

Pharmacologic stress myocardial perfusion imaging: A practical approach

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Pharmacologic stress myocardial perfusion imaging (MPI) has assumed a prominent role in the evaluation of patients with suspected or known ischemic heart disease. Many patients who cannot adequately perform exercise stress testing may nevertheless undergo pharmacologic stress testing, most commonly with the vasodilator agents adenosine and dipyridamole, as well as the positive inotropic agent dobutamine. The prognostic information of MPI yielded by such studies has been demonstrated to be comparable to that from exercise stress studies, in multiple settings.¹⁻⁵ However, the optimal performance of pharmacologic stress testing presents unique challenges and requirements that should be addressed to produce optimal diagnostic myocardial perfusion images.

In 2006 in our outpatient nuclear cardiology laboratory, adenosine stress testing was performed in 44% of studies, and dobutamine stress in 2%. The reasons for using pharmacologic stress testing over exercise stress testing most commonly include the patient's inability to perform adequate exercise, because of orthopedic or cardiopulmonary limitations. In addition, patients with resting left bundle branch block, as well as ventricular pacing, are often referred for pharmacologic stress testing because of the concern over the potential production of perfusion defects related to abnormal patterns of myocardial depolarization, although the magnitude of this effect remains somewhat controversial.⁶⁻⁸

Our preferred vasodilator stress agent is adenosine, rather than dipyridamole, because of its shorter half-life and associated reduced monitoring time requirement. In addition, if significant side effects occur

with dipyridamole infusion, reversal of the drug action with aminophylline is often required, whereas termination of adenosine infusion alone may suffice. The choice of which agent to use, however, must also take into consideration the difference in cost and accessibility and may vary with the situation of the individual laboratory.

Increasingly, patients undergoing vasodilator stress testing with either dipyridamole or adenosine also perform simultaneous low-intensity exercise, which has been demonstrated to be safe, to reduce vasodilator-related side effects, and to improve myocardial imaging characteristics.⁹⁻¹⁴ Between 2003 and 2005, the proportion of all vasodilator MPI studies performed with adjunctive exercise increased from 7% to 16%.^{15,16} As the majority of patients can perform at least some degree of exercise, the addition of low-level exercise to vasodilator stress has become commonplace in our laboratory, accounting for approximately two thirds of all vasodilator stress MPI studies, or 30% of all MPI studies. Of note, the addition of low-level exercise to dobutamine stress has not been completely evaluated. Leg-raising exercise performed in the latter stages of dobutamine infusion has been demonstrated to reduce the need for atropine administration, however.¹⁷

PATIENT SELECTION AND SCHEDULING

To perform pharmacologic stress MPI testing safely and obtain meaningful results, we perform 3 different levels of review of patient characteristics and safety factors. The first level of selection of patients for pharmacologic stress imaging is performed by the referring physician. Laboratory test requisition forms allow for the specification of the mode of stress. Referring physicians have varying levels of ability to assess their patients' functional capacity and ability to perform treadmill exercise. Even among referring cardiologists, the considerations for selection of vasodilator versus dobutamine stress are not universally well recognized. Because of the higher incidence of side effects and the potential for dobutamine-related reduction in the efficiency of myocardial tracer uptake, this mode of stress is reserved only for patients in whom exercise and vasodilator stress are

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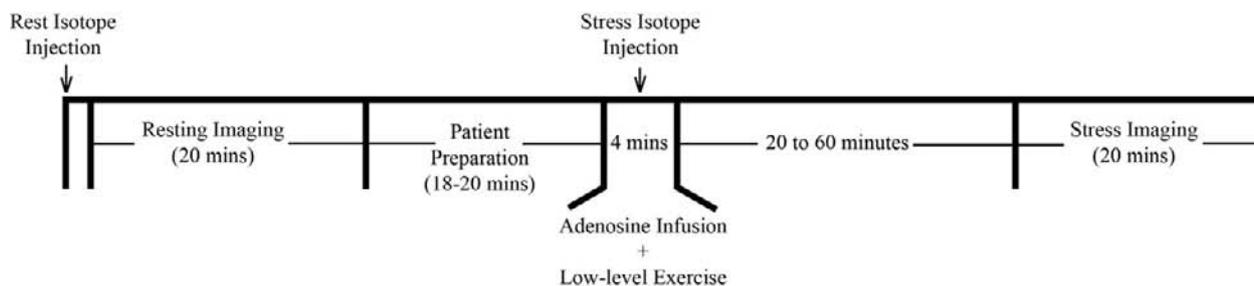


Figure 1. Flowchart of typical 1-day adenosine stress MPI study.

both contraindicated¹⁸ or, in select instances, for patients with inadvertent recent caffeine consumption. On the basis of this initial test order, patients are scheduled for the respective type of stress testing and imaging protocol. During the scheduling process, patient information, including medications and the presence or absence of asthma, diabetes, and pacemakers, is recorded.

The second level of patient screening is then performed by the panel of nurses working in the laboratory, who review this information on the day before the scheduled examination. If a potential contraindication to a specific mode of pharmacologic stress testing (eg, reactive airways disease or significant heart block for vasodilator stress) is observed or suspected, the referring physician is contacted and an alternate method of stress is selected, if appropriate.

The final level of screening occurs at the time of the examination by the nurse or physician supervising the test, who briefly interviews and examines the patient and reviews the medical record just before initiation of the pharmacologic stress test. Again, contraindications to vasodilator stress may be noted, at which point dobutamine infusion may instead be performed, and vice versa. Finally, it may be determined that the patient may actually be able to attempt to perform adequate exercise, obviating the need for vasodilator stress completely.

PATIENT PREPARATION

Upon scheduling the examination, patients receive a set of written instructions that outline the time requirements, anticipated sequence of events, and possible side effects of pharmacologic stress testing. These instructions are available by mail, fax, and E-mail and are posted on our laboratory Web site. Patients are instructed to fast after midnight or, for tests starting after noon, to fast for 4 hours before testing. Diabetic patients are told to test their blood sugar level at home, if possible, and to bring the results to the testing suite. Patients are instructed to take their oral diabetes medications on a regular schedule. Morning insulin doses are withheld, and patients are

asked to bring their insulin to the testing suite. To simplify management of diabetic patients, their testing is routinely scheduled for early morning appointments. As many patients will perform adjunctive low-level exercise, appropriate clothing and shoes are recommended.

For vasodilator stress studies, caffