

Bon Secours Richmond
Pharmacy & Therapeutics Committees
Adenosine Versus Dipyridamole for Myocardial Perfusion Scintigraphy
1/2004

Recommendation:

- Adenosine is not recommended for formulary inclusion as it does not demonstrate equivalent sensitivity to dipyridamole and is eight to ten (8-10) times much more expensive than dipyridamole (\$16-32 costing per test).

Findings:

- Indication: adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise.
- Adenosine induces coronary vasodilation by activation of the adenosine₂ (A₂) cell surface receptor.
- Adenosine produces coronary vasodilation and dilates resistance vessel in all tissues except the kidney and liver where it produces vasoconstriction.
- Adenosine significantly increases blood flow in normal coronary arteries with little or no increase in stenotic arteries.
- Myocardial uptake of thallium-201 is directly proportional to coronary blood flow.
- Adenosine produces a direct negative chronotropic, dromotropic and inotropic effect on the heart.
- Adenosine's half-life is 10 seconds and it is cleared via cellular uptake (nucleoside transport) by RBCs and vascular endothelial cells.
- Adenosine 140 mcg/kg/min produces maximum coronary hyperemia in approximately 95% of cases in 2-3 minutes. Blood flow returns to basal levels within one to two minutes after discontinuation of adenosine.
- Dose: 140 mcg/kg/min for 6 minutes. Inject thallium at midpoint of adenosine infusion.
- Contraindications:
 - 2nd or 3rd degree heart block in patient without a functional artificial pacemaker
 - Sinus node disease (sick sinus syndrome or symptomatic bradycardiac, except in patients with a functional artificial pacemaker)
 - Known or suspected broncho constrictive or bronchospastic lung disease (asthma)
- Warnings
 - Fatal cardiac arrest, life threatening ventricular arrhythmias, and myocardial infarction have been reported coincident with adenosine infusion. Patients with USA appear to be at greater risk.
 - Sinoatrial and atrioventricular nodal block
 - 6.3% develop AV block, all have been asymptomatic, transient, and did not require intervention.
 - Hypotension
 - Use with caution in patients with autonomic dysfunction, stenotic valvular heart disease, pericarditis or pericardial effusion, stenotic carotid artery disease with cerebrovascular insufficiency, or uncorrected hypovolemia.
- Drug interactions:
 - Vasoactive effects of adenosine are inhibited by *adenosine receptor antagonists*: methylxanthines (caffeine and theophylline).
 - Vasoactive effects of adenosine are potentiated by *nucleoside transport inhibitors* such as dipyridamole.
 - Drugs that augment or inhibit the effects of adenosine should be withheld for ≥ 5 half-lives prior to adenosine use.

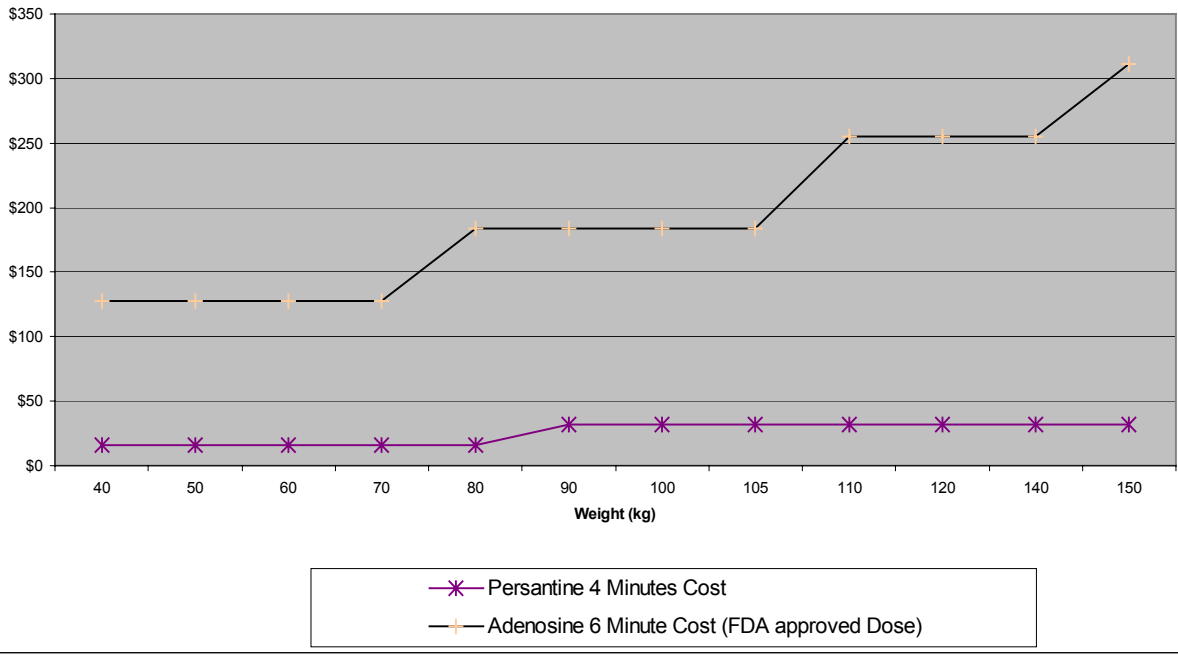
Comparison to dipyridamole

- Adenosine produces a greater increase in heart rate, greater decrease in diastolic and systolic blood pressure
- Adenosine incidence of adverse effects is higher, but dipyridamole has a higher incidence of late onset adverse effects.

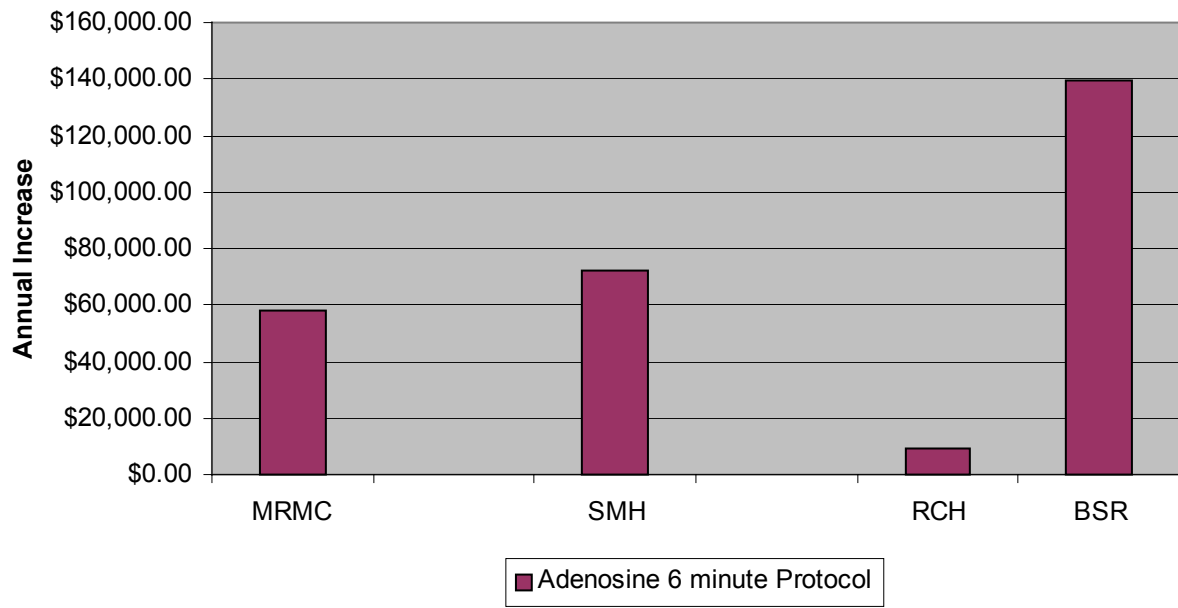
	Persantine	Adenosine
Mechanism of Action	Indirect acting, inhibits cellular uptake of adenosine	Direct acting on A ₁ and A ₂ receptor
Half life	11.6-15 hours	10 seconds
Indication	Adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise	
Package insert Sensitivity	85% (Coronary arteriography vrs Persantine assisted thallium imaging)	64% (Coronary arteriography vrs Adenosine assisted thallium imaging)
Package insert Specificity	50%	54%
Reversal agent	Aminophylline injection	Aminophylline injection
Dosage	140 mcg/kg/min for 4 minutes	140 mcg/kg/min for 6 minutes
Contraindications		2 nd or 3 rd degree heart block* Sinus node disease (sick sinus syndrome or symptomatic bradycardiac)* Known or suspected broncho constrictive or bronchospastic lung disease (asthma)

* In patient without a functional artificial pacemaker

Cost Comparison of Persantine & Adenosine



Annual Cost Increase To Convert To Adenosine From Persantine



Review of the Literature:

Radionuclide Perfusion Imaging

Cardiology. 1997 Mar-Apr;88(2):180-8. Related Articles, Links

Comparison of adenosine, dobutamine, and exercise radionuclide ventriculography in the detection of coronary artery disease.

Nagaoka H, Isobe N, Kubota S, Iizuka T, Imai S, Suzuki T, Nagai R. Second Department of Internal Medicine, Gunma University School of Medicine, Japan.

The diagnostic values of adenosine, dobutamine, and exercise radionuclide ventriculography (RNVG)(technetium-99m pertechnetate) in the detection of coronary artery disease (CAD), and the characteristics of those patients who showed myocardial ischemia during the infusion of adenosine or dobutamine were assessed in 41 patients with suspected CAD. Exclusion criteria: CHF, USA, severe congenital or valvular heart disease, or documented cardiomyopathy. Sensitivity, specificity, and accuracy, respectively, for detecting patients with CAD were 35% ($p < 0.01$ vs. exercise RNVG), 100% and 46% ($p < 0.01$ vs. exercise RNVG) with adenosine RNVG, 74%, 100% and 78% with dobutamine RNVG and 88%, 71% and 85% with exercise RNVG. There was a significant difference in physiologic parameters during the provocation of ischemia by adenosine versus exercise RNVG, although these parameters were similar by dobutamine and exercise RNVG. Stepwise discriminant analysis revealed that the number of stenotic vessels was an important and independent predictor for the myocardial ischemia induced by each stress; the peak filling rate was the only predictor for adenosine-induced ischemia. Dobutamine induced myocardial ischemia in a way similar to that of exercise, and was more useful than adenosine for pharmacologic stress RNVG. The mechanism of the adenosine-induced ischemia seemed to differ from that of the ischemia induced by dobutamine or exercise, and to be closely associated with left ventricular diastolic function. Adenosine RNVG seems unlikely to be useful as a routine clinical test for the detection of patients with CAD because of its lower sensitivity and accuracy.

Cross Over Study N=41

	Adenosine 180 mcg/kg/min x 5 minutes	Dobutamine 5 mcg/kg/min, increased by same q3minutes to 40 mcg/kg/min	Exercise
Overall Sensitivity	35%	74%	88%
Multivessel Sensitivity	55%	85%	95%
Specificity	100%	100%	71%
Accuracy	46%	78%	85%

J Nucl Cardiol. 1996 May-Jun;3(3):281-3.

Comparison between dipyridamole and adenosine as pharmacologic coronary vasodilators in detection of coronary artery disease with thallium 201 imaging.

Taillefer R, Amyot R, Turpin S, Lambert R, Pilon C, Jarry M.

Department of Nuclear Medicine, Hotel-Dieu de Montreal, Universite de Montreal, Canada.

BACKGROUND: Both dipyridamole and adenosine are widely used as pharmacologic stressors with 201Tl imaging for detection of coronary artery disease. The purpose of this study was to compare dipyridamole and adenosine 201Tl imaging directly in patients with angiographically proved coronary artery disease. METHODS AND RESULTS: Fifty-four patients were submitted to two planar 201Tl studies: one with dipyridamole and the other with adenosine. Exclusion criteria: recent MI, USA, class III/IV CHF, symptomatic valvular heart disease, uncontrolled arrhythmias, history of asthma or severe COPD requiring steroids or bronchodilators, second or third degree AV block, prior CABG or PCI, severe HTN or significant hypotension. The interval between the two studies varied from 2 to 7 days and the order was assigned randomly. Three standard planar views were obtained 10 minutes and 4 hours after the injection of 3.0 mCi 201Tl. Administration of dipyridamole was as follows: 0.142 mg/kg/min during 4 minutes, followed by a slight exercise and 201Tl injection. The infusion of adenosine was as follows: 0.140 mg/kg/min during 6 minutes with injection of 201Tl after the third minute of infusion. Patients were asked to give their preference considering the number, type, severity, and duration of side effects on a scale from 0 (worst) to 5 (best). Two experienced observers did the readings. The heart was divided into three segments per view. The change in systolic blood pressure was -12 ± 11 mm Hg for adenosine and -5 ± 10 mm Hg for dipyridamole ($p < 0.001$), and the change in heart rate was 18 ± 10 beats/min for adenosine and 8 ± 7 beats/min for dipyridamole ($p < 0.001$). With regions of interest, ischemic/normal wall ratios were determined: 0.78 ± 0.06 for adenosine and 0.83 ± 0.08 for dipyridamole ($p < 0.001$). Adenosine detected 295 normal, 170 ischemic, and 21 scar segments, whereas dipyridamole detected 326, 135, and 25 segments, respectively. Patients preferred adenosine (4.3 ± 1.0 for adenosine vs 3.8 ± 1.5 for dipyridamole; $p < 0.04$) mainly because of the short duration of side effects. CONCLUSION: This study shows that the use of adenosine with 201Tl imaging may have some advantages over dipyridamole.

Mayo Clin Proc. 1995 Apr;70(4):331-6. Related Articles, Links

Hemodynamic responses and adverse effects associated with adenosine and dipyridamole pharmacologic stress testing: a comparison in 2,000 patients.

Johnston DL, Daley JR, Hodge DO, Hopfenspirger MR, Gibbons RJ. Division of Cardiovascular Diseases, Mayo Clinic Rochester, MN 55905.

OBJECTIVE: To compare the hemodynamic responses and the adverse effects associated with two coronary vasodilators used for pharmacologic stress testing. **DESIGN:** We retrospectively studied the results of adenosine and dipyridamole perfusion imaging in a large group of patients who underwent pharmacologic stress radionuclide perfusion imaging. **MATERIAL AND METHODS:** One thousand patients given dipyridamole between April 1989 and April 1991 (before adenosine became available) were compared with 1,000 patients given adenosine between April 1991 and October 1992. A standard protocol was used to infuse the drugs before myocardial perfusion imaging with 201Tl or 99mTc sestamibi. **RESULTS:** Peak heart rate was higher (85 versus 83 beats/min; $P = 0.02$) and systolic blood pressure was lower (129 versus 133 mm Hg; $P < 0.0001$) with adenosine than with dipyridamole. More patients had a decrease in systolic blood pressure of 30 mm Hg or more with adenosine than with dipyridamole ($P = 0.002$). Horizontal or down sloping ST-segment depression of 1 mm or more occurred in 9% of patients who received adenosine and in 8% of those who received dipyridamole. Adverse effects occurred in 78% of the adenosine study group and in 50% of the dipyridamole group ($P < 0.0001$). Chest pain was the most common symptom with both drugs. Atrioventricular block occurred in 76 patients who received adenosine but in none who received dipyridamole. Because of adverse effects, 28% of patients who received dipyridamole required extra monitoring time (mean, 6 +/- 5 minutes beyond the standard protocol). Aminophylline was administered to 163 and 6 patients, respectively, in the dipyridamole and adenosine study groups. **CONCLUSION:** Adenosine causes slightly greater systemic vasodilation than does dipyridamole. Adverse effects occur less often with dipyridamole but, in comparison with adenosine, are more difficult to manage and necessitate more monitoring time as well as fairly frequent intravenous use of aminophylline for reversal.

	Adenosine N=1000	Dipyridamole N=1000
Dose	140 mcg/kg/min x 6 minutes	140 mcg/kg/min x 6 minutes
At Rest		
Heart Rate	72 +14	72 +14
SBP	141 +24	143 + 24
DBP	78 +12	79 + 11
Peak Response		
HR	85 +16	83 + 14
SBP	129 + 23	133 +23
DBP	70 +12	72 + 11
Change		
HR	13 +13	12 +9
SBP	-13 + 17	-10 +14
DBP	-7 + 10	-7 +8
Decrease in SBP > 30 mm Hg	11.6% (116/1000)	7.7% (77/1000)

	Adenosine	Dipyridamole
Chest Pain	53%	30%
Dyspnea	25%	5%
Flushing	26%	3%
Headache	13%	20%
Light-headedness	6%	6%
GI distress	7%	5%
Nervousness	< 1%	<1%
AV block		
1 st degree	<1%	
2 nd degree	6%	
3 rd degree	1%	
Required Extra Monitoring Time (6 ± 5 minutes) 2 nd ADR	0.6%	28%
Aminophyllin required	0.6% (6/1000)	16.3% (163/1000)
Any adverse effect	78%	50%
Admitted to Hospital 2 nd persistent chest pain		0.2% (2/1000)

J Am Coll Cardiol. 1994 Feb;23(2):384-9. Related Articles,

Comment in: J Am Coll Cardiol. 1994 Feb;23(2):390-2.

Safety profile of adenosine stress perfusion imaging: results from the Adenoscan Multicenter Trial Registry.

Cerqueira MD, Verani MS, Schwaiger M, Heo J, Iskandrian AS. Department of Radiology, University of Washington School of Medicine, Seattle.

OBJECTIVES. The purpose of this study was to determine the safety of adenosine infusion at 140 micrograms/kg per min for 6 minutes in conjunction with radionuclide imaging in 9,256 consecutive patients. *Exclusion criteria: SBP < 80 mm Hg, asthma, decompensated or COPD, severe aortic stenosis, USA or Acute MI within 24 hours of the study.* **BACKGROUND.** Adenosine produces maximal myocardial hyperemia directly with a rapid onset of action. In addition, when used in conjunction with radionuclide perfusion imaging, it has proven efficacy for the diagnosis of coronary artery disease in patients unable to exercise. Because the ultrashort half-life (< 10s) allows dose titration and rapid reversal of side effects, it may be safer than other available pharmacologic agents. **METHODS.** Patients were prospectively entered at 21 clinical sites. Information on safety and adverse events during and immediately after adenosine infusion was maintained in the Adenoscan Multicenter Trial Registry. *Exclusion criteria were: hypotension SBP < 80, asthma, decompensated or chronic obstructive pulmonary disease that did not allow termination of bronchodilator therapy, severe aortic stenosis, US or AMI within 24 hours of the study.* **RESULTS.** The infusion protocol was completed in 80% of patients, required dose reduction in 13% and was terminated early in 7%. Interpretable imaging studies were obtained in 98.7% of patients, and 0.8% of patients received aminophylline. Minor and well tolerated side effects were reported in 81.1% of patients. There were no deaths, one myocardial infarction, seven episodes of severe bronchospasm and one episode of pulmonary edema. Transient atrioventricular (AV) node block occurred in 706 patients (first-degree in 256, second-degree in 378 and third-degree in 72) and resolved spontaneously in most patients (n = 508) without alteration in the adenosine infusion. There were no sustained episodes of AV block. Patients > 70 years of age had an increased risk of developing AV block (age < 70, 7.05% vs. > or = 70, 9.44%, p = 0.001, relative risk 1.37). **CONCLUSIONS.** Adenosine infusion is safe. Vasodilator and negative dromotropic side effects are generally well tolerated. Serious side effects are relatively rare, and they reverse with termination of adenosine infusion. Interpretable radionuclide studies were obtained in 98.7% of patients and aminophylline reversal was seldom required.

	N=9055
Completed Protocol	80% (7226/9055)
Dosage Reduced	13% (1165/9055)
Terminated Early	7% (664/9055)
Aminophylline Required	0.8% (71/9055)
Adverse Effects	
Any	81.1% (7507/9256)
Mild	78.4%
Moderate	9.6%
Severe	4.7%
AV block	7.6%
1 st degree AV block	2.8%
2 nd degree AV block	4.1%
3 rd degree AV block	0.78%
Adenosine Terminate 2 nd AV block	0.62%
Hypotension	1.8%
Bradycardia	0.2%
Bronchospasm	0.1% (SEVERE IN 7)
Myocardial Infarction	1 patient
Pulmonary Edema	1 patient
Flushing	36.5%
SOB/dyspnea	35.2%
Chest Pain	34.6%
GI discomfort	14.6%
HA	14.2%
Throat, neck, jaw discomfort	11.6%
Light-headedness	8.5%
AV block	7.6%
ST-T Changes	5.7%
Arrhythmia	3.3%
Upper Extremity discomfort	2.3%

Am Heart J. 1992 Jun;123(6):1569-74. Related Articles, Links

Atrioventricular block during adenosine thallium imaging.

Lee J, Heo J, Ogilby JD, Cave V, Iskandrian B, Iskandrian AS. Philadelphia Heart Institute, Presbyterian Medical Center of Philadelphia, PA 19104.

Transient atrioventricular (AV) block has been reported during adenosine thallium imaging. This study examined the predictors and hemodynamic implications in 55 patients who had second- or third-degree AV block (group 1) and compared the results with those in 803 patients who did not have AV block (group 2). There were no significant differences in age, sex, or heart rate at baseline between the two groups. ST segment depression was observed in 25% of patients in group 1 and 16% in group 2 (p = NS). Chest pain occurred in 56% in group 1 and 44% in group 2 (p = NS). Preexisting conduction abnormalities (17% vs 16%) and treatment with digitalis (15% vs 15%) and beta-blockers (31% vs 36%) were similar in the two groups. The results of thallium imaging were abnormal in 66% in group 1 and 67% in group 2 (p = NS). Reversible thallium defects were seen in 51% in group 1 and 52% in group 2 (p = NS). The AV block appeared during the first 2 minutes of infusion in 40 patients (73%) and disappeared despite continuation of infusion in 43 (78%). The heart rate during AV block was 79 +/- 18 beats/min, and the systolic blood pressure was 127 +/- 27 mm Hg. Premature termination of adenosine infusion was required in one patient (2%). Aminophylline was used in 5% in group 1 and 2% in group 2 (p = NS). Thus AV block is transient, occurs during the early minutes of infusion, is not aggravated by digitalis or beta-blocker therapy, can be seen in patients with normal perfusion images, and is often well tolerated. AV block disappeared despite continuation of infusion in 78% (43/55), and all episodes terminated shortly after the discontinuation of the adenosine infusion.

Circulation. 1990 Apr;81(4):1425-7.

The safety of intravenous dipyridamole thallium myocardial perfusion imaging. Intravenous Dipyridamole Thallium Imaging Study Group.

Ranhosky A, Kempthorne-Rawson J. Department of Clinical Research, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT 06877.

Clinical data on 3,911 patients were collected from 64 individual investigators to evaluate the safety of intravenous dipyridamole-thallium imaging as an alternative to exercise thallium imaging for the evaluation of coronary artery disease. There were two deaths because of myocardial infarctions, two nonfatal myocardial infarctions, and six cases of acute bronchospasm. Chest pain occurred in 770 patients (19.7%). Headache and dizziness were reported by 476 patients (12.2%) and 460 patients (11.8%), respectively. ST-T changes on the electrocardiogram were seen in 292 patients (7.5%). Use of parenteral aminophylline to treat adverse events associated with intravenous dipyridamole brought complete relief of symptoms in 439 of 454 patients (96.7%). There is a potential for increased risk for serious ischemic events in patients with a history of unstable angina who are administered intravenous dipyridamole. In patients with acutely unstable angina (i.e., continuing chest pain) or in the acute phase of myocardial infarction, use of intravenous dipyridamole in thallium scintigraphy should be avoided. There is also an increased risk for bronchospasm in patients with a history of asthma; acute bronchospasm can be relieved immediately by administration of aminophylline. These results demonstrate that intravenous dipyridamole-thallium scintigraphy is a relatively safe, noninvasive technique for the evaluation of coronary artery disease.

Adverse Effects		
	N= 3911	Comments
Major Adverse Events	0.26% (10/3911)	
Fatal MI	0.05% (2/3911)	All had USA
Nonfatal MI	0.05% (2/3911)	All had USA
Acute Bronchospasm with wheezing	0.15% (6/3911)	All responded to aminophylline
Minor Adverse Events	46.5% (1820/3911)	96.7% of those treated with aminophylline experience complete relief of symptoms
Aminophylline Used for Adverse Reactions	11.6% (454/3911)	

Echocardiography

Coron Artery Dis. 1997 Oct;8(10):633-43. Related Articles,

Echocardiographic detection of the extent of coronary artery disease in the elderly using dobutamine and adenosine infusion.

Anthopoulos LP, Bonou MS, Sioras EP, Kranidis AI, Kardaras FG, Antonellis IP. First Department of Cardiology, Evangelismos' Hospital, Athens, Greece.

BACKGROUND: The high prevalence of asymptomatic multivessel disease in the elderly and the fact that most of them can not carry out an exercise stress testing renders the application of other stress modalities necessary. The aim of this study is to compare the diagnostic value of dobutamine and adenosine stress echocardiography and their accuracy in determining the extent of coronary artery disease in elderly people. **METHODS:** Dobutamine and adenosine stress echocardiography were performed in 128 consecutive patients ≥ 70 years-of-age with known or suspected coronary artery disease. All patients underwent coronary angiography within 2 weeks of the stress tests. **RESULTS:** The presence of any echocardiographic abnormality on dobutamine (odds ratio 30.8) and adenosine (odds ratio 18.1) test, the need for cessation of dobutamine test and the ST depression during dobutamine infusion, were independent predictors of significant coronary artery disease. Both tests proved more sensitive for detecting multivessel disease (89% for dobutamine, 74% for adenosine test), than one-vessel disease (74% and 39%, respectively). This difference was statistically significant only for the adenosine echocardiography test ($P = 0.008$). In patients with localized resting wall motion abnormalities, the accuracy of dobutamine test to predict a remotely diseased vessel (70%), was statistically superior to the accuracy of adenosine test (57%, $P = 0.008$). Patients with multivessel disease showed delayed resolution of test-induced wall motion abnormalities, during the recovery period after both tests, compared with those who suffered from one-vessel disease. **CONCLUSIONS:** Dobutamine echocardiography was more sensitive and accurate than adenosine echocardiography in detecting and determining the extent and the severity of coronary artery disease in the elderly. A positive adenosine echocardiography result reflected the presence of advanced coronary artery disease. The two tests, combined with clinical data, could classify the elderly into low- and high-risk subgroups for ischemic heart disease.

Am J Cardiol. 1997 Oct 1;80(7):847-51.

Diagnostic and prognostic value of dipyridamole and dobutamine stress echocardiography in patients with Q-wave acute myocardial infarction.

Minardi G, Di Segni M, Manzara CC, Pulignano G, Chiantera A, De Santis F, Armiento G, Vajola FS, Giovannini E.

Department of Cardiology, San Camillo Hospital, Rome, Italy.

The aim of this study was to compare dipyridamole and dobutamine stress echocardiography, performed early in patients with acute myocardial infarction (AMI) to evaluate residual ischemia, viability, and prognosis. Fifty patients (mean age 55 ± 9 years, 47 men, 3 women) with AMI, all treated with thrombolytic therapy, underwent standard dipyridamole and dobutamine tests, within the fifth day of the event. Wall motion score index and the 16 segments model were used to evaluate contractility. Forty-seven patients underwent coronary angiography within the tenth day of the event. The mean follow-up was 24 ± 12 months. No side effects occurred during both tests. Both dipyridamole and dobutamine tests were positive for ischemia, in 32 and 33 of 47 patients, respectively (sensitivity 73% and 75%; specificity 67% and 67%); these tests induced an improvement of contractility in 23 and 38 of 139 abnormal segments at baseline, respectively (sensitivity 52% and 86%; specificity 100% and 100%). Cardiac events occurred in 26 of 50 patients, 22 with a positive dipyridamole test and 21 with positive dobutamine test. Thus, both tests were feasible, safe, and useful to evaluate residual ischemia, viability, and prognosis. No significant differences were found in sensitivity and specificity between tests.

Coron Artery Dis. 2000 Mar;11(2):151-9. Related Articles, Links

The comparable diagnostic accuracies of dobutamine-stress and dipyridamole-stress echocardiographies: a meta-analysis.

Picano E, Bedetti G, Varga A, Cseh E.

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BACKGROUND: Dobutamine-stress and dipyridamole-stress echocardiographies are widely used for pharmacological stress echocardiography, with wide geographical variations. **OBJECTIVE:** To assess whether evidence derived from the literature indicates or disapproves that either stress modality confers diagnostic superiority. **METHODS:** We performed a meta-analysis of peer-reviewed literature of published trials with head-to-head comparison, on the same population, of high-dose (0.84 mg/kg) dipyridamole-stress versus high-dose (up to 40 micrograms/kg per min) dobutamine-stress echocardiography. Data from 12 studies performed in 12 institutions in seven countries were analysed. Angiographic information about 818 patients was considered. **RESULTS:** The diagnostic accuracies of the two tests were similar (631 of 818, 77%, for dipyridamole versus 654 of 818, 80%, for dobutamine, NS). Overall sensitivities were 403 of 568 (71%) for dipyridamole and 437 of 568 (77%) for dobutamine ($P < 0.05$). Sensitivities for patients with single-vessel disease were 177 of 275 (64%) for dipyridamole and 203 of 275 (74%) for dobutamine ($P < 0.05$). Sensitivities for patients with multivessel disease were 162 of 203 (80%) for dipyridamole and 163 of 203 (80%) for dobutamine (NS). Specificities were 232 of 250 (93%) for dipyridamole and 217 of 250 (87%) for dobutamine ($P < 0.05$). Data from an additional 26 studies with dipyridamole alone and 47 studies with dobutamine alone were analysed. The diagnostic accuracies were 80% for dipyridamole ($n = 2038$ patients; 95% confidence interval 75-82%) and 82% for dobutamine ($n = 4264$ patients; 95% confidence interval 79-84%). **CONCLUSION:** High-dose dobutamine-stress and high-dose dipyridamole-stress echocardiographies have comparable diagnostic accuracies, with a slightly higher sensitivity with dobutamine and a slightly higher specificity with dipyridamole.

J Am Coll Cardiol. 1996 Jul;28(1):52-9. Related Articles, Links

Stress echocardiography in elderly patients with coronary artery disease: applicability, safety and prognostic value of dobutamine and adenosine echocardiography in elderly patients.

Anthopoulos LP, Bonou MS, Kardaras FG, Sioras EP, Kardara DN, Sideris AM, Kranidis AI, Margaris NG. First Department of Cardiology and Hemodynamic Laboratory, The Evangelismos Hospital, Athens, Greece.

OBJECTIVES: Our aim was to determine the applicability, safety and prognostic value of adenosine and dobutamine stress echocardiography in patients ≥ 70 years old. **BACKGROUND:** These tests are sometimes mandatory because of difficulties and inaccuracies in interpreting traditional electrocardiographic stress tests. Furthermore, if these tests could be used to avoid coronary arteriography and cardiac catheterization, they would become essential in the care of the elderly, whose numbers are increasing.

