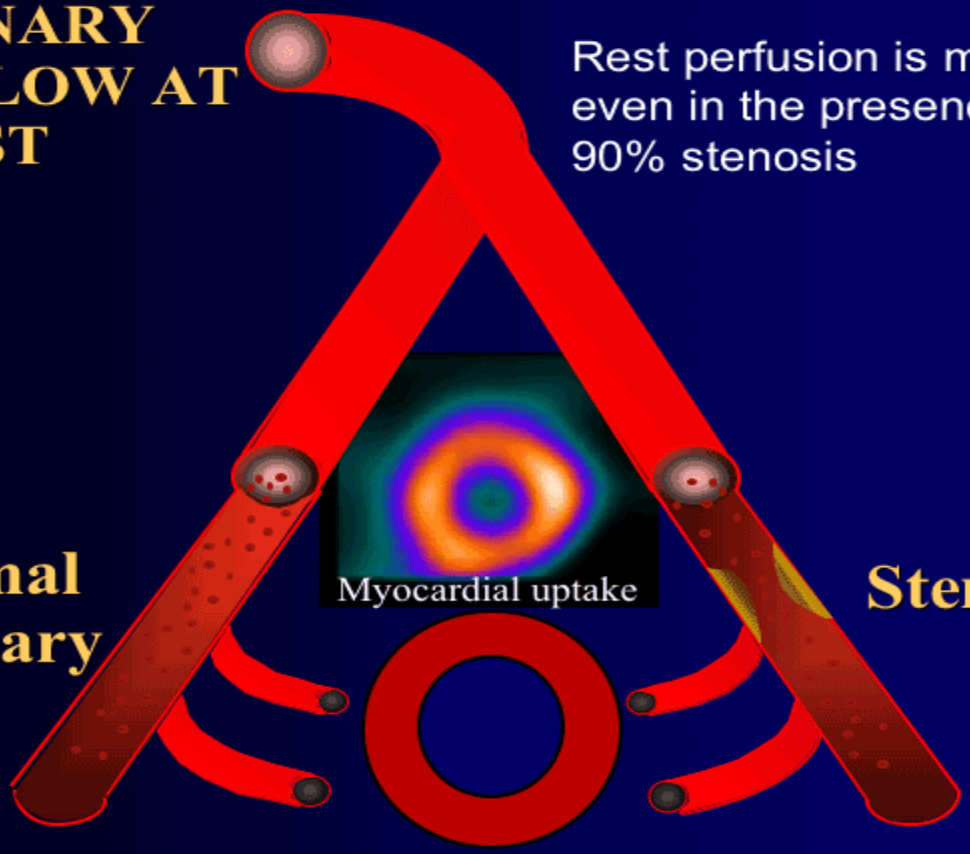
Maximal coronary blood flow

Greater disparity in blood flow

Normal > > Stenosed

CORONARY BLOOD FLOW AT REST

Rest perfusion is maintained even in the presence of a 80-90% stenosis

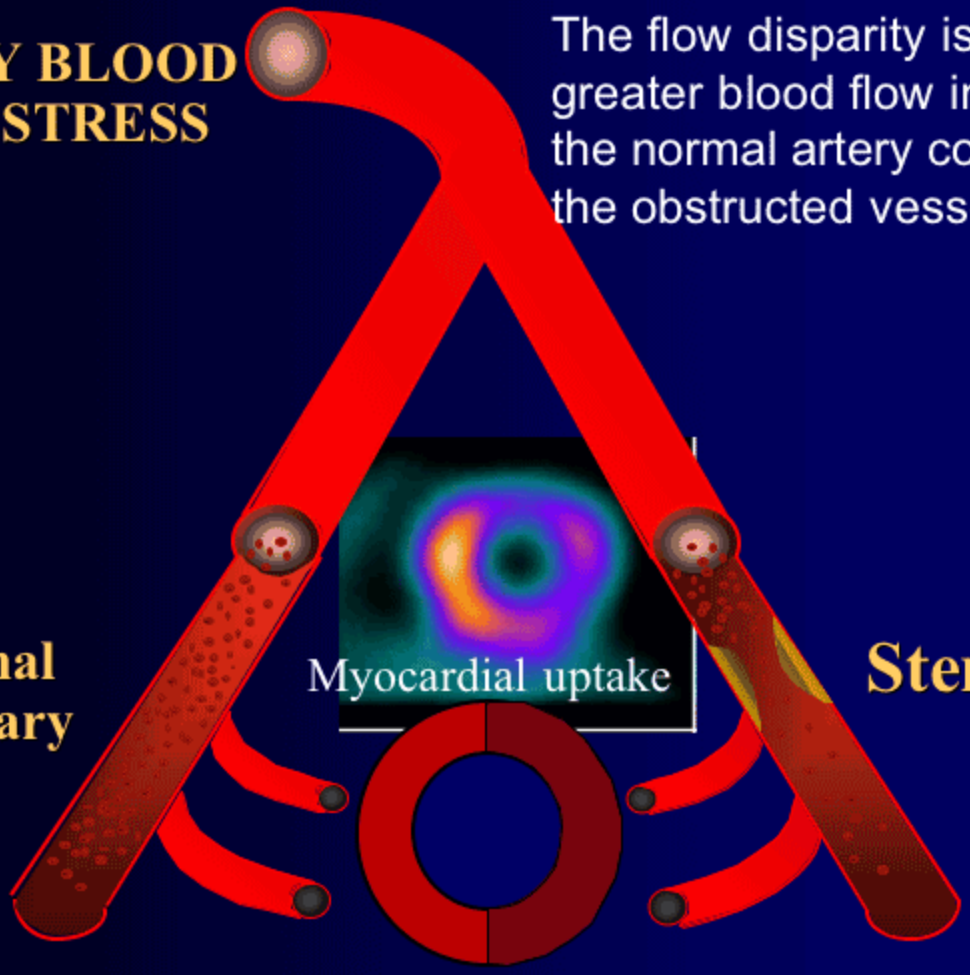


Normal coronary

Stenosis

CORONARY BLOOD FLOW AT STRESS

The flow disparity is due to a greater blood flow increase in the normal artery compared to the obstructed vessel.

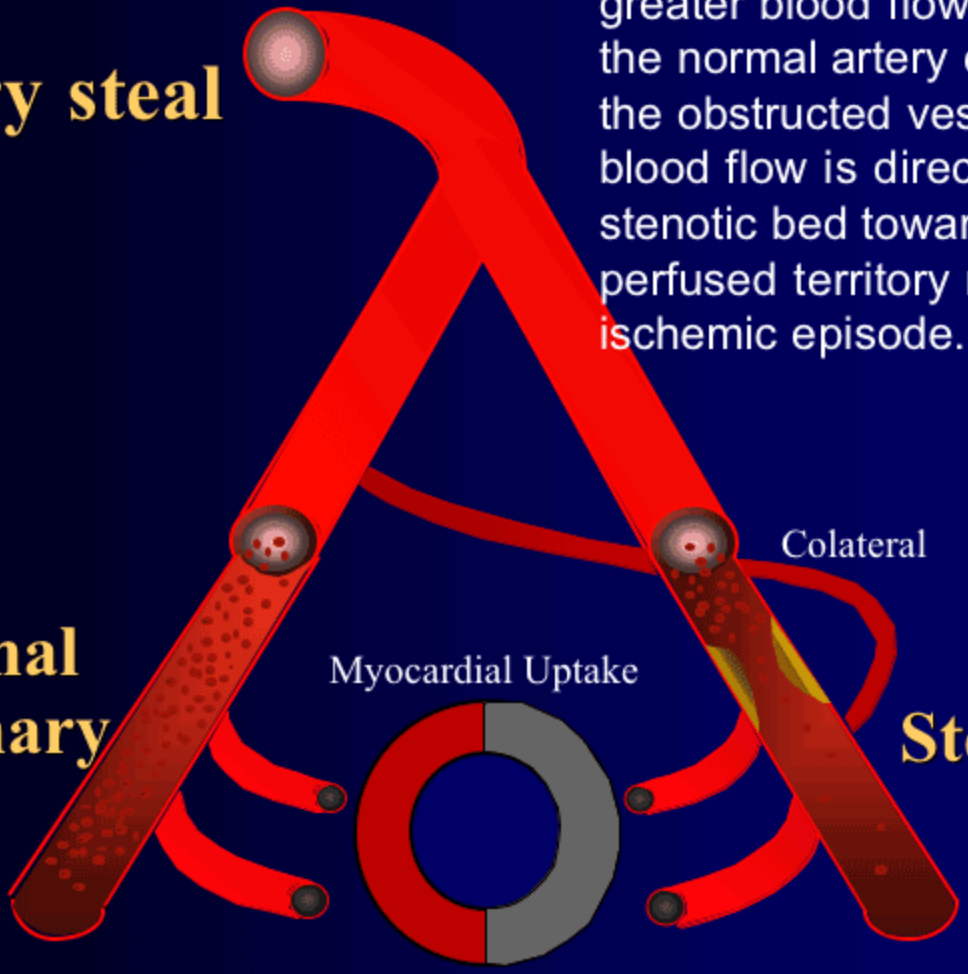


Normal coronary

Stenosis

Coronary steal

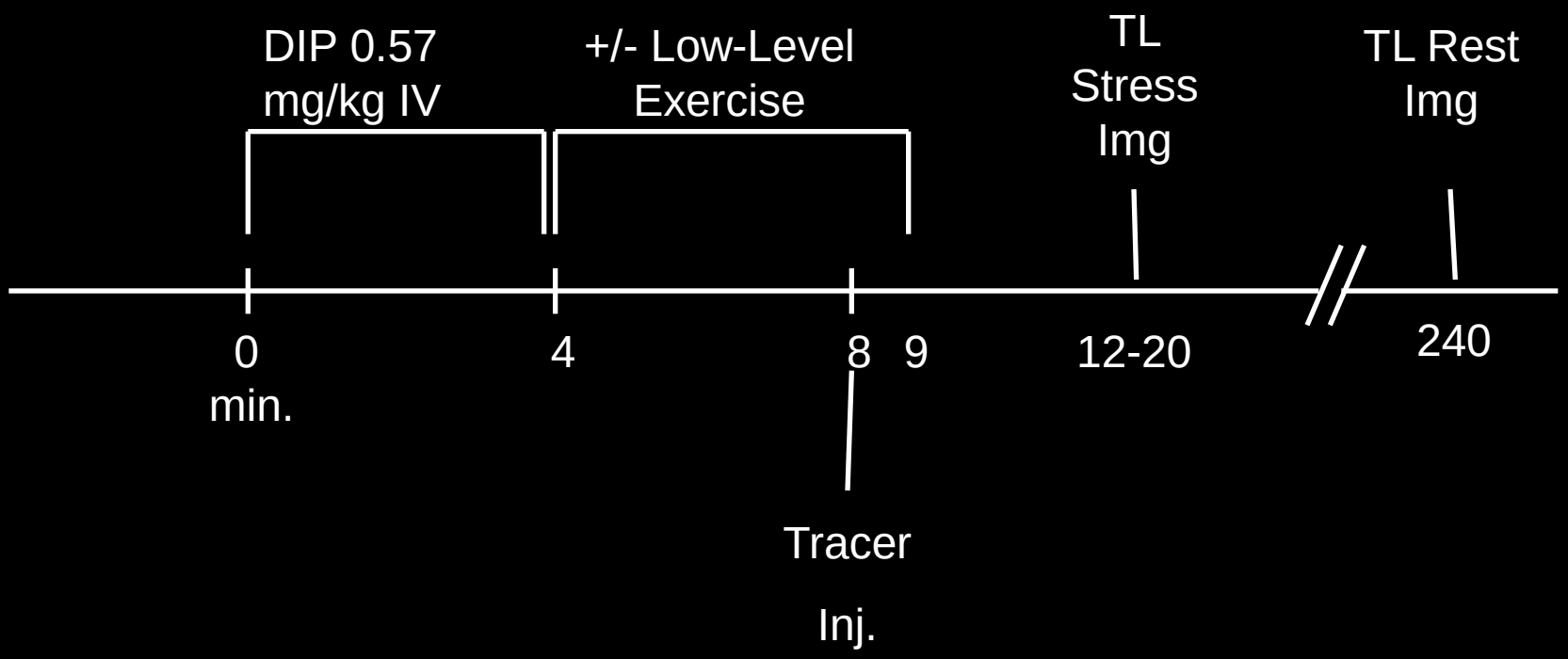
The flow disparity is due to a greater blood flow increase in the normal artery compared to the obstructed vessel. The blood flow is directed from the stenotic bed towards the well perfused territory resulting in an ischemic episode.