METHODS: We performed coronary arteriography and dobutamine and adenosine stress echocardiographic tests in 120 patients consecutive (72 men) ≥ 70 years old who entered the hospital because of chest pain and had known or suspected coronary artery disease. The stress tests were performed on separate days, within 2 weeks of coronary arteriography. Both the arteriograms and the echocardiograms were analyzed by two experts who had no knowledge of the patients' other data or the other interpreter's report. Tests were judged to have positive or negative results, and the patients were followed up for the development of cardiac events. Univariate and multivariate analyses and other statistical modalities were applied for comparisons. **RESULTS:** Documented coronary artery disease was found in 89 patients. During the 14 ± 7 months of follow-up, cardiac events developed in 50 patients, including 3 (7.9%) of 38 patients with negative dobutamine and 12 (20.7%) of 58 patients with negative adenosine test results. Demonstration of any abnormality on stress echocardiography was an independent factor for cardiac events, both for dobutamine (relative risk 7.3) and for adenosine (relative risk 3.0). Both cessation of dobutamine or adenosine tests and diagnosis of disease in two or more coronary vessels were also independent predictors. ST segment depression ≥ 1 mm was related to future events only with the dobutamine test.

CONCLUSIONS: These echocardiographic stress tests proved safe and well tolerated. They successfully stratified this cohort of elderly patients with coronary artery disease to low or high risk subgroups for subsequent cardiac events. The dobutamine test was superior to adenosine in predicting cardiac events.

Dobutamine Stress Test		
	Cardiac Events N=50	No Cardiac Events N=70
Positive Result	94% (47/50)	50% (35/70)
Angina	48% (24/50)	14.3% (10/24)
ST depression ≥ 1 mm	54%	14.3%
Infusion duration (minutes)	17.5 +/- 5.3	21.8 +/- 4.5
Discontinuation of the test*	68%	21.4%
SBP reduction ≥ 20 mm Hg	10%	4.3%
Sensitivity		
Overall		86.5%
1 Vessel Disease		74%
2 Vessel Disease		88%
3 Vessel Disease		91%
Specificity		84%
Accuracy		86%
Adenosine Stress Test		
	Cardiac Events N=50	No Cardiac Events N=70
Positive Result	76%	34.3%
Angina	48%	27.1%
ST depression ≥ 1 mm	18%	4.3%
Infusion duration (minutes)	5.1 +/- 1.3	5.7 +/- 0.7
Discontinuation of the test*	38%	11.4%
SBP reduction ≥ 20 mm Hg		
Sensitivity		
Overall		66.3%
1 Vessel Disease		42%
2 Vessel Disease		76%
3 Vessel Disease		71%
Specificity		90%
Accuracy		72.5%

* Due to chest pain, ST segment depression ≥ 1 mm or extensive wall motion abnormality.

Am J Cardiol. 1992 Jul 15;70(2):252-8. Related Articles, Links

Safety of intravenous high-dose dipyridamole echocardiography. The Echo-Persantine International Cooperative Study Group.

Picano E, Marini C, Pirelli S, Maffei S, Bolognese L, Chiriatti G, Chiarella F, Orlandini A, Seveso G, Colosso MQ, et al.

CNR Institute of Clinical Physiology, Pisa, Italy.

Clinical data on 10,451 high-dose (up to 0.84 mg/kg over 10 minutes) dipyridamole-echocardiography tests (DET) performed in 9,122 patients were prospectively collected from 33 echocardiographic laboratories, each contributing greater than 100 tests. All patients were studied for documented or suspected coronary artery disease (1,117 early [less than 18 days] after acute myocardial infarction and 293 had unstable angina). Significant side effects including major adverse reactions and minor but limiting side effects occurred in 113 patients (1.2%). Major adverse reactions occurred in 7 cases (0.07%). In 6 of these cases, adverse reactions were associated with echocardiographically assessed ischemia and included 1 prolonged cardiac asystole (complicated by acute myocardial infarction and coma, with death after 23 days), 1 short-lasting cardiac asystole, 2 myocardial infarctions, 1 pulmonary edema and 1 sustained ventricular tachycardia. In all 6 cases, the cardiologist-echocardiographer performing the study had a limited experience (less than 100 tests) with DET, and at off-line reading in 5 cases, the obvious echo-positivity preceded the onset of complications by 1 to 5 minutes. The only ischemia-independent major side effect was a short-lasting cardiac asystole that was reversed by aminophylline and atropine. Significant side effects associated with echocardiographically assessed ischemia occurred in 89 additional cases (21 with and 68 without concomitant echocardiographically assessed myocardial ischemia). The most frequent of these side effects was hypotension or bradycardia, or both, which occurred in 40 patients with negative and 6 with positive DET. In all cases, side effects promptly subsided after aminophylline. In 1,857 cases, the high dose was not given for echo-positivity before the eighth minute.(ABSTRACT TRUNCATED AT 250 WORDS)

Ann Intern Med. 1992 Feb 1;116(3):190-6. Related Articles,

Comment in: Ann Intern Med. 1992 Jul 15;117(2):168; discussion 168-9. Ann Intern Med. 1992 Jul 15;117(2):168; discussion 168-9.

Comparison of adenosine, dipyridamole, and dobutamine in stress echocardiography.

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OBJECTIVE: To compare adenosine, dipyridamole, and dobutamine in stress echocardiography with regard to sensitivity, specificity, accuracy, and side effects. DESIGN: *Crossover, single blind comparison*, with coronary angiography serving as the criterion standard.

SETTING: U.S. Army tertiary care hospital. PARTICIPANTS: Forty participants, 25 with coronary disease and 15 without coronary disease. Patients were eligible if they had coronary angiography within 6 weeks of stress testing or if they had a risk for coronary disease of less than 5%. Exclusion criteria: severe COLD, valvular heart disease, CHF, CABG, and recent angina at rest.

MEASUREMENTS: Left ventricular wall motion was recorded after dobutamine (0.38 mg/kg body weight), adenosine (0.84 mg/kg body weight), and dipyridamole (0.84 mg/kg body weight) stress testing. Stress echocardiographic evaluation was considered to be abnormal if the patient developed new or progressive wall motion abnormalities. The rate of side effects for the types of echocardiography and the patient preference were recorded. MAIN RESULTS: The sensitivity of dobutamine stress echocardiography (76%; 95% CI, 59% to 93%) was significantly higher than that of adenosine echocardiography (40%; CI, 21% to 59%; P less than 0.001) and that of dipyridamole echocardiography (56%; CI, 37% to 75%; P = 0.019). The specificity of adenosine testing (93%; CI, 80% to 100%) was significantly higher than that of dobutamine echocardiography (60%; CI, 35% to 85%; P = 0.008) and that of dipyridamole echocardiography (67%; CI, 43% to 91%; P = 0.028). Symptoms were more frequent with adenosine echocardiography (100%) than with dipyridamole (88%; P less than 0.001) or dobutamine (80%; P less than 0.001) echocardiography. Treatment for persistent symptoms was required in more patients after dipyridamole echocardiography (40%) than after dobutamine (12%; P less than 0.001) or adenosine (0%; P less than 0.001) echocardiography. More patients preferred dobutamine (48%) or dipyridamole (40%) echocardiography to adenosine echocardiography (12%; P less than 0.001). CONCLUSIONS: Dobutamine stress echocardiography is more sensitive and is better tolerated than adenosine or dipyridamole stress echocardiography. Adenosine echocardiography is more specific than dobutamine or dipyridamole echocardiography and is less likely to cause persistent symptoms.

Cross over, single blind (patient) comparison			
N=40	Adenosine	Dipyridamole	Dobutamine
Any symptom	100%	88%	80%
Severe symptom	20%	12%	12%
2 nd AV Block	10%	0%	0%
Hypotension	15%	20%	5%
Decrease dose	8%	8%	16%
Additional therapy*	0%	40%	12%
Patient Preference	12.5% (5/40)	40% (16/40)	47.5% (19/40)
New or Worse Wall Motion Abnormality			
Sensitivity	40%	56%	76%
Specificity	93%	67%	60%
Accuracy	62%	60%	70%
ST-Segment Abnormality			
Sensitivity	12%	20%	24%
Specificity	100%	100%	100%
Accuracy	42%	47%	50%

*Aminophylline after dipyridamole, metoprolol after dobutamine

J Am Coll Cardiol. 1997 Nov 15;30(6):1451-60. Related Articles,

Accuracy of currently available techniques for prediction of functional recovery after revascularization in patients with left ventricular dysfunction due to chronic coronary artery disease: comparison of pooled data.

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OBJECTIVES: This study evaluated the relative merits of the most frequently used techniques for predicting improvement in regional contractile function after coronary revascularization in patients with left ventricular dysfunction due to chronic coronary artery disease. **BACKGROUND:** Several techniques have been proposed for predicting improvement in regional contractile function after revascularization, including thallium-201 (Tl-201) stress-redistribution-reinjection, Tl-201 rest-redistribution, fluorine-18 fluorodeoxyglucose with positron emission tomography, technetium-99m sestamibi imaging and low dose dobutamine echocardiography (LDDE). **METHODS:** A systematic review of all reports on prediction of functional recovery after revascularization in patients with chronic coronary artery disease (published between 1980 and March 1997) revealed 37 with sufficient details for calculating the sensitivity and specificity of each imaging modality. From the pooled data, 95% and 99% confidence intervals were also calculated. **RESULTS:** Sensitivity for predicting regional functional recovery after revascularization was high for all techniques. The specificity of both Tl-201 protocols was significantly lower ($p < 0.05$) and LDDE significantly higher ($p < 0.01$) than that of the other techniques. **CONCLUSIONS:** Pooled analysis of 37 studies showed that although all techniques accurately identify segments with improved contractile function after revascularization, the Tl-201 protocols may overestimate functional recovery. The evidence available thus far indicates that low dose dobutamine echocardiography appears to have the highest predictive accuracy.

SPECT (Single Photon Emission Computer Tomographic imaging)

J Nucl Cardiol. 1999 Jul-Aug;6(4):389-96. Related Articles,

Comparison of exercise, dipyridamole, adenosine, and dobutamine stress with the use of Tc-99m tetrofosmin tomographic imaging.

Levine MG, Ahlberg AW, Mann A, White MP, McGill CC, Mendes de Leon C, Piriz JM, Waters D, Heller GV. Nuclear Cardiology Laboratory, Hartford Hospital, Conn. 06102-5037, USA.

PURPOSE: The purpose of this study was to compare defect extent and severity and myocardial uptake with exercise and pharmacologic stress with technetium-99m (Tc-99m) tetrofosmin tomographic myocardial perfusion imaging. **BACKGROUND:** Detection of stress-induced myocardial perfusion defects depends on both a disparity in blood flow between normal and stenotic vessels and the extraction fraction and linearity of myocardial uptake of the tracer. There are limited clinical data for exercise or pharmacologic stress with Tc-99m tetrofosmin tomographic myocardial perfusion imaging. **METHODS:** Thirty-one patients with coronary artery disease and 7 with a $< 5\%$ likelihood of coronary artery disease underwent on separate days Tc-99m tetrofosmin single-photon emission computed tomographic imaging at rest and after exercise, dipyridamole, adenosine, and dobutamine stress. Images were interpreted by a blinded consensus of 3 experienced readers with a 17-segment model and 5-point scoring system. **RESULTS:** Compared with exercise, the summed stress score was smaller with dipyridamole ($P < .01$), and the reversibility score was smaller with both dipyridamole ($P < .01$) and dobutamine ($P < .05$), whereas the number of abnormal and reversible segments was less with both dipyridamole ($P < .01$ and $P < .001$, respectively) and dobutamine both $P < .05$. No significant differences were found in the summed stress or reversibility scores and the number of abnormal or reversible segments between exercise and adenosine. **CONCLUSIONS:** Compared with exercise, defect extent, severity, and reversibility are less with dipyridamole and dobutamine with Tc-99m tetrofosmin single photon emission computed tomographic imaging.

Heart. 1998 Oct;80(4):370-6. Related Articles, Links

Selection of the optimal stress test for the diagnosis of coronary artery disease.

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OBJECTIVE: To compare the value and limitations of exercise testing, dipyridamole echocardiography, dobutamine-atropine echocardiography, and MIBI-SPECT (technetium-99m methoxyisobutyl nitrile single photon emission computed tomography) during dobutamine infusion in the diagnosis of coronary artery disease. **DESIGN:** The performance of these four tests was assessed in random order on a consecutive cohort of patients. The presence or absence of coronary artery disease was confirmed by coronary angiography. **SETTING:** Two tertiary care and university centres. **PATIENTS:** 102 consecutive patients with chest pain and no previous history of coronary artery disease. Ten patients with left bundle branch block were excluded for further analysis of exercise testing and scintigraphy results. **RESULTS:** MIBI-SPECT was the most sensitive (87%) but the least specific test (70%). Exercise stress testing had a sensitivity of 66%, which increased to 80% when patients with inconclusive results were excluded. Dipyridamole and dobutamine echocardiography had similar sensitivity (81%, 78%) and specificity (94%, 88%). All four tests had similar accuracy and positive and negative predictive values. Agreement between the echocardiographic techniques was excellent (detection of coronary artery disease 87%, kappa = 0.72; regional analysis 93%, kappa = 0.72; diagnosis of the "culprit" vessel 95%, kappa = 0.92), and it was good between echocardiographic techniques and MIBI-SPECT (diagnosis of the culprit vessel 90%, kappa = 0.84 with dobutamine and 92%, kappa = 0.85 with dipyridamole). **CONCLUSIONS:** Exercise stress testing has a sensitivity comparable to other tests in patients capable of exercising and with no basal electrical abnormalities. The greatest sensitivity is offered by MIBI-SPECT and the greatest specificity is obtained with stress echocardiography. Redundant information is obtained with dipyridamole echocardiography, dobutamine echocardiography, and MIBI-SPECT.

Nucl Med Commun. 2001 Dec;22(12):1305-11. Related Articles,

Assessment of adenosine, arbutamine and dobutamine as pharmacological stress agents during (99m)Tc-tetrofosmin SPECT imaging: a randomized study.

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We evaluated the use of adenosine, dobutamine and arbutamine with (99m)Tc-tetrofosmin myocardial perfusion imaging. Forty patients under investigation for suspected coronary artery disease were recruited. Each had a resting scan and two separate stress scans on different days, in a randomized cross-over study. Resultant images were blindly reported in 13 segments per scan as normal, reversible or fixed defects. A score was given (0-3) for segmental defect severity. Haemodynamic responses were as expected for each agent. Subjective side effect scores did not differ overall between agents. Adenosine caused a significantly higher incidence of abnormal taste (54%) than dobutamine and arbutamine (both 23%) and a lower incidence of palpitations (25% vs 69% and 54%, respectively), all $P < 0.05$. Arbutamine caused significantly more chest pain than adenosine (77% vs 46%) though less flushing (35% vs 68%), both $P < 0.05$. Comparison of the results obtained showed highly significant levels of segmental agreement for visual and semi-quantitative analysis between adenosine and arbutamine, kappa value and correlation coefficient of 0.78 and 0.86, respectively, dobutamine and adenosine 0.69 and 0.78, and arbutamine and dobutamine 0.75 and 0.78, all $P < 0.0001$. Adenosine, arbutamine and dobutamine differ in their haemodynamic response and side effect profile but provide highly comparable results during (99m)Tc SPECT imaging.