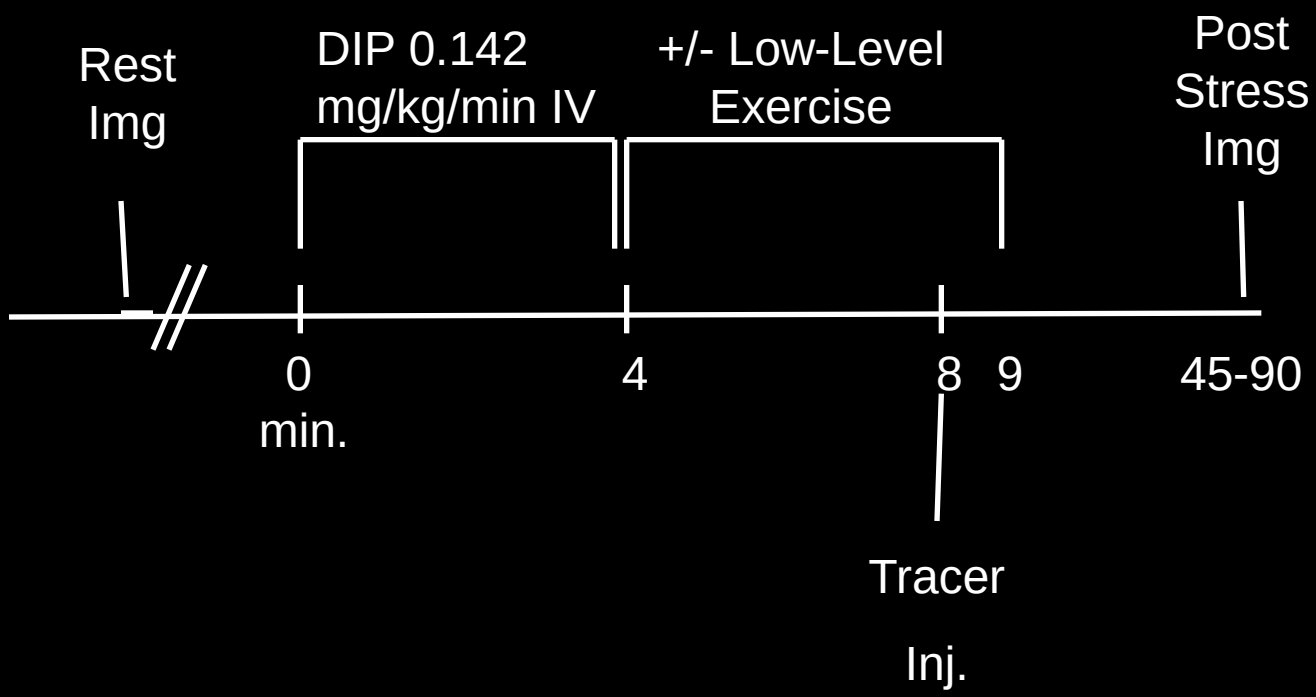
Normal Coronary

Stenosis

TL-201/Dipyridamole Protocol



Tc-99m/Dipyridamole Protocol



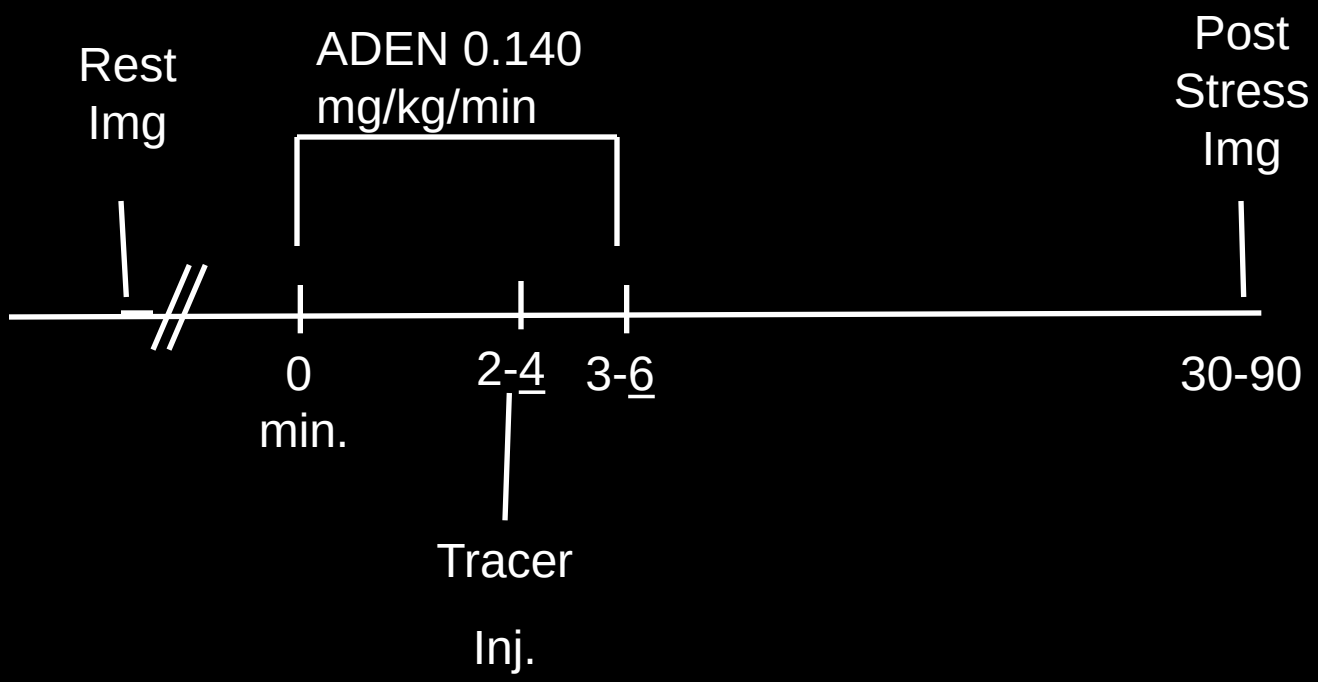
Points for Dipyridamole Administration

- Dosing is per kg with a package insert maximum of 60 mg; maximum dose level is not solidly established
- There was limited dose ranging to determine optimal dose/kg for standard patients
- Despite the above, diagnostic accuracy is equivalent to exercise stress for MPI and superior to submaximal stress
- Timing of infusion over 2-6 minutes is not shown to be critical, but too-rapid infusion creates burning at injection site
- Timing of peak blood flow is not precise but reliably a few minutes after intravenous injection.
- Oral dipyridamole use was abandoned due to lack of predictability of timing of peak flow (30-90 minutes after 300-400 mg)
- Ideally inject radiotracer 3-5 minutes after 4 minute infusion but inject earlier if patient has evidence of ischemia

Points for Dipyridamole MPI Imaging

- Image quality is inferior to maximal exercise stress due to increased body background activity, despite increased target uptake
- Longer wait between tracer injection and imaging improves image quality
- Despite decreased image quality, diagnostic accuracy is equivalent to exercise stress MPI.