DRUG CONSULTS

PHARMACOLOGIC AGENTS USED IN STRESS ECHOCARDIOGRAPHY

- PATIENT DATA/BACKGROUND:
- Echocardiography is a noninvasive test that employs ultrasound to visualize internal cardiac structures and assess hemodynamics to assist in the diagnosis and prognosis of cardiovascular disorders. In order to properly evaluate myocardial ischemia, the heart must be placed under stress during echocardiographic imaging. This can be accomplished through exercise or pharmacologic means. Typical endpoints for stress echocardiography include reaching 85% of the maximum predicted heart rate, new wall motion abnormalities, sustained arrhythmias or intolerable adverse effects. Pharmacologic agents used in stress echocardiography include dobutamine, dipyridamole, adenosine and atropine.
- RESPONSE:
- I: DOBUTAMINE:
- A. SUMMARY
- (1) As a beta-1 agonist, dobutamine simulates physical exercise by causing an increase in heart rate, blood pressure, contractility, wall stress, and oxygen demand. In ischemic myocardium, the resulting decrease in oxygen supply creates dysfunction that is detected by echocardiography as a wall motion abnormality. Dobutamine stress echocardiography (DoSE) is useful in the evaluation of patients with coronary artery disease (CAD), chest pain syndromes, in the prognosis of post-myocardial infarction (MI), for the diagnosis of coronary artery stenosis, in predicting myocardial viability after an ischemic insult, to assess hibernating myocardium following revascularization procedures, to detect viable myocardium and to predict improvement in contractile function after revascularization in patients with CAD and reduced left ventricular function, and in preoperative risk stratification, especially for patients undergoing surgery for aortic aneurysms or peripheral vascular disease (Senior et al, 1998; Afridi et al, 1997; Smart et al, 1997a; Shaw et al, 1996; Elhendy et al, 1996a; Wu et al, 1996; Chan et al, 1995; Vanoverschelde et al, 1995; Davila-Roman et al, 1993; McNeill et al, 1992; Marcovitz & Armstrong, 1991; Barilla et al, 1991; Anon, 1988). DoSE also appears to be an accurate method for diagnosis of vascular compromise in patients after coronary artery bypass grafting and provides useful information for selection of patients for whom coronary angiography may be indicated (Elhendy et al, 1996). In addition, DoSE appears to be an effective method for detection of cardiac allograft vasculopathy in heart transplant recipients. DoSE may be useful in providing short- and long-term prognostic information and identifying patients at high risk of cardiac events or mortality following heart transplantation, MI, and in patients with CAD (Spes et al, 1996; Akosah et al, 1996; Nagueh & Zoghbi, 1996). Although observer bias is possible in the clinical setting, it is unlikely to cause significant error in the interpretation of DoSE results (Tighe et al, 1997).
- (2) Normal as well as fixed-negative DoSE results were associated with an excellent long-term prognosis in terms of "hard" cardiac events and cardiac mortality in a retrospective review of all DoSE procedures performed at one institution between 1992 and 1994. Among 171 subjects with normal DoSE results, the per-patient per-year incidences of myocardial infarction and cardiac death were 1.5% and 0.13%, respectively. The 53 patients with fixed-negative DoSE results (abnormal segmental resting echocardiogram with no new or worsening abnormalities under dobutamine stress) exhibited corresponding incidences of 0.7% and 0%, respectively. "Soft" cardiac events (ie, cardiac-related hospitalizations, revascularization procedures) occurred with 9.7% and 17.5% per-patient per-year incidences in the normal and fixed-negative DoSE groups, respectively (Dhond et al, 1999).
- B. DOSING
- (1) Dobutamine intravenous (IV) infusions are administered in a stepwise fashion starting with 5 to 10 micrograms/kilogram/minute (mcg/kg/min) for 3 minutes and increasing by 10 mcg/kg/min every 3 minutes to a maximum of 30 to 50 mcg/kg/min (Hennessy et al, 1998, Wang et al, 1998; Ho et al, 1998, Geleijnse et al, 1998; Derumeaux et al, 1998). One study used 5-minute stages instead of the usual 3 minutes at each dose level (Akosah et al, 1998). If sufficient heart rate is not attained, negative results on DoSE are not interpretable (Ballal et al, 1997).
- (2) Atropine has been added in some patients in order to achieve maximal heart rate and improve diagnostic sensitivity and accuracy (Poldermans et al, 1998; Sicari et al, 1997; Williams et al, 1996; Ling et al, 1996; Chan et al, 1995; Vanoverschelde et al, 1995; Davila-Roman et al, 1993). As an alternative to atropine, some investigators have safely extended the final stage (peak dose) of the dobutamine protocol from 3 minutes to 5 minutes (Weissman et al, 1997). In patients unable to receive atropine, isometric exercise during DoSE may provide another method for achieving target heart rate. Isometric exercise at peak dose dobutamine was effective in 29% of patients (Chauvel et al, 1998).
- (3) A low-dose dobutamine protocol consisting of 5 mcg/kg/min and 10 mcg/kg/min for 5 minutes each has been used in the early post-MI period (Leclercq et al, 1997), in the setting of moderate to severe heart failure (Pagano et al, 1998) and in patients with chronic CAD (Pace et al, 1998).
- (4) Equivalent diagnostic accuracy was demonstrated in a retrospective comparison of three dosing protocols (n=1090): 5-minute stages up to 30 mcg/kg/min, 3-minute stages up to 40 mcg/kg/min and 3-minute stages up to 40 mcg/kg/min with atropine as needed. Corresponding diagnostic accuracy rates were 86%, 84%, and 84%, respectively (p = NS). Complication rates also did not differ significantly between groups. In general, more aggressive dosing protocols gain a degree of sensitivity while sacrificing a similar degree of specificity as compared to less aggressive dosing protocols (Takeuchi et al, 1999).

- (5) In a new accelerated dosing protocol for diagnostic DoSE, dobutamine is administered by continuous infusion at 50 micrograms/kilogram/minute until a study endpoint is reached, or for a maximum of 10 minutes. Significant dose- and time-sparing benefits were evident with the continuous infusion versus the standard stepwise incremental regimen. Although adverse effects did not differ between dosing regimens, comparative diagnostic accuracies were not assessed in this preliminary study (Burger et al, 2000).
- (6) In studies of pediatric populations, initiation doses range from 0.5 to 5 mcg/kg/min, while maximum doses range from 5 to 50 mcg/kg/min (Larsen et al, 1998; De Wolf et al, 1998; Noto et al, 1996).
- C. SAFETY/ADVERSE EFFECTS
- (1) Minor ventricular arrhythmias are frequent with dobutamine echocardiographic studies, occurring in 13% to 31% of patients. Ventricular premature beats are reported in 10% to 19% of patients, ventricular bigemini and couplets in 7% to 14%, and nonsustained ventricular tachycardia in 1% to 6% (Chauvel et al, 1996; Poldermans et al, 1994; Mertes et al, 1993; Mazeika et al, 1993; Davila-Roman et al, 1993; Previtali et al, 1993; Cohen et al, 1991; Previtali et al, 1991). Sustained ventricular tachycardia or ventricular fibrillation are rare, but have been reported at higher doses (ie, 40 to 50 mcg/kg/min) (Poldermans et al, 1994; Mertes et al, 1993). Pre-existing evidence of frequent or repetitive ventricular arrhythmias during Holter monitoring or exercise stress testing should be considered a marker of increased risk of ventricular arrhythmias, particularly in patients with left ventricular dysfunction (Bigi et al, 1995). The incidence of tachyarrhythmias in one study was 13%; independent predictors included higher resting wall motion score index and male gender (Elhendy et al, 1999). Transient atrioventricular block (occurring in 4% of 302 DoSE tests) was characterized as Mobitz I block (n=6) and Mobitz II block (n=6). Coronary artery disease was confirmed in all subjects with DoSE-induced Mobitz II block (Hung et al, 1999).
- (2) Based on a prospective evaluation of over 3000 consecutive DoSE tests at a single institution, major complications (sustained ventricular tachycardia, MI) occur rarely (0.3% incidence rate). No deaths or ventricular fibrillation were reported. The overall incidence of arrhythmias was 15%: minor ventricular ectopic beats (8%), nonsustained ventricular tachycardia (2.4%), supraventricular tachycardia (1.8%), and atrial fibrillation (1%). The most frequent cardiovascular complication was hypotension (7%). Nausea (1.8%) and shortness of breath (0.6%) were the most common noncardiac adverse effects. These data demonstrate that DoSE is remarkably safe and well-tolerated (Secknus & Marwick, 1997). Other large series (total n=1474) confirm the overall safety of DoSE (Hennessy et al, 1997; Zahn et al, 1996).
- (3) The incidence of procedure-limiting adverse effects was 4% in a prospective evaluation of over 4000 consecutive DoSE tests at a single institution (1991 to 1998). Major cardiac complications occurred in 0.25%, including ventricular fibrillation (n=1), myocardial infarction (n=1), and sustained ventricular tachycardia (n=8). No deaths were attributed to DoSE in this series. The most common minor events were chest pain (11%), hypotension (5%), nausea (4%), hypertension (2%), headache (2%), and shivering (1%) (Mathias et al, 1999).
- (4) DoSE is generally safe in patients with hypertension (Elhendy et al, 1997), in the early post-MI period (Bigi et al, 1995) and in the presence of left ventricular apical thrombus (Cusick et al, 1997). DoSE appears to be safe in patients with atrial fibrillation (AF); however, patients with AF may have an increased chronotropic response compared with patients in sinus rhythm (Hobday et al, 1998). DoSE (up to 50 micrograms/kilogram/minute) appears to be well tolerated and safe in middle-aged (less than 65 years old), elderly (65 to 79 years old), and very elderly (more than 80 years old) patients (Chenzbraun et al, 1999).
- (5) Hypotension occurs in 14% to 38% of patients undergoing DoSE. The mechanism of hypotension may be related to a decrease in systemic vascular resistance (peripheral vasodilation), a decrease in cardiac output, and left ventricular cavity obliteration (Heinle et al, 1995; Tanimoto et al, 1995; Marcovitz et al, 1993; Mazeika et al, 1992; Rosamond et al, 1992). In one study, hypotension occurred in 28% of patients (n=412). Hypotension was more common in women than men (36% vs 24%, p=0.01), in older adults (p=0.004), in patients with a higher baseline blood pressure (p less than 0.0001), and in patients taking diuretics (p=0.025) or ACE-inhibitors (p=0.01). Hypotension was not related to the use of beta-blockers, calcium channel blockers, digoxin, nitrates, left ventricular dimensions, or ejection fraction (Khanal et al, 1998a). Hypotension, defined as systolic pressure reduction of at least 20 mmHg, was an independent predictor of mortality in a subset of patients with poor ejection fraction in the early post-myocardial infarction period (Wang et al, 1999). Profound hypotension, defined as a drop of at least 50 mmHg, is infrequent (3% incidence) and may indicate a greater risk of subsequent cardiac events (Dhond et al, 2000).
- D. THERAPEUTIC USES
- 1. KNOWN/SUSPECTED CAD, CHEST PAIN
- (a) The overall sensitivity and specificity of DoSE for detection and localization of CAD ranges from 70% to 94% (Ho et al, 1998; Hennessy et al, 1997b; Wu et al, 1996; Elhendy et al, 1996a; Hansen & Segar, 1996; Shahi et al, 1996; Chan et al, 1995), although relatively low (50% to 52%) specificities have been reported (Hennessy et al, 1998; Steinberg et al, 1997). In a comprehensive overview of 28 studies using DoSE for suspected CAD (total n=2246), the average sensitivity was 80% (95% confidence interval: 78% to 82%) and the average specificity was 84% (95% confidence interval: 82% to 86%) (Geleijnse et al, 1998). The sensitivity of DoSE increases in relation to the severity and proximal location of the lesion (Tousoulis et al, 1999; Ho et al, 1997; Shahi et al, 1996). Transesophageal DoSE was associated with a relatively high specificity (96%) in patients with known CAD (Shahi et al, 1996).
- (b) Two studies demonstrated the long-term prognostic value of DoSE in subjects with known or suspected CAD. With an average of 3 years follow-up (n=1659), the risk of cardiac death or infarction increased significantly among subjects with stress-induced ischemia or extensive wall motion abnormalities at rest. Corresponding hazard ratios were 3.3 (95%

confidence interval, 2.4 to 4.4) and 1.9 (95% CI, 1.3 to 2.6) as compared to normal DoSE results, respectively (Poldermans et al, 1999). One-year follow-up (n=1183) revealed greater risk of subsequent cardiac events with positive versus negative DoSE results (34% and 10% incidence, respectively, p less than 0.001). This study also found that wall-motion abnormalities at rest were highly predictive of future cardiac events (Krivokapich et al, 1999).

- (c) In a review of 860 DoSE tests performed in 1991 to 1992 with average follow-up of 24 months, 10% went on to experience a cardiac event. Of that 10%, 86% had an abnormal DoSE at baseline. The rate of cardiac events in subjects with a normal DoSE was 4%. In addition to history of heart failure, the independent predictors of cardiac events were the percentage of abnormal segments at peak stress (p less than 0.0005) and an abnormal left ventricular end-systolic volume (p less than 0.05). The event-free probability was significantly lower in those subjects who had ischemia or fixed wall motion defects during DoSE (Chuah et al, 1998).
- (d) An average 21-month follow-up of 200 subjects whose DoSE evaluation for chest pain was normal revealed a total of 2 cardiac deaths and 4 revascularizations. All 6 subjects had a high (at least 80%) pre-test probability of CAD. Three did not attain the desired heart rate during DoSE due to concomitant beta-blockers, possibly explaining the erroneous "normal" DoSE result (Geleijnse et al, 1998).
- (e) Dobutamine-induced ST-segment elevation during DoSE has occurred in 30% to 50% of patients with a previous myocardial infarction (MI). In patients without a previous MI, ST-segment elevation during DoSE has been reported in 3% to 6% of patients (Lanzarini et al, 1996; Elhendy et al, 1995; Mairesse et al, 1994; Previtali et al, 1993a; Mazeika et al, 1992a); however, in 1 report ST elevation occurred in 22% of patients without a previous MI (Coma-Canella, 1991). In patients without a previous MI, ST elevation during DoSE is a specific marker of severe reversible ischemia in the region corresponding to the site of ST elevation (Previtali et al, 1998a).
- (f) DoSE findings were strongly predictive of subsequent cardiac events in subjects (n=121) evaluated for suspected CAD and followed for 15 months on average. The strongest independent predictor of morbidity and mortality was wall motion score index at peak stress. Event-free survival was 11% and 53% in patients with and without inducible ischemia during DoSE, respectively. The yearly cardiac event rate in patients with a normal DoSE was 1.8% (Senior et al, 1997).
- (g) The prognostic value of DoSE persisted for 5 years in a long-term, prospective study of 120 consecutive patients (99% male) being evaluated for chest pain. Of 78 patients with positive results, the incidences of overall mortality and coronary bypass grafting were 28% and 37%, respectively; significantly worse than the 9.5% incidence for each outcome seen in patients with negative tests. All cardiac-related deaths (n=7) occurred in the group with positive DoSE results (Steinberg et al, 1997).
- (h) Negative results of transesophageal DoSE were associated with 97% and 93% event-free survival for 12 and 22 months, respectively (n=46 men at high risk for CAD). The image quality for wall motion changes is enhanced with transesophageal as opposed to transthoracic echocardiography (Kamalesh et al, 2000). In individuals with poor acoustic windows, transesophageal was superior to transthoracic DoSE. The transesophageal technique permitted adequate visualization of virtually all left ventricular (LV) segments, providing 88% sensitivity and 100% specificity. In contrast, transthoracic echocardiography visualized 76% of LV segments, lowering sensitivity and specificity to 75% (Chaudhry et al, 2000).
- (i) In two studies of patients with left bundle branch block, DoSE elicited high overall specificities (91% to 96%) and lower sensitivities (68% to 88%) for diagnosis of suspected CAD. Diagnostic accuracies were in the range of 84% to 93% (Geleijnse et al, 2000; Yanik et al, 2000).
- (j) DoSE demonstrated sensitivity, specificity and accuracy of 85%, 87%, and 86%, respectively, in detecting CAD in patients with left ventricular hypertrophy. Concentric remodeling, defined as increased wall thickness and normal mass, was a significant multivariate predictor of a false-negative result; sensitivity in this subset was only 36% (Smart et al, 2000).
- (k) Severe worsening of regional function (by at least two grades in at least one segment) during diagnostic DoSE was associated with statistically greater average numbers of stenotic arteries (2.31 versus 1.97, p=0.04), stress perfusion defects (3.8 versus 2.8, p=0.0009), rest perfusion defects (3 versus 2, p=0.001), and incidence of left anterior descending CAD (95% versus 73%, p=0.01) compared to mild worsening of regional function, respectively (Elhendy et al, 2000a).
- 2. POST-MI
- (a) In the early post-MI period (4 days to 2 weeks), DoSE has demonstrated prognostic value in terms of predicting functional recovery (Leclercq et al, 1997; Afridi et al, 1996) and adverse cardiac events (Wang et al, 1998; Previtali et al, 1998; Smart et al, 1997; Carlos et al, 1997). Positive DoSE results are associated with a higher rate of all cardiac events (cardiac mortality rate, reinfarction, and unstable angina) than negative results in patients with acute and chronic MI (Cherng et al, 1998). The overall sensitivity and specificity of DoSE in this setting ranges from 42% to 97% (Hoffer et al, 1999; Ricci et al, 1997; Leclercq et al, 1997; Smart et al, 1997); although a very low sensitivity (22%) has been reported (Smart et al, 1997). A positive DoSE result is an independent predictor of all cardiac events after acute and chronic MI, whereas a negative DoSE finding is associated with a low likelihood of subsequent cardiac events (Salustri et al, 1999; Cherng et al, 1998). Other independent predictors of hard cardiac endpoints (MI or death) include the extent of ischemic myocardium and angina during DoSE (Previtali et al, 1998); ischemic wall motion score index (a measure of stress/rest variation in wall motion) (Salustri et al, 1999); peak stress wall motion score index (a measure of left ventricular dysfunction at peak stress) and ischemic threshold in patients with Q-wave and non-Q-wave infarcts, respectively (Wang et al, 1998; Sicari et al, 1997). Myocardial viability (improved regional function with dobutamine) was associated with an increased incidence of cardiac events (Sicari et al, 1997), especially when occurring with ischemia (Previtali et al, 1998). When DoSE was performed after thrombolytic treatment of acute MI, improved wall motion score index demonstrated 84% accuracy at predicting functional

improvement during an average 18 months of follow-up (Samad et al, 1999). DoSE has also been efficacious in detecting residual artery stenosis (Smart et al, 1997) and multivessel disease (Smart et al, 1997; Carlos et al, 1997).