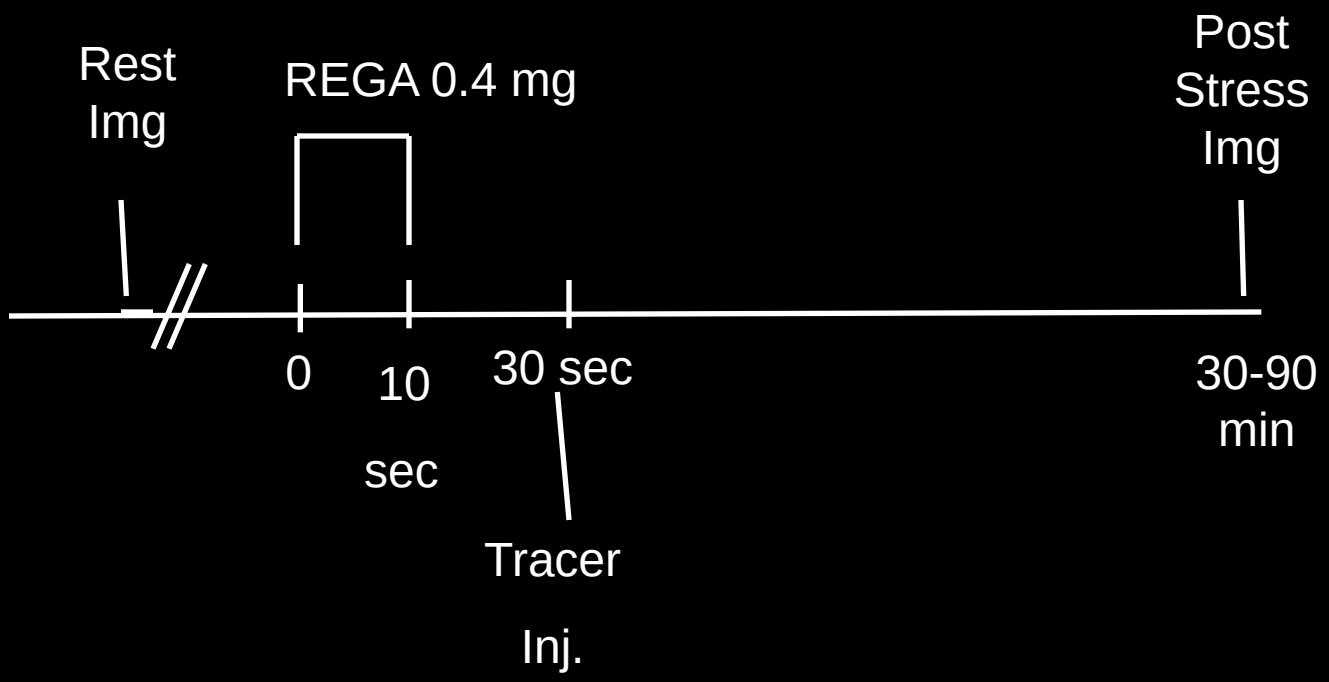
Tc-99m/Adenosine Protocol



Points for Adenosine Administration

- Dosing is per kg with a package insert maximum of 60 mg; maximum dose level is not solidly established and remarkably similar to dipyridamole despite different mechanisms of action
- Despite the above, diagnostic accuracy is equivalent to exercise stress for MPI and superior to submaximal stress
- Timing of infusion over 3-6 minutes is not shown to be critical,
- Timing of peak blood flow is not precise but reliably 2-3 minutes after starting intravenous injection.
- Ideally inject radiotracer near midpoint of adenosone infusion but inject earlier if patient has evidence of ischemia
- Arrange IV lines so as not to bolus adenosine into the patient (due to risk of heart block)

Tc-99m/Regadenoson Protocol



Points for Regadenoson Administration

- Regadenoson is relatively specific for A_{2a} receptors
- A_{2a} receptors also occur outside coronary arteries and other adenosine receptors occur in coronary arteries
- Dosing is NOT per kg with a standard of 0.4 mg.
- There is limited data available on dose ranging for very large patients; maximum dose level is not solidly established
- There was limited dose ranging to determine optimal dose/kg for standard patients
- Despite the above, diagnostic accuracy is equivalent to adenosine for MPI
- Timing of infusion over 10-20 seconds is theoretically critical though there is limited data on slower infusions. Similarly no data on more rapid infusion effects
- Data on timing of peak blood flow assumes 10-second infusion.
- Time to peak flow, duration of increased flow, and side effect profiles are not known for other infusion protocols

Dobutamine Protocol

- Similar to dobutamine-echo
- Initial low-dose infusion at 5-10 followed by 20, 30, 40, and perhaps 50 mg/kg/min, each dose infused for 3 minutes
- Atropine 0.5 mg iv x 1-4 if 85% of max. heart rate is not achieved

Dobutamine Protocol Endpoints

- Achievement of max dose (40-50 mg/kg/min
- ³ 85% max. predicted heart rate
- Severe angina
- ST segment depression of ³ 2 mm
- Severe hypertension
- Symptomatic hypotension or systolic pressure less than 90 mmHg
- Significant atrial/ventricular arrhythmias
- Dyspnea
- Syncope

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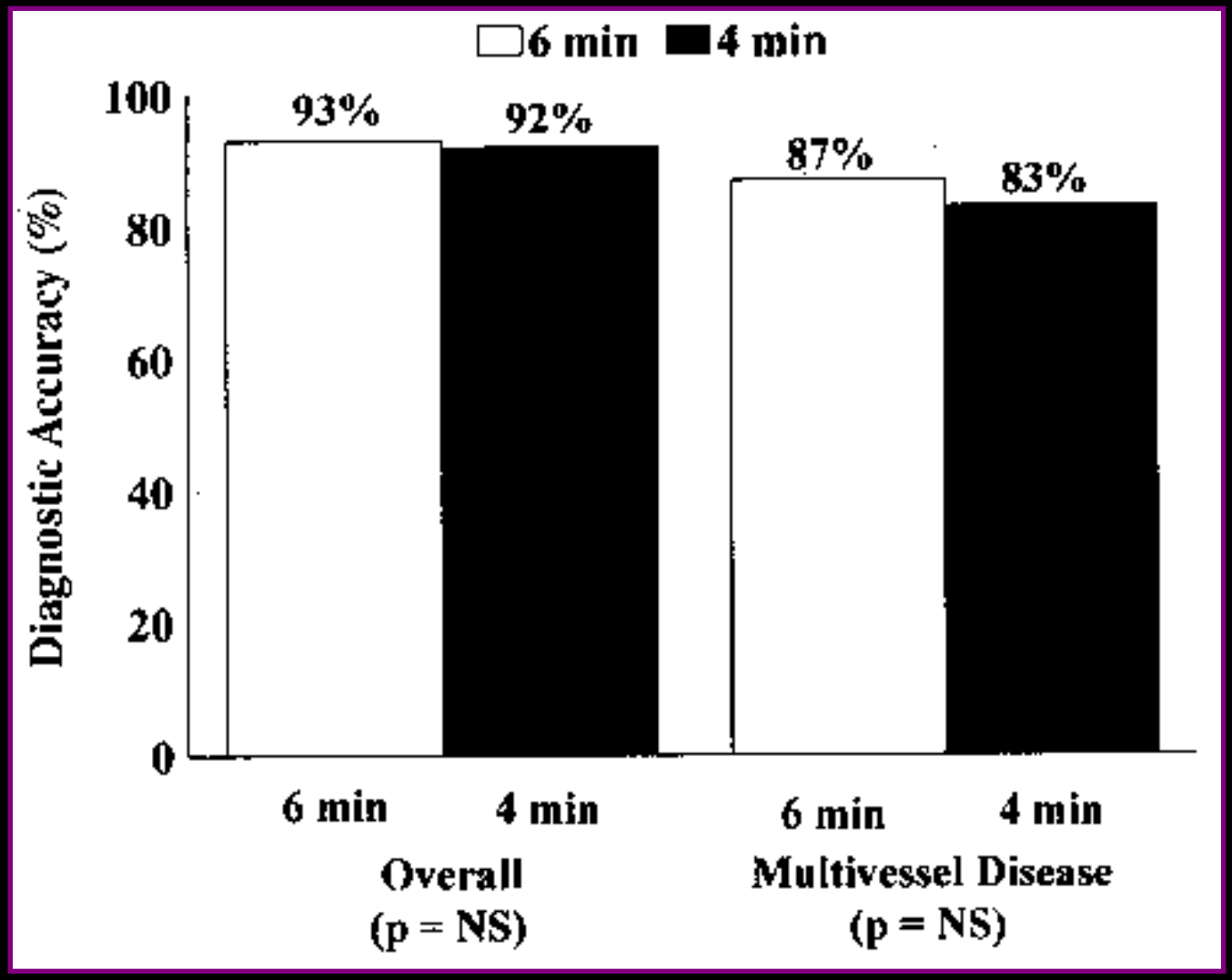
Clinical Effectiveness - Diagnosis