- (b) Dobutamine-induced ST-segment elevation was associated with larger infarct size and dyskinesia in the infarct area (Lanzarini et al, 1996), as well as with resting wall motion abnormalities (Ricci et al, 1997). ST-segment elevation during DoSE exhibited 74% accuracy at predicting functional recovery in the early post-MI period. This study also found that a biphasic response to dobutamine stress was an independent predictor of functional recovery (Pierard et al, 1999). Reversible contractile dysfunction, defined as improved wall motion with dobutamine stress, had high (78% to 86%) sensitivity, specificity, and predictive values for functional recovery. The positive predictive accuracy in hypokinetic segments (73%) was significantly higher than in akinetic segments (21%) (Leclercq et al, 1997).
- (c) A biphasic response to dobutamine stress (improvement at low dose, worsening at high dose) was predictive of residual infarct artery stenosis, while wall motion abnormalities outside the infarct area accurately detected multivessel disease (Smart et al, 1997). Adverse cardiac outcomes were associated with significantly higher resting wall motion abnormalities, fewer dobutamine-responsive segments and greater likelihood of remote ischemia (suggestive of multivessel disease) (Carlos et al, 1997).
- (d) Event-free survivals following non-Q-wave MI were 61% and 85% after 14 months among those with positive and negative DoSE findings, respectively (p less than 0.0001) (Wang et al, 1998), while 15-month event-free survivals were 90% for those with both viability and ischemia on DoSE and 100% for those without both findings after an initial MI (Previtali et al, 1998). A large international study ($n=778$) failed to find any overall difference in cardiac endpoints during the 9 months following initial MI among those with and without dobutamine-inducible ischemia (Sicari et al, 1997).
- (e) DoSE-induced T-wave changes in the early post-Q-wave-MI period failed to reliably predict myocardial viability (De Felice et al, 1999). The presence of positive T-waves 1 year or more after Q-wave MI may indicate greater regional viability versus negative T-waves. As assessed by DoSE, 11 of 13 patients with positive T-waves experienced wall motion improvement versus zero of 17 with negative T-waves (p less than 0.001) (Watanabe et al, 2000).
- (f) Three days after acute MI with successful revascularization ($n=157$), DoSE predicted early and late functional recovery and reversible dysfunction with 81% to 89% accuracy (Bolognese et al, 2000). When DoSE was performed an average of 21 days post-MI in 68 patients with residual stenosis of the infarct-related artery, its sensitivity and specificity were 83% and 82%, respectively, for predicting recovery following delayed (average 28 days post-MI) revascularization (Monin et al, 1999).
- (g) With F18-fluorodeoxyglucose SPECT imaging as the reference method, longitudinal pulsed-wave Doppler tissue sampling during DoSE improved sensitivity from 75% to 87% (p less than 0.005) but not specificity (51% to 52%) over DoSE alone in identifying viable myocardium in a study of 40 patients with CAD and LV dysfunction (mean ejection fraction: 33%) (Rambaldi et al, 2000).
- 3. LEFT VENTRICULAR DYSFUNCTION
- (a) DoSE was 60% to 86% sensitive and specific in the assessment of patients with left ventricular (LV) dysfunction (average ejection fraction of 25% to 33%) (Pagano et al, 1998; Belardinelli et al, 1998; Elhendy et al, 1996a).
- (b) DoSE is an accurate method for detection of significant coronary artery stenosis in symptomatic patients with regional LV dysfunction after MI. Sensitivity was higher in multivessel disease (82% to 85%) than in single vessel disease (66%). Sensitivity was also higher in the presence of mild to moderate wall motion abnormalities (73%) than in the setting of normal wall motion (53%) or severe wall motion abnormalities (56%) (Elhendy et al, 1996a).
- (c) Several studies attest to the prognostic value of DoSE in LV dysfunction. Inducible ischemia and reduced LV ejection fraction at peak dobutamine dose were independent predictors of "hard" cardiac events in 350 subjects with moderate to severe LV dysfunction (Smart et al, 1999). A positive contractile response to dobutamine indicated hibernating myocardium and effectively predicted left ventricular functional capacity gained after exercise training (Belardinelli et al, 1998). In patients with severe CAD and LV dysfunction, detection of viable or ischemic myocardium using DoSE was associated with an increased incidence of cardiac events and an adverse long-term outcome compared with those without viability or ischemia. These findings were independent of age and ejection fraction (Williams et al, 1996). Patients with CAD and severe LV dysfunction (LV ejection fraction less than 35%) who demonstrated myocardial viability during DoSE and were revascularized had significantly ($p=0.01$) improved survival compared with those who were not revascularized, but were treated medically. Revascularization did not improve survival in patients without preoperative evidence of myocardial viability (Afridi et al, 1998). Similar results were reported in another study ($n=87$) in which myocardial viability of at least 5 segments with subsequent revascularization was strongly predictive of reduced mortality (by 93% on average) (Senior et al, 1999).
- (d) Preoperative DoSE is useful in identifying which patients are likely to have improved LV function following revascularization. A smaller end-diastolic volume and fewer wall motion abnormalities indicated a higher likelihood of functional recovery. Reversible LV dysfunction after revascularization is associated with the maintenance of significant inotropic reserve in the area of dysfunction, the severity of LV dilation and remodeling, and the magnitude of the perfusion defect at peak exercise (Vanoverschelde et al, 1995).
- (e) DoSE successfully distinguished reversible atrial fibrillation-induced LV dysfunction from idiopathic dilated cardiomyopathy ($n=13$). Eight patients experienced significantly improved ejection fraction and wall motion score index with low-dose dobutamine; no signs or symptoms of LV dysfunction were evident during post-cardioversion follow-up. In contrast, dobutamine stress did not affect ejection fraction and wall motion score index in five patients. They were diagnosed

with dilated idiopathic cardiomyopathy after cardioversion failed to improve LV function. The 100% sensitivity and specificity observed in this small series for predicting functional recovery after cardioversion requires further confirmation (Paelinck et al, 1999). Another small study also found that improvement in ejection fraction and wall motion during DoSE was predictive of subsequent LV systolic functional improvement in 18 patients with dilated cardiomyopathy (Kitaoka et al, 1999). In recent-onset idiopathic dilated cardiomyopathy (n=26), increased left ventricular ejection fraction during DoSE correlated with functional improvement 6 months later (Naqvi et al, 1999).

- (f) A blunted response to DoSE in terms of heart rate and contractility was diagnostic of Chagas' disease, despite angiographic evidence of normal coronary arteries and no overt signs or symptoms of LV dysfunction. Beta-receptor insensitivity or down-regulation (due to autoantibody production) coupled with impaired coronary microcirculatory reserve might explain the blunted response in Chagas' disease (Acquatella et al, 1999).
- (g) With F18-fluorodeoxyglucose SPECT imaging as the reference method, longitudinal pulsed-wave Doppler tissue sampling during DoSE improved sensitivity from 75% to 87% (p less than 0.005) but not specificity (51% to 52%) over DoSE alone in identifying viable myocardium in a study of 40 patients with CAD and LV dysfunction (mean ejection fraction: 33%) (Rambaldi et al, 2000).
- 4. AORTIC REGURGITATION
- (a) Low-dose DoSE may aid in predicting the clinical outcome of patients following aortic valve replacement for aortic regurgitation by accentuating the differences in ventricular size and function between those patients with and without subsequent complete recovery following valve surgery. In this study involving 16 patients with chronic aortic regurgitation, dobutamine was infused at 7.5 micrograms/kilogram/minute. Baseline (preoperative) left ventricular end-systolic dimensions (LVESD) were smaller (22.4 vs 29.9 mm/m(2); p less than 0.05) and left ventricular ejection fraction (LVEF) higher (53% vs 37%; p less than 0.01) in patients with complete recovery following valve surgery than patients without complete recovery. Following infusion of dobutamine, differences in ventricular size and function were augmented between patients with and without complete recovery (LVESD 18.9 vs 28.8 mm/m(2), p=0.004; LVEF 61% vs 41%, p less than 0.0008, respectively). Assessment of left ventricular contractile reserve using low-dose dobutamine (ie, increase in LVEF during dobutamine infusion) improves the diagnostic predictability of the preoperative evaluation and aids in the discrimination between patients with and without complete recovery after surgery (Tam et al, 1999).
- 5. POST-CARDIAC TRANSPLANTATION
- (a) The long-term outcome of cardiac transplants is sometimes limited by accelerated CAD, which is of unclear etiology, marked by diffuse myointimal hyperplasia, and often clinically silent until well-advanced. DoSE is useful in providing short- and long-term prognostic information and identifying patients at high risk of cardiac events or mortality following cardiac transplantation. Some experts consider DoSE the test of choice to screen for allograft CAD (Akosah & Mohanty, 1998; Akosah et al, 1998).
- (b) Dobutamine-induced abnormal wall motion was associated with a high risk for major cardiac events or mortality, even in patients with angiographically normal coronary arteries. A negative result from DoSE appears to be an important predictor for a good long-term (2 years) prognosis in heart transplant patients (Akosah et al, 1996). In a study of 22 new cardiac transplant recipients evaluated with serial DoSE beginning 2 months post-transplant, 50% had persistent wall motion abnormalities. Of those 11 patients, 73% developed cardiac events. No events or deaths occurred in subjects with normal or transient wall motion abnormalities on DoSE (Akosah et al, 1998). Another group of investigators suggested that serial DoSE may replace routine serial angiograms in cardiac transplant patients with normal DoSE results. In a series of 37 subjects, DoSE performed at the same time as angiography yielded sensitivities and specificities of 65% and 95%, respectively, at an average 37 months post-transplant, and 92% and 73%, respectively, at an average 56 months post-transplant (Derumeaux et al, 1998). Data from 109 cardiac transplant recipients also support the value of serial DoSE for routine monitoring. With an average between-test interval of 11.6 months, serial DoSE exhibited a high 96% negative predictive value. The relative risk of cardiac events was 7.26 for individuals with deteriorating versus normal DoSE results (Spes et al, 1999).
- (c) In a review of 3 studies (total n=124) of the accuracy of DoSE in the detection of transplant-associated accelerated CAD, the sensitivity ranged from 79% to 95%, specificity from 55% to 95%, with a high negative predictive value of 91% to 92%. Another 3 studies (total n=162) assessed DoSE's prognostic value over 8 to 32 months average follow-up. Only 1% of subjects with a negative DoSE went on to experience a cardiac event, whereas 39% of subjects with a positive DoSE experienced a cardiac event. The authors concluded that all cardiac transplant recipients should undergo an early (within the first year) baseline angiogram. Asymptomatic patients should be evaluated with serial DoSE. Those with negative DoSE results need not undergo routine cardiac catheterization. However, subjects with persistent wall motion abnormalities on DoSE are at higher risk of cardiac events, necessitating close monitoring and further evaluation, particularly if the wall motion score index is equal to or greater than 1.7 (Akosah & Mohanty, 1998).
- 6. PRE-LIVER TRANSPLANTATION
- (a) According to the results of 1 study, DoSE is effective for detection of CAD and is useful for preoperative cardiac risk stratification in patients undergoing orthotopic liver transplantation. In this study, abnormal DoSE results, based on wall motion abnormalities, were associated with a sensitivity, specificity, and positive and negative predictive value of 100% (Plotkin et al, 1998).
- 7. PRE-RENAL TRANSPLANTATION
- (a) In a study of 50 renal transplant candidates, the accuracy of DoSE was 62% and 72% for detection of coronary artery stenosis of at least 50% and greater than 70%, respectively. With long-term follow-up (average 22.5 months), the combined

endpoint of cardiac death, myocardial infarction or revascularization occurred in 55% and 20% of individuals with positive and negative DoSE results, respectively ($p=0.01$) (Herzog et al, 1999).

- 8. ORGAN DONATION

- (a) Preliminary data suggest a possible role for DoSE in evaluating the reversibility of myocardial dysfunction in brain-dead donor heart candidates. Of 7 individuals with left ventricular fractional shortening of less than 30% at the time of brain death, systolic function normalized at 7 days in the 3 patients with DoSE-responsive wall motion improvement (Kono et al, 1999).

- 9. NON-TRANSPLANT SURGERIES

- (a) DoSE conducted prior to non-vascular surgery in 530 patients with known or suspected CAD demonstrated 100% sensitivity and 63% specificity in predicting postoperative cardiac events. Significant multivariate predictors included history of congestive heart failure (odds ratio (OR): 4.7) and ischemia at less than 60% of age-predicted maximum heart rate (OR: 7). Ischemia occurring at higher thresholds (at least 60% of maximal heart rate) was associated with moderate risk, while no ischemia was consistent with low risk (0% incidence of postoperative cardiac events) (Das et al, 2000).
- (b) Resting wall motion abnormalities and hypotensive response to DoSE performed prior to vascular and noncardiac thoracic surgery in 300 patients were significant multivariate predictors of perioperative cardiac events according to a retrospective review. The associated odds ratios were 4.7 ($p=0.005$) and 4.1 ($p=0.002$), respectively (Day et al, 2000).
- (c) Transesophageal DoSE (5 micrograms/kilogram/minute for 5 minutes) after anesthesia induction and intubation for coronary artery bypass graft surgery effectively predicted functional recovery ($n=40$). Dobutamine-induced improvement in regional wall motion was associated with 88% and 94% positive predictive values for early (immediately after separation from bypass) and late (30 minutes after protamine reversal) functional recovery, respectively. The negative predictive value at both time-points was 70% (Aronson et al, 2000).

- 10. UNSTABLE ANGINA

- (a) DoSE exhibited safety and 81% prognostic accuracy when performed 48 hours after admission in 122 patients hospitalized for unstable angina who remained symptom-free during that time interval with medical treatment. Subjects with secondary or post-MI angina, heart failure, increased cardiac enzymes, T-wave inversion or other severe disease were excluded. Dobutamine was initiated at 10 micrograms/kilogram/minute (mcg/kg/min) and increased in intervals of 10 mcg/kg/min (with or without atropine as needed) until reaching a study endpoint. Facial paresthesia was the most common adverse event during DoSE (74%), but no serious or procedure-interrupting complications were noted. The 1-year event-free survival rates were 57% and 91% for subjects with positive and negative DoSE findings, respectively (p less than 0.0001) (Sitges et al, 2000).