- High sensitivity, fair specificity, and good predictive accuracy
- Good accuracy in detection individual diseased arteries
- Higher specificity with pharmacologic testing over exercise stress may be in part be related to fewer artifacts owing to hyperventilation, patient motion, and upward creep that may occur with exercise thallium studies
- As with exercise testing, the sensitivity is higher in multivessel disease
- Similar accuracy whether thallium, sestamibi, or tetrofosmin was used



O'Keefe et al. *Am Heart J* 129;482-7,1995

Clinical Effectiveness - Prognosis

- LVEF accuracy and reproducibility is equivalent between exercise and pharmacologic stress, but stress EF with vasodilator stress is of questionable value.
- As with exercise testing, increased lung/heart ratio correlates with extent of CAD and the size of perfusion abnormality. Thallium data is superior to Tc-99m data for prognosis.
- Transient LV dilation is due to subendocardial ischemia and apparent myocardial thinning/cavity dilatation correlates with severity and extent of perfusion abnormality

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Side Effects

Symptom %	Dipy	Aden	Rega	Dobut
Completed Protocol	95	100	100	84
Any Symptom	77	83	80	75
Flushing	12	37	16	14
SOB	23	35	28	14
Chest pain/discomfort	30	35	32	31
GI discomfort, N/V	9	15	11	9
Headache	12	14	26	14
Neck/jaw discomfort	-	12	-	7
Arm/Back discomfort	-	-	-	14
Lightheadiness/Dizziness	12	9	8	4
Paresthesia	-	-	-	12
AV block	7	8	2	-
ST-T changes	7	6	12	-
Arrhythmia	-	3	-	-
Palpitations	-	-	-	29
Given aminophylline	10-30	<7	<3	-

Safety

- Rare cardiac and severe adverse events
- Although patients for pharmacologic stress are generally more debilitated, overall safety is comparable to or slightly worse than dynamic exercise stress
- With dipyridamole, 9 deaths and 13 nonfatal MI out of 73,806 patients
  - Lette et al. *J Nucl Cardiol*,1995
- With dipyridamole, 6 deaths and 3 additional nonfatal MI in >150,000 patients (SLEH)
- With adenosine, no deaths and 1 MI out of 9,256 patients
  - Cerqueira. *JACC*,1994

Vasodilator “Stress” Tests

1. Safer than TMT for “all-comers,” but not proven safer in routine outpatient populations. Low LVEF <25% is a major risk factor. (1/8,000-30,000 die)
2. Not necessarily safer than limited exercise in unstable angina or within 48 hours of acute infarction. (Insufficient data)
3. Methylxanthines (aminophylline, caffeine, chocolate) are specific antagonists to dipyridamole, adenosine, and regadenoson.
4. Bronchoconstriction is at least as big a risk as is myocardial ischemia in that it may be harder to treat.
5. If you must stop the stress test, inject the tracer. (Preferably wait 1-2 minutes, but skip the wait if the clinical situation requires it.)
6. The patient is in trouble because coronary vessels are maximally dilated, why would you use nitroglycerin?