- E. COMPARATIVE EFFICACY VERSUS OTHER DIAGNOSTIC TESTS

- 1. EXERCISE TESTING

- (a) DoSE has been shown to be more sensitive, specific, and accurate than treadmill exercise electrocardiographic (ECG) testing for the detection of CAD, with the ability to detect ischemia at an earlier stage. In direct comparative trials, DoSE's sensitivity ranged from 76% to 94%; DoSE's specificity ranged from 63% to 100%; exercise testing's sensitivity ranged from 40% to 76%; and exercise testing's specificity ranged from 29% to 79% (Hennessy et al, 1997c; Iwase et al, 1996; Senior et al, 1996; Wu et al, 1996; San Roman et al, 1996; Martin et al, 1992). DoSE was superior to exercise ECG in patients with underlying hypertension and following MI (Senior et al, 1996; Wu et al, 1996). One group of investigators note that conventional signs of myocardial ischemia, including left ventricular cavity dilation, ST segment depression, decreased ejection fraction, and ECG changes, occurred significantly more often with exercise than with dobutamine stress. Therefore, the assessment of ischemia during DoSE was based mainly on regional wall motion abnormalities (Attenhofer et al, 1996).
- (b) Low-dose DoSE (5 to 15 mcg/kg/min) was comparable to low-level bicycle exercise echocardiography in the early post-MI period ($n=52$). In predicting functional recovery, the sensitivity, specificity, positive and negative predictive values ranged from 73% to 95% for exercise echocardiography and from 84% to 92% for DoSE ($p=NS$) (Hoffer et al, 1999). Another study found equivalent sensitivity, specificity and accuracy with DoSE and bicycle stress echocardiography for the diagnosis of chest pain ($n=60$). Both were superior to heavy 2-arm isometric exercise echocardiography (Loimaala et al, 1999).

- 2. RADIONUCLIDE IMAGING

- (a) In direct comparative trials, DoSE and thallium-201 single photon emission tomography (SPECT) have similar sensitivities (49% to 95% for DoSE versus 71% to 92% for thallium-201 SPECT) and specificities (77% to 95% for DoSE versus 56% to 98% for thallium-201 SPECT) (Previtali et al, 1999; Elsasser et al, 1998; Ho et al, 1997b; Macieira-Coelho et al, 1997; Vanovershelde et al, 1996; Kostopoulos et al, 1996; Takeuchi et al, 1996; Senior et al, 1995). One trial suggests the superiority of DoSE prior to revascularization (Smart et al, 1997b). In the early post-MI period, one study notes the superiority of thallium-201 imaging (Macieira-Coelho et al, 1997), while another reports improved specificity (88% versus 36%, p less than 0.001) and accuracy (84% versus 49%, p less than 0.001) in predicting myocardial viability with low-dose DoSE over thallium-201 SPECT scintigraphy (Anselmi et al, 2000). The preponderance of evidence, however, demonstrates comparable efficacy to predict functional recovery after revascularization (Lin et al, 2000; Elsasser et al, 1998; Vanovershelde et al, 1996; Senior et al, 1995); to detect CAD (Ho et al, 1997b; Takeuchi et al, 1996); to identify myocardial viability after MI (Le Feuvre et al, 1996); and to diagnose critical stenosis of the infarcted artery and multivessel disease post-MI treated with thrombolysis (Previtali et al, 1999). Concordance between DoSE and thallium-201 SPECT for segmental viability was 62% in 54 patients with ischemic cardiomyopathy (Amanullah et al, 1999), 76% in 17 patients with recent MI (Ozdemir et al, 2000), and 48% in 19 patients with recent MI (Anselmi et al, 2000). One trial suggests the

combination of low-dose dipyridamole and dobutamine is more sensitive and specific than thallium-201 imaging for identifying myocardial viability and predicting functional recovery after coronary revascularization in patients with a previous MI (Sicari et al, 1999).

- (b) In a study of 46 subjects with chronic CAD (prior MI in 85%), the combination of low-dose DoSE and rest-redistribution thallium-201 tomography was more accurate than either test alone. Because thallium tomography assesses cell integrity and DoSE assesses preserved contractile function, the two tests provide complementary information to predict functional recovery 30 days post-revascularization. The sensitivities and specificities of DoSE alone (52% and 87%) and thallium-201 tomography alone (76% and 74%) were inferior to the combination (78% and 87%). Accuracy increased from 70% with DoSE and 75% with thallium-201 tomography to 83% for both tests given on the same day (p less than 0.05) (Pace et al, 1998).
- (c) Dobutamine stress technetium-99m methoxyisobutyl isonitrile (MIBI) single-photon emission computed tomography (SPECT) and dobutamine stress echocardiography (DSE) have similar moderate sensitivity (56%) for the diagnosis of single-vessel coronary artery disease (CAD). There was a fair (76%) overall agreement between both methods on the diagnosis of myocardial ischemia. The mean number of ischemic segments was not different between both techniques. For detection of ischemia, the sensitivity, specificity, and accuracy of DSE and MIBI SPECT were 56%, 84%, and 67% and 56%, 73%, and 63%, respectively (p=NS, DSE vs MIBI SPECT). Sensitivity for both techniques was higher than electrocardiography (p less than 0.05). For both techniques, the sensitivity was significantly higher in patients with left anterior descending than in patients with left circumflex or right coronary artery stenosis (75% vs 40%, p less than 0.05). Diagnostic accuracy did not improve by use of the combination of both techniques for the diagnosis of single-vessel CAD compared with the accuracy of either technique alone. Dobutamine was administered to patients (n=91) with single-vessel CAD or without significant CAD starting at 5 micrograms/kilogram/minute (mcg/kg/min) and increasing to a maximum of 40 mcg/kg/min. Atropine (up to 1 milligram) was given to patients not achieving 85% maximal heart rate (Elhendy et al, 2000).
- (d) DoSE and methoxy-isobutyl-isonitrile (MIBI)-SPECT perfusion scintigraphy demonstrated similar sensitivity (91% and 94%), specificity (81% and 75%) and diagnostic accuracy (88% for both) in 50 patients with suspected CAD without prior MI. In 50 patients with a previous MI, the sensitivity of DoSE in detecting coronary artery stenosis was 63%, compared with 77% for MIBI-SPECT (Hoffmann et al, 1996). In a study of 84 hypertensive patients, DoSE and technetium-MIBI SPECT imaging demonstrated equivalent diagnostic efficacy in the evaluation of myocardial ischemia, in the presence or absence of left ventricular hypertrophy. The overall sensitivity, specificity, and accuracy for technetium-MIBI SPECT as compared to DoSE were 67% versus 73%, 83% versus 83%, and 70% versus 75%, respectively (Elhendy et al, 1998). Sensitivity, accuracy, positive and negative predictive values were statistically similar between technetium-MIBI SPECT and DoSE in the diagnosis of CAD in 101 patients with hypertension. DoSE offered superior specificity over MIBI SPECT (80% versus 36%, p less than 0.0006) (Fragrasso et al, 1999).
- (e) Technetium-sestamibi-SPECT was more sensitive than DoSE for the prediction of segmental recovery (87% versus 66%, p less than 0.001) and functional recovery (100% versus 71%, p less than 0.01) after revascularization post-MI. Specificity for both parameters did not differ statistically between tests. Akinetic or dyskinetic segments demonstrating contractile reserve during DoSE are likely to recover spontaneously and sestamibi imaging offers no additional advantage. However, sestamibi imaging is recommended to determine the likelihood of recovery with revascularization of segments showing no contractile reserve during DoSE (Spinelli et al, 1999). Technetium-sestamibi SPECT conducted during infusion of low-dose dobutamine elicited comparable diagnostic sensitivity (80% to 90%), specificity (75% to 83%) and accuracy (78% to 87%) as DoSE in predicting post-revascularization functional recovery (n=23). However, technetium-sestamibi SPECT at rest (without dobutamine) was inferior to the same test with dobutamine (65% versus 87% accuracy; p less than 0.05) (Leoncini et al, 2000).
- (f) In a study of 60 patients with stable CAD and left ventricular dysfunction, the extent of viable dysfunctional myocardium with contractile reserve appeared to correlate more closely with positron emission tomography (PET) than with DoSE. Dobutamine-induced contractile reserve identified fewer viable dysfunctional myocardial segments than PET (Chan et al, 1996). In a study of 30 subjects with CAD, prior MI and New York Heart Association Class III to IV heart failure (average ejection fraction = 25%), low-dose DoSE was inferior to PET just prior to coronary artery bypass grafting. The sensitivity, specificity, and accuracy of DoSE were 60%, 62%, and 61%, respectively, as compared to 99%, 33%, and 71% for PET, respectively (p less than 0.05). The authors recommend DoSE as an initial screening test for viability, and PET in cases of negative results on DoSE (Pagano et al, 1998).
- (g) A pooled analysis of 37 studies comparing the accuracy of imaging techniques in predicting myocardial viability in patients with chronic ischemic left ventricular dysfunction favored low-dose-dobutamine-echocardiography (LDDE), with a sensitivity and specificity of 84% and 81% respectively, as the technique of choice over (18F)FDG PET, thallium 201 SPECT, and technetium 99mTc sestamibi. Sensitivity and specificity of fludeoxyglucose F 18 were 88% and 73%, respectively. Thallium 201 stress-redistribution-reinjection and thallium 201 rest redistribution techniques had a high sensitivity (86% and 90%, respectively), but low specificity (47% and 54%, respectively). Technetium 99mTc sestamibi is adequate in detecting coronary artery disease, but less accurate in detecting myocardial viability. Local availability and expertise, particularly for the acquisition and interpretation of LDDE, remains a consideration in the choice of imaging modality (Bax et al, 1997).
- (h) In a study involving 17 patients (average ejection fraction = 36%), fluorine-18 fluorodeoxyglucose/thallium-201 SPECT was superior to low-dose DoSE and thallium-201 reinjection SPECT for detection of regional functional recovery following

revascularization. However, in akinetic segments the accuracy of fluorine-18 fluorodeoxyglucose/thallium-201 SPECT and low-dose DoSE are comparable (Bax et al, 1996).

- 3. MAGNETIC RESONANCE IMAGING

- (a) For detection of stress-induced wall motion abnormalities in patients with suspected coronary artery disease, dobutamine stress magnetic resonance imaging (DSMRI) has a significantly higher diagnostic accuracy and superior image quality compared with DoSE. All patients received standard dobutamine stress test dosing and mean doses of dobutamine and atropine were similar for both tests. Maximal blood pressure was higher during peak stress with DSMRI compared with DoSE (p less than 0.01) and heart rate was significantly lower (p less than 0.01). There were no significant differences between the two modalities for rate-pressure product at rest or peak stress. Image quality at target heart rate was very good in 40 (19.6%) of 204 patients with DoSE and 131 (69%) of 189 patients with DSMRI (p less than 0.001), good in 63 (31%) and 25 (13%) (p less than 0.01), moderate in 83 (41%) and 30 (16%) (p less than 0.001), and nondiagnostic in 18 (8.8%) and 3 (1.6%) (p less than 0.001), respectively. Sensitivity was 74.3% and 86.2% and specificity was 69.8% and 85.7% for DoSE and DSMRI, respectively (both p less than 0.05). Test accuracy was 72.7% and 86.0% for DoSE and DSMRI, respectively (p less than 0.005). In comparison to the complete cohort, there were no significant differences in sensitivity, specificity, and test accuracy in a subgroup analysis for women (Nagel et al, 1999).

- 4. MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY

- (a) Two studies demonstrated similar sensitivity (89% to 94%) and specificity (43% to 92%) with myocardial contrast echocardiography and DoSE in predicting functional recovery following revascularization (Nagueh et al, 1997; deFilippi et al, 1995). One trial found superior overall accuracy with DoSE as compared to myocardial contrast echocardiography (90% versus 47%, p less than 0.001) for predicting functional recovery after acute-MI-related revascularization (Bolognese et al, 1996).
- (b) When both myocardial contrast echocardiography and DoSE are used in the post-revascularization period ($n=39$), sensitivity and specificity are improved over either method alone. The sensitivities and specificities of the combination in predicting functional recovery were 90% to 93% and 48% to 50%, respectively. Corresponding figures for myocardial contrast alone were 84% sensitivity and 19% to 26% specificity, and for DoSE alone, 79% to 80% sensitivity and 30% to 36% specificity (Meza et al, 1997).

- 5. VENTRICULOGRAPHY

- (a) When performed a few days prior to coronary artery bypass graft surgery, low-dose DoSE and low-dose dobutamine ventriculography were equivalent in predicting post-CABG left ventricular functional recovery. The sensitivity, specificity and accuracy of DoSE were 63%, 71% and 68%, respectively. Corresponding values for ventriculography were 66%, 75% and 71%, respectively. Ventriculography may be preferred in cases of limited transthoracic visualization, as DoSE was less sensitive and accurate in this subset (Dalla Vecchia et al, 2000).

- 6. ATRIAL PACING STRESS ECHOCARDIOGRAPHY

- (a) Transesophageal atrial pacing stress echocardiography was a feasible and time-saving alternative to standard diagnostic DoSE in a preliminary comparative trial ($n=36$). Investigators used atrial pacing in a two-stage process to bring the heart rate up to targets of 85% and 100% of the age-predicted maximum. With a mean pacing current of 18 milliamps, the target was reached in 86% of subjects. Significantly higher mean peak heart rate (144 versus 129 beats/minute, $p=0.0001$), peak wall motion score index (1.5 versus 1.4, $p=0.001$), and rate of new or worsening regional wall motion (37% versus 14%, $p=0.005$) occurred with atrial pacing versus dobutamine, respectively. The peak stroke volume (62 versus 77 milliliters, $p=0.0001$) and peak ejection fraction (61% versus 69%, $p=0.0001$) were statistically lower with atrial pacing versus dobutamine, respectively. Atrial pacing significantly shortened the recovery, videotape, and review times by averages of 4 to 9 minutes each. Adverse effects were more frequent with dobutamine (83% versus 34%, $p=0.0001$). Additional study is needed to compare diagnostic accuracies (Rainbird et al, 2000).

- F. SPECIAL POPULATIONS

- 1. WOMEN

- (a) In terms of hemodynamic effects in healthy women, DoSE increases cardiac output (by 93%), heart rate (by 68%) and stroke volume (by 15%), and decreases peripheral vascular resistance (by 50%) and diastolic blood pressure (by 21%). Systolic blood pressure was unchanged (Blomstrand et al, 1995). Among patients undergoing DoSE, hypotension appears to occur more frequently in women than men (36% vs 24%, $p=0.01$) (Khanal et al, 1998a). The incidence of chest pain during DoSE was 26% in a retrospective review of 154 procedures in women with suspected CAD. However, chest pain did not correlate with DoSE results or coronary artery stenosis (Sizemore & Lewis, 1999).
- (b) Conflicting data exist regarding the influence of gender on DoSE results. A study of 2886 consecutive procedures (44% female) found that sensitivity was significantly lower in female subjects as compared to male subjects (78% versus 88%); however, specificity was similar (55% versus 46%). The relatively low specificity was attributed to post-test referral bias (Secknus & Marwick, 1997a). A study of 306 patients (31% female) found similar sensitivity between males and females (73% and 76%, respectively), but significantly higher specificity in females (77% and 94%, respectively). Overall accuracy did not differ (Elhendy et al, 1997a). A third study of 288 patients (35% female) reported equivalent sensitivity, specificity, and accuracy across genders (Dionisopoulos et al, 1997).
- (c) Overall sensitivity and specificity of DoSE in 92 women with suspected CAD were 40% and 81%, respectively. Only 27% of this cohort had angiographic evidence of CAD. Sensitivity was poor in subjects with single-vessel disease, but improved to 60% in multivessel disease. The accuracy, positive predictive value and negative predictive value were 70%,

71%, and 84%, respectively (Lewis et al, 1999). Transesophageal echocardiography performed under dobutamine stress was 82% sensitive and 100% specific in detecting CAD in a study of 84 women. This compared favorably to more traditional testing methods (Laurienzo et al, 1997).

- (d) A DoSE response termed "left ventricular cavity obliteration" (LVCO) represents a vigorous inotropic response to stress. This is defined as contact of the opposite LV walls in apical views during DoSE. LVCO occurs in 16% to 25% of patients undergoing DoSE. LVCO may reduce the sensitivity of DoSE and it may make analysis of wall motion more difficult. LVCO may cause hypotension. LVCO is more common in women with small LV dimensions, thicker LV walls, and higher baseline LV ejection fractions. Chest pain and reversible stress-induced wall motion abnormalities are reported less in patients who have cavity obliteration. Investigators report that LVCO was an independent predictor of event-free survival (Khanal et al, 1998; Secknus et al, 1998).
- (e) The long-term prognosis for women with normal DoSE results is excellent, as evidenced by 3% and 5% incidences of cardiac events and noncardiac deaths, respectively, after an average 2 years of follow-up (n=120). Cardiac events included 2 hospitalizations for congestive heart failure and 2 revascularization procedures; no myocardial infarctions were reported (Mesa et al, 1999).
- (f) Two studies comparing DoSE and thallium-201 SPECT in women reported similar sensitivities (72% to 93% for DoSE versus 78% to 79% for SPECT). Specificities were slightly improved with DoSE (82% to 91%) as compared to SPECT (70% to 75%) (Ho et al, 1998; Takeuchi et al, 1996). Both DoSE and SPECT were superior to exercise ECG (sensitivity and specificity of 71% and 44%, respectively) in women with known or suspected CAD (Ho et al, 1998).
- (g) DoSE provides a higher accuracy than dobutamine stress technetium-99m sestamibi (MIBI) SPECT for the diagnosis of CAD and for identifying regional coronary artery stenoses in women. In a study involving 70 women, sensitivity, specificity, and accuracy for DoSE were 78%, 92%, and 83%, respectively, and 64%, 72%, and 67%, respectively, for MIBI SPECT. The overall accuracy of DoSE was significantly higher than MIBI SPECT for the overall diagnosis of CAD (p less than 0.05). DoSE was significantly more sensitive than MIBI SPECT for identifying individual coronary stenoses (69% vs 51%; p less than 0.05), but specificity was similar (89% vs 88%, respectively) (Elhendy et al, 1998b).
- **2. DIABETES**
- (a) DoSE, with or without atropine, appears to be equally safe and effective for the diagnosis of CAD in diabetic and nondiabetic patients with suspected myocardial ischemia. In a study involving 1446 consecutive patients (184 diabetics), there were no deaths or myocardial infarctions during the test and there was no significant difference in heart rate increase, peak rate pressure product, or the incidence of hypotension, ventricular tachycardia, or supraventricular tachycardia between diabetic and nondiabetic patients. DoSE was feasible in 92% and 90% of the diabetic and nondiabetic patients, respectively. Sensitivities, specificities, and accuracies of DoSE for the diagnosis of CAD were 81%, 85%, and 82%, respectively, in diabetic patients and 74%, 87%, and 77%, respectively, in nondiabetic patients (NS) (Elhendy et al, 1998a).
- (b) Two studies suggest that diabetes-related microvascular disease and/or diabetic cardiomyopathy may elicit positive DoSE findings, despite "normal" circulation on the angiogram (Griffin et al, 1998; Hennessy et al, 1997a). In a study of 52 patients with diabetes mellitus, DoSE demonstrated 82% sensitivity and 54% specificity for the detection of CAD. The corresponding positive and negative predictive values were 84% and 50%, respectively (Hennessy et al, 1997a). In a study of 18 subjects (average age 38 years) with Type I diabetes mellitus, long-term nephropathy (not end-stage) without known or suspected CAD, 7 subjects had abnormal DoSE results. Confirmatory angiography was abnormal in only 2 of 6, yielding a low positive predictive value of 33% for DoSE. Three cases of significant arrhythmia occurred during dobutamine infusion, leading to safety concerns (Griffin et al, 1998).
- (c) Following acute MI, the prognostic value of DoSE was lower among 116 diabetics as compared to 222 non-diabetics. During an average 21 months of follow-up, significantly more diabetics with positive as opposed to negative DoSE results experienced any cardiac event (39% versus 20%, p=0.04) and unstable angina (22% versus 4.4%, p= 0.010). However, DoSE results were not related to the outcomes of cardiac death, nonfatal reinfarction or hard cardiac events in the diabetic group. In contrast, positive DoSE results were predictive of all of the above parameters except cardiac death in the non-diabetic group. Shorter dobutamine time was an independent predictor of poor outcome among diabetics (Hung et al, 1999a).
- **3. CHRONIC RENAL FAILURE**
- (a) In a follow-up study (average 38 months) of 193 patients (average age 63 years) with chronic renal failure (post-renal transplant, on dialysis, or being considered for such), DoSE was employed because of the risk of accelerated atherogenesis. This study sample had a number of cardiovascular risk factors, including hypertension (80%), hyperlipidemia (45%), diabetes (42%), chest pain (35%), prior MI (31%) and current smoking (26%). No major adverse events accompanied DoSE. A large percentage (35%) had non-diagnostic DoSE results, due to submaximal heart rate while on concomitant beta-blockers or calcium channel blockers, and 19% of this subgroup went on to a cardiac event. About one-quarter of subjects had a normal DoSE, of whom only 8% later experienced a cardiac event. The 19% with a scar revealed on DoSE had a 14% rate of cardiac events. The remaining 19% with ischemia during DoSE had a significantly higher cardiac event rate (31%) than the other subgroups (Marwick et al, 1998).
- **4. GERIATRICS**
- (a) High dose DoSE (up to 50 micrograms/kilogram/minute) does not lead to a loss of specificity and appears to be well tolerated and safe in middle-aged (less than 65 years old), elderly (65 to 79 years old), and very elderly (more than 80 years old) patients. In this study, the very elderly patients had no more adverse effects than younger patients. Average change in

heart rate was similar in all age groups. However, blood pressure response was reduced in the elderly and hypotension was associated with an ischemic response in the very elderly patients (Chenzbraun et al, 1999).

- (b) Slightly different safety and adverse effect profiles of DoSE were recorded in subjects under 75 years of age versus those 75 years and over. The older patients had significantly more asymptomatic hypotension (25%) and ventricular arrhythmias (41%) than younger patients (7% to 13% hypotension and 26% to 30% arrhythmias). In contrast, chest pain was more frequent in younger (23% to 32%) than older (17%) subjects (Hiro et al, 1997).
- (c) The results of 1 study indicate that, while using a 40 micrograms/kilogram/minute maximal dobutamine dosage, there is no difference in diagnostic accuracy and incidence of adverse effects in patients younger or older than 60 years (Baudhuin et al, 1993). Another study reported a low incidence of adverse effects using a maximal dobutamine dosage of 40 micrograms/kilogram/minute in patients older than 69 years (Poldermans et al, 1994a).
- 5. OBESITY
- (a) In a study of 23 morbidly obese individuals (mean weight: 164 kilograms) being evaluated for CAD, positive transesophageal DoSE findings were objectively confirmed via cardiac catheterization and/or cardiac events in 7 of 9 subjects (78%) over 18 months average follow-up. Negative DoSE findings were uniformly associated with no subsequent cardiac events over this time period. The test itself was generally well-tolerated, although hypotension necessitated dobutamine discontinuation in 43% without interfering with test completion (Madu, 2000).
- 6. PEDIATRICS
- (a) DoSE has been safely and effectively used in pediatric populations with Kawasaki disease, post-cardiac transplant and prior anthracycline exposure (Larsen et al, 1998; De Wolf et al, 1998; Noto et al, 1996).
- (b) DoSE appears to be an effective diagnostic test for detection of CAD in children with Kawasaki disease, particularly for patients unable to exercise adequately. The sensitivity and specificity of DoSE (up to 30 mcg/kg/min) were 90% and 100%, respectively (Noto et al, 1996).
- (c) When performed approximately 5 years post-cardiac transplant, DoSE was safe and effective in the evaluation of 78 pediatric patients (average age 5.7 years). Dobutamine dosing was 5 mcg/kg/min with incremental increases of 5 to 10 mcg/kg/min every 3 minutes, to a maximum dose of 50 mcg/kg/min, 75% of maximal heart rate, or development of complications. DoSE's sensitivity and specificity were 72% and 80%, respectively. With a mean follow-up of 21 months, cardiac events occurred in 27% and 4% of children with positive and negative DoSE results, respectively. The authors recommend annual DoSE post-cardiac transplantation, reserving angiography for children with symptoms or abnormal DOSE. Their current protocol employs angiography every other year (Larsen et al, 1998).
- (d) In a dose-ranging DoSE study of children and young adults following anthracycline exposure versus healthy controls (n=71, age 6 to 26 years), there were no major complications. Dobutamine dosing was 0.5 mcg/kg/min for 15 minutes, 2.5 mcg/kg/min for 10 minutes and 5 mcg/kg/min for 10 minutes. The 2 higher doses induced statistically significant changes in systolic and diastolic function, successfully differentiating the two groups of subjects. With the 5 mcg/kg/min dose, almost all DoSE variables exceeded a 5% threshold of change from baseline (De Wolf et al, 1998).
- II. DIPYRIDAMOLE:
- A. SUMMARY
- (1) Dipyridamole stress echocardiography (DiSE) is useful in the diagnosis of myocardial ischemia or CAD (Parthenakis et al, 1997; Bjoernstad et al, 1993; Agati et al, 1992; Mazeika et al, 1991; Ferrara et al, 1991); and has demonstrated prognostic value following vascular surgery or a first MI (Pezzano et al, 1997; Neskovic et al, 1995; Tischler et al, 1991). The majority of data concerning DiSE are taken from comparative trials versus DoSE.
- B. DOSING
- (1) The usual dipyridamole dosing protocol for stress echocardiography consists of 0.56 milligram/kilogram (mg/kg) IV over 4 minutes, followed 4 minutes later by 0.28 mg/kg IV over 2 minutes, for a total dose of 0.84 mg/kg infused over 10 minutes (Schroder et al, 1997; Kozakova et al, 1997; Poli et al, 1996; Deutsch et al, 1994). A low-dose protocol in which a total dose of 0.56 mg/kg is infused over 4 minutes has been studied (Kozakova et al, 1997). Oral dosing of dipyridamole for stress echocardiography is not as sensitive as IV administration in detecting CAD (Lattanzi et al, 1992).
- C. SAFETY/ADVERSE EFFECTS
- (1) The safety record for dipyridamole is similar to non-pharmacologic (ie, exercise) stress testing with a major complication rate of 1 in 1500 cases and mortality rate of 1 in 10,000 cases, based on over 10,000 patients for echocardiography and over 73,000 patients for nuclear medicine perfusion imaging. Dipyridamole is well-tolerated by patients, with a high (98%) overall feasibility rate (Picano et al, 1997).
- D. THERAPEUTIC USES
- 1. KNOWN/SUSPECTED CAD
- (a) Dipyridamole stress echocardiography (DiSE) effectively detects myocardial ischemia or CAD (Parthenakis et al, 1997; Bjoernstad et al, 1993; Agati et al, 1992; Mazeika et al, 1991; Ferrara et al, 1991). The diagnostic hallmark is transient regional left ventricular dysfunction. In terms of diagnostic accuracy, sensitivity increases with multivessel, severe (greater than 75%) disease with complex plaque morphology, good coronary collateral circulation, and no concomitant antianginal medication. The addition of atropine to the DiSE protocol improves sensitivity (to approximately 82%) and specificity (to approximately 94%), and is recommended as a means of optimizing the trade-off between accuracy and tolerability. The prognostic value of DiSE is such that the lower the dose required to induce ischemia, the higher the risk of cardiac death (Picano et al, 1997).

- 2. POST-VASCULAR SURGERY/POST-MI
- (a) DiSE was 81% sensitive and 87% specific in predicting perioperative cardiac events in a cohort of 509 subjects undergoing vascular surgery. Baseline clinical assessment classified 77% and 23% of subjects as high and intermediate risk, respectively. The positive predictive value was 28% (25 of 88 subjects with positive DiSE had a cardiac event). The negative predictive value was 99% (415 of 421 subjects with negative DiSE had no cardiac event) (Sicari et al, 1999a).
- (b) The use of dipyridamole stress transthoracic pulsed Doppler echocardiography accurately detected significant stenosis of left internal mammary artery grafts in a study of 87 patients (Pezzano et al, 1997). DoSE also identified patients at risk for subsequent adverse cardiac events after undergoing peripheral vascular surgery (Tischler et al, 1991), and after a first MI (Neskovic et al, 1995).
- E. COMPARATIVE EFFICACY VERSUS OTHER DIAGNOSTIC TESTS
- 1. EXERCISE TESTING
- (a) In a comparison of DiSE and ergometer echocardiography (EE) in 80 patients with suspected CAD, DiSE had a higher feasibility level than did EE (95% versus 84%, p less than 0.05) and a slightly higher incidence of adverse effects. In other respects (sensitivity and specificity), the two echocardiographic methods were similar. Both tests were more sensitive in patients with multiple-vessel rather than single-vessel disease, and both methods proved to be superior to ECG stress testing in terms of sensitivity (Deutsch et al, 1994).
- (b) DiSE and bicycle stress echocardiography provided similar sensitivity, specificity, and accuracy in the assessment of 60 individuals with chest pain. Both tests were superior to heavy 2-arm isometric exercise echocardiography (Loimaala et al, 1999).
- 2. RADIONUCLIDE IMAGING
- (a) DiSE provided superior specificity (91% versus 36%, p less than 0.0006) and positive predictive value (90% versus 67%, $p=0.04$) as compared to technetium-MIBI SPECT imaging for the diagnosis of CAD in 101 patients with hypertension. While MIBI-SPECT offered improved sensitivity over DiSE (98% versus 61%, p less than 0.0006), the accuracy and negative predictive values did not differ between tests (Fragrasso et al, 1999).
- (b) DiSE was superior to dipyridamole-SPECT in terms of specificity (88% versus 68%, p less than 0.001) and accuracy (84% versus 72%, $p=0.02$) of predicting early (within 24 hours) cardiac events post-vascular surgery ($n=129$). However, sensitivity was numerically but not statistically higher with SPECT (90% versus 66%, $p=NS$). During long-term follow-up averaging 33 months, sensitivity was low (33%) for both tests. DiSE again demonstrated improved specificity (80% versus 58%, p less than 0.001) and accuracy (76% versus 56%, p less than 0.01) over SPECT (Pasquet et al, 1998).
- III. ADENOSINE:
- A. SUMMARY
- (1) Adenosine stress echocardiography (ASE) is a useful diagnostic tool for detection of CAD (Djordjevic-Dikic et al, 1996). However, one author notes that ASE has poor sensitivity in patients without previous MI, particularly in those with single-vessel disease (Marwick, 1997). Sensitivity may be improved in this setting by increasing the dose of adenosine (Djordjevic-Dikic et al, 1996).
- B. DOSING
- (1) Standard adenosine dosing for stress echocardiography is a 140 mcg/kg/min IV infusion over 5 minutes (Kozakova et al, 1997; Kranidis et al, 1997; Anthopoulos et al, 1996). In one study, an initial dose of 100 mcg/kg/min over 3 minutes was followed by 140 mcg/kg/min over 4 minutes. The dose was increased to 200 mcg/kg/min (high dose) over 4 minutes if no new wall motion abnormalities appeared during standard dosing. Higher than usual adenosine dosing appears to improve the diagnostic value of ASE particularly by increasing sensitivity in patients with single-vessel disease (Djordjevic-Dikic et al, 1996).
- C. SAFETY/ADVERSE EFFECTS
- (1) Although adenosine stress is safe, adverse effects occur in 80% of patients, with chest pain occurring in 20% to 30% of patients (Marwick, 1997). Second- or third-degree AV block occurs in approximately 4% to 6% of patients, but heart transplant recipients are at an even higher risk of developing AV block (Toft et al, 1998). Adverse effects are typically short-lived because of adenosine's brief half-life (Johnston et al, 1995).
- D. THERAPEUTIC USES
- 1. KNOWN/SUSPECTED CAD
- (a) ASE is a useful diagnostic tool for detection of CAD. The sensitivity of ASE was 75% for the standard dose regimen and 92% for the high dose regimen (p less than 0.05). The sensitivity of ASE for detecting single-vessel CAD improved from 75% to 90% with the high dose regimen (p less than 0.05). The sensitivities for detection of multivessel disease for the standard dose and high dose regimens were 71% and 100%, respectively ($p=NS$). The respective specificities were 100% and 88% ($p=NS$). The higher dose improved the overall diagnostic accuracy (82% versus 91%, $p=0.01$) (Djordjevic-Dikic et al, 1996).
- IV. ATROPINE:
- A. SUMMARY
- (1) The addition of atropine to DoSE, when the target heart rate is not achieved, is safe and effective for detection of viable myocardium in patients with coronary artery disease and a left ventricular ejection fraction (LVEF) of less than or equal to 35%. In a study involving 200 patients undergoing DoSE, the addition of atropine was necessary and improved the accuracy

of DoSE for myocardial ischemia assessment in 34% of patients. The addition of atropine was required more frequently in patients with a LVEF of less than or equal to 25% (Poldermans et al, 1998).