Vasodilator “Stress” Tests

7. Absolute*/Relative Contraindications
   a. 2° or 3° heart block (adenosine* and regadenoson*)
   b. asthma/RAD (adenosine* and dipyridamole*)
   c. acute MI*/unstable angina
   d. methylxanthine intake
   e. severe hypotension
   f. pregnancy
   g. low cardiac output
   h. allergy to agent* and/or aminophylline

Vasodilator “Stress” Tests

8. Treatment of complications
   a. Stop the infusion! Inject the tracer <u>if possible</u>
   b. administer the antagonist
      aminophylline 75-150 mg iv over 1-2 minutes
   c. treat life-threatening arrhythmia as usual
   d. treat bronchospasm aggressively
   e. treat ischemia
      add oxygen, repeat aminophylline in 2-3 min.
      add NTG sl
   f. treat heart failure/pulmonary edema as usual

Mechanism of Action of Caffeine and Methylxanthines

- Binds to adenosine receptors and/or immediately adjacent sites
- No direct stimulatory or inhibitory effects on receptor activation
- Exerts effect by blocking adenosine and adenosine analogs from binding to the receptor
- Therefore vasodilatory effects of adenosine are blocked and flow heterogeneity is not established

- Caffeine decreases quantitative sensitivity, but is controversial with respect to clinical accuracy effect.

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Summary-1

- Vasodilators allow a large number of patients to undergo “stress” testing who could not perform adequate exercise stress.
- MPI with vasodilators (and probably dobutamine) have diagnostic accuracy equivalent to MPI with maximal treadmill/ECG.
- MPI with vasodilators have prognostic accuracy equivalent to MPI with maximal treadmill/ECG.
- MPI with vasodilators have diagnostic and prognostic accuracy superior to MPI with submaximal treadmill/ECG.
- Safety of vasodilators is equivalent to or slightly worse than treadmill/ECG.

Summary-2

- Common vasodilators all act via adenosine-related mechanisms but differ by exact mode of action.
- Patient selection among pharmacologic stress methods depends primarily on co-morbid conditions.
- Patient preparation (e.g. caffeine) and side effects are similar for common vasodilators but different from chronotropic agents

Summary-3

- Dobutamine (+ inotropic/chronotropic)
  is not superior to vasodilators for MPI accuracy.
- Vasodilators are preferable to dobutamine for pre-existing tachyarrhythmias.
- Serious heart block is more common with adenosine and regadenoson than dobutamine or possibly dipyridamole
- Reactive airways disease is best handled with dobutamine or regadenoson

1. Aminophylline is relatively contraindicated for treating serious side effects of vasodilator stress agents for patients with which of the following situations?

A. Marked ST depression

B. Recent history of coronary stent placement

C. Remote history of reactive airways disease

D. Recent history of reactive airways disease

E. Recent history of seizure disorder

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B. Recent history of coronary stent placement

C. Remote history of reactive airways disease

D. Recent history of reactive airways disease

E. Recent history of seizure disorder

2. Compared to other vasodilator stress agents, regadenoson is relatively preferred in patients with which of the following clinical situations?

A. Recent caffeine ingestion

B. Aortic valvular stenosis

C. Recent abdominal surgery

D. History of reactive airways disease

E. Pregnancy

2. Compared to other vasodilator stress agents, regadenoson is relatively preferred in patients with which of the following clinical situations?

A. Recent caffeine ingestion

B. Aortic valvular stenosis

C. Recent abdominal surgery

D. History of reactive airways disease

E. Pregnancy

3. Which method of stress testing should be used in patients undergoing MPI who have complete left bundle branch block (LBBB)?

A. Treadmill exercise

B. Adenosine infusion

C. Dobutamine infusion

D. Atrial pacing

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4. Patients complain of which of the following symptoms with greatest frequency during vasodilator stress testing?

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B. Angina/ischemic chest pain

C. Variant angina, such as jaw pain

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5. Which of the following statements is true about stress testing with vasodilator agents in association with MPI?

A. Vasodilator stress is safer than maximal exercise stress MPI for the diagnosis of CAD.

B. Patients undergoing vasodilator stress have more overall symptoms than patients undergoing exercise stress.

C. Vasodilator stress MPI is more accurate than maximal exercise stress MPI for the diagnosis of CAD.

D. Positive MPI with reversible perfusion defects performed after vasodilator stress indicates stress-induced ischemia.

E. Vasodilator stress MPI has sensitivity approximately equal to submaximal exercise stress MPI for detecting ongoing ischemia in a patient with recent myocardial infarction.

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