- (2) Atropine is used as an adjuvant to other pharmacologic stress-inducing agents for the purpose of maximizing heart rate. In a study involving 1171 patients undergoing DoSE, the supplemental use of atropine in patients with a suboptimal stress response increased diagnostic sensitivity for ischemia by 16% and for CAD by 5%. Atropine was given to 299 patients (26%) who did not achieve target heart rate on dobutamine alone. Augmentation of heart rate with atropine was of greatest value in patients taking beta-blockers, those with single-vessel disease, and those with normal resting wall motion (Ling et al, 1996).

• B. DOSING

- (1) Patients who do not achieve 85% of their predicted maximal heart rate and have no signs or symptoms of ischemia while receiving the maximum dose of a pharmacologic stress-inducing agent, may be given atropine 0.25 milligram (mg), increasing to a maximum of 1 mg (Sicari et al, 1997; Picano et al, 1994; Poldermans et al, 1994; Baptista et al, 1994). In some studies, a maximum atropine dose of 2 mg was both safe and effective (Poldermans et al, 1998; Ling et al, 1996).

• C. SAFETY/ADVERSE EFFECTS

- (1) In a study involving 200 patients with coronary artery disease and a left ventricular ejection fraction (LVEF) of less than or equal to 35%, the addition of atropine to DoSE was safe and effective. In this study, cardiac arrhythmias and hypotension were the most frequent adverse effects. However, there was no association between the addition of atropine and the induction of cardiac arrhythmias or the occurrence of hypotension. Although not statistically significant, there was a tendency for hypotension to occur more frequently after the addition of atropine (Poldermans et al, 1998).
- (2) The overall safety and tolerability of dobutamine-atropine stress echocardiography was confirmed in a large series (2949 tests in 2799 patients). The test could not be completed in 341 cases (11.6%) for reasons such as tachyarrhythmia, nausea, hypotension, bradycardia, or hypertension. Fourteen patients had life-threatening complications or side effects requiring medical treatment/hospitalization, or lasting more than 3 hours. Five complications resulted from atropine intoxication (Picano et al, 1994).
- (3) Atropine toxicity, manifesting as torpor and hallucinations in elderly patients, developed in 0.12% of over 4000 consecutive DoSE tests at a single institution (1991 to 1998) (Mathias et al, 1999).

• V. COMBINATION REGIMENS:

• A. DOBUTAMINE AND DIPYRIDAMOLE

- (1) The addition of low dose dipyridamole increases the diagnostic accuracy of low dose DoSE, by improving sensitivity without loss of specificity. The combination can make pharmacologic stress echocardiography more effective for the detection of myocardial viability after an ischemic insult. In a study involving 34 patients with rest wall motion dyssynergy and CAD, patients were administered either a low dose dobutamine infusion (5 to 10 mcg/kg/min over 3 minutes), a low dose dipyridamole infusion (0.28 mg/kg over 4 minutes), or a low dose combination of the two drugs. Following coronary revascularization, the sensitivities and specificities of dobutamine, dipyridamole, and the combination of dipyridamole-dobutamine for predicting recovery were 72%, 67%, and 94% and 92%, 95%, and 89%, respectively. The accuracies of dobutamine, dipyridamole, and the combination of dipyridamole-dobutamine were 80%, 79%, and 92%, respectively (Picano et al, 1996).

• VI. COMPARATIVE THERAPEUTIC USES:

• A. DOBUTAMINE VERSUS DIPYRIDAMOLE

- 1. SUMMARY: DoSE and DiSE are generally similar in efficacy and safety. Neither drug has demonstrated clear superiority over the other as an echocardiographic stress-inducing agent.
- 2. KNOWN/SUSPECTED CAD
- (a) A meta-analysis of 12 randomized, comparative studies (total n=818) found equivalent overall CAD diagnostic accuracies with DoSE (80%) and DiSE (77%). Improved sensitivity with DoSE (77% versus 71%, p less than 0.05) was counterbalanced by an improved specificity with DiSE (93% versus 87%, p less than 0.05). Dipyridamole may be preferable in cases of severe hypertension with or without history of significant arrhythmia. Dobutamine may be preferable in cases of severe conduction disturbance, advanced asthmatic disease, or in the presence of xanthine/caffeine. The choice of agent should be individualized based on patient characteristics, cost differences, and physician discretion (Picano et al, 2000).
- (b) When DoSE and DiSE were compared, the overall sensitivity and specificity for detection of CAD and myocardial ischemia did not significantly differ (Pingitore et al, 1999; Loimaala et al, 1999; Shaw et al, 1996; Salustri et al, 1992). One group of investigators recommends the following: perform exercise stress testing whenever possible; use dipyridamole to induce pharmacologic stress if the patient is not receiving antianginal treatment to avoid dobutamine complications; use dobutamine when the patient is protected from possible complications of dobutamine (San Roman et al, 1996).
- (c) In a comparison of exercise stress testing with pharmacologic stress testing using dipyridamole or dobutamine with atropine on a "as needed" basis, testing was positive in 68%, 77% and 77% of 102 patients with CAD, respectively (p = NS). Echocardiography with either drug regimen exhibited an overall specificity significantly higher than exercise testing (dipyridamole 97%, dobutamine 95%, exercise 79%, p less than 0.05). When patients received antianginal treatment, the sensitivity of dipyridamole decreased from 93% to 61% (p = 0.002) while the sensitivity of dobutamine-atropine (77%) was not affected (San Roman et al, 1996).
- (d) The prognostic and diagnostic value of dipyridamole (n=576) and dobutamine (n=178) stress echocardiography were virtually identical in patients with single-vessel disease. Investigators employed the standard high-dose protocols with atropine. Of the 754 enrolled, 260 had revascularization within 3 months of testing, while the remaining 494 were maintained

on medical therapy. After an average 3-year follow-up, infarct-free survival occurred in 87% and 97% (medical and invasive treatment, respectively) with positive echocardiography results, as compared to 94% and 97% (medical and invasive treatment, respectively) with negative echocardiography results. The only independent risk factor for MI or cardiac death in medically-treated patients was a positive stress echocardiography finding (Cortigliani et al, 1998).

- (e) In a study comparing exercise stress testing, DiSE and DoSE, and dipyridamole and dobutamine technetium 99m sestamibi tomography, both pharmacologic agents were similarly safe and effective in the assessment of chest pain (n=60). In general, pharmacologic stress testing exhibited greater specificity than exercise testing. Technetium 99m sestamibi tomography was more sensitive than echocardiography in this trial (Santoro et al, 1998).
- (f) In an uncontrolled series of 134 patients undergoing both high-dose DiSE (up to 0.84 milligram/kilogram over 10 min) and DoSE (up to 40 micrograms/kilogram/minute plus atropine as needed), the tests demonstrated similar prognostic value and a 94% agreement rate. Similarly high negative predictive values (92% and 94%) and lower positive predictive values (27% and 31%) were observed for DiSE and DoSE, respectively (Schroder et al, 1997).
- (g) For the diagnosis of CAD in 101 patients with hypertension, DiSE and DoSE demonstrated statistically equivalent specificity, accuracy, positive and negative predictive values. Only sensitivity (88% versus 61%, p=0.006) favored the use of dobutamine over dipyridamole, respectively (Fragrasso et al, 1999).
- (h) In a prospective, comparative trial of 460 patients with known or suspected CAD and follow-up of 38 months on average, the positive and negative predictive values for DiSE (19% and 84%, respectively) and for DoSE (17% and 83%, respectively) were statistically equivalent (Pingitore et al, 1999).
- (i) DiSE, DoSE, and bicycle exercise exhibited statistically similar sensitivity (91% to 95%), specificity (44% to 75%), and accuracy (78% to 88%) in a trial of 60 patients being evaluated for chest pain. All three modalities were superior to heavy 2-arm isometric exercise (30% sensitivity, 47% accuracy, p less than 0.05) with the exception of specificity (94%) (Loimaala et al, 1999).
- (j) In a study of 133 patients, DoSE was more specific than dipyridamole technetium-sestamibi SPECT scintigraphy in detecting CAD (91% versus 73%, respectively, p less than 0.05). Corresponding sensitivities did not differ significantly (87% versus 80%, respectively, p=NS). Angiography confirmed significant CAD in 65% of this sample (Smart et al, 2000a).
- 3. POST-MI
- (a) In the early post-infarct period (n=50), DoSE and DiSE demonstrated equivalent diagnostic and prognostic efficacy. Sensitivity (75% versus 73%), specificity (67% versus 67%), and accuracy (74% versus 72%) in detecting greater than 50% coronary artery stenosis were statistically similar with DoSE and DiSE, respectively. Testing with either drug had a high (97%) positive predictive value and low (14% to 15%) negative predictive value for significant stenosis. With an average 2-year follow-up, both agents exhibited 100% sensitivities and negative predictive values for the occurrence of hard cardiac events (Minardi et al, 1997).
- (b) DoSE identified functional recovery, suggesting the presence of myocardial viability in a greater number of patients, and showed a higher sensitivity but lower specificity in predicting spontaneous functional recovery of the infarct area than DiSE. Regional functional recovery was detected by low dose dobutamine in 75% of patients compared to 49% of patients with dipyridamole. The sensitivities of DoSE and DiSE for predicting spontaneous functional recovery were 72% and 51%, respectively, and specificities were 68% and 82%, respectively (Poli et al, 1996).
- B. DOBUTAMINE VERSUS ADENOSINE
- 1. SUMMARY: DoSE and ASE are similarly effective for detecting CAD in elderly patients. However, in patients (including elderly patients) without a previous MI, DoSE is superior to ASE for detecting CAD, particularly in patients with single-vessel disease. DoSE in combination with nitroglycerin is superior to ASE for detecting viable myocardium in post-MI patients.
- 2. KNOWN/SUSPECTED CAD
- (a) DoSE and ASE are similarly capable of detecting CAD in elderly patients. ASE was less sensitive but more specific than DoSE in detecting coronary stenoses. ASE was least sensitive in the presence of single-vessel disease. DoSE was more sensitive in detecting milder forms of CAD. The positive and negative predictive values for cardiac events were 57% and 92% for DoSE, and 61% and 79% for ASE, respectively. Both tests were equally well tolerated. Abnormal findings on either test can be used as an independent risk factor for cardiac events and can identify patients who are at the greatest risk (Anthopoulos et al, 1996).
- (b) The sensitivity (76% versus 59%) and accuracy (79% versus 71%) of DoSE were statistically greater than that of ASE in detecting CAD in 128 elderly patients without a previous MI. Specificity was similar in this subgroup (83% and 90%, respectively). In subjects with a previous MI, the stress tests gave equivalent results. Adenosine was significantly more sensitive in detecting multivessel disease as opposed to single-vessel disease. The authors concluded that dobutamine is preferred over adenosine as a pharmacologic stress-inducing agent for echocardiography in the elderly (Anthopoulos et al, 1997). Another author suggests that in patients unable to exercise, dobutamine is preferable to adenosine for stress echocardiography; however, for perfusion imaging, the drugs are comparable (Marwick, 1997).
- 3. POST-MI
- (a) DoSE with supplemental nitroglycerin is superior to ASE in detecting viable myocardium. In this study involving 52 CAD patients with left ventricular dysfunction due to a previous MI, patients received either adenosine alone or low-dose dobutamine plus nitroglycerin at an initial dose of 20 mcg/min, gradually increased until systolic blood pressure decreased by 5 to 10 mmHg. The sensitivity, specificity, and positive and negative predictive values of ASE in detecting viable

myocardium were 54%, 86%, 65%, and 80%, respectively. Corresponding figures for DoSE with nitroglycerin were 91%, 89%, 78%, and 96%, respectively (Kranidis et al, 1997).

- C. DIPYRIDAMOLE VERSUS ADENOSINE

- 1. SUMMARY: Insufficient data are available to draw definitive conclusions about the comparative efficacy of DiSE and ASE, although their hemodynamic effects appear to be similar.

- 2. KNOWN/SUSPECTED CAD

- (a) In a comparison of adenosine bolus (5 mg), adenosine infusion (140 mcg/kg/min over 5 min), low-dose dipyridamole (0.56 mg/kg over 4 min) and high-dose dipyridamole (0.84 mg/kg over 9 min) infusion with transesophageal Doppler echocardiography, investigators report that adenosine infusion is the preferred method for evaluation of coronary reserve. The adenosine infusion elicited the highest flow velocity and lowest coronary resistance in both groups. Low-dose dipyridamole underestimated the coronary vasodilator response (Kozakova et al, 1997).

- 3. HEMODYNAMIC AND ADVERSE EFFECTS

- (a) Adenosine and dipyridamole elicited equivalent increases in myocardial blood flow in normal volunteers (Chan et al, 1992).

- (b) The results of a retrospective study involving 2000 patients undergoing pharmacologic stress testing indicate only slight hemodynamic differences between adenosine and dipyridamole. Adenosine produced slightly greater systemic vasodilation than dipyridamole. Peak heart rate was higher (85 versus 83) and systolic blood pressure was lower (129 versus 133 mmHg) with adenosine than with dipyridamole, respectively. Adverse effects, most commonly chest pain, occurred more often with adenosine (78%), but were of brief duration because of adenosine's short half-life. Second- or third-degree AV block occurs more frequently with adenosine (4% to 6%) than dipyridamole. Heart transplant recipients are at an even higher risk of developing AV block with adenosine, dipyridamole may be the preferred agent in this patient population (Toft et al, 1998). Adverse effects were less frequent with dipyridamole (50%), but were more difficult to manage, sometimes necessitating reversal with aminophylline (Johnston et al, 1995).

- CONCLUSION:

- As an alternative to exercise, dobutamine (with or without supplemental atropine) is the most commonly used pharmacologic agent in stress echocardiography. A large quantity of published literature confirms its efficacy and safety both in the diagnosis and prognosis of patients with known or suspected CAD, left ventricular hypertrophy, post-MI, post-revascularization, and post-cardiac transplantation. Data are also available to support its use in the pediatric and geriatric populations. Dipyridamole and adenosine are considered acceptable alternatives to dobutamine. At this time, neither drug has demonstrated any significant advantage over dobutamine in the vast majority of patients.

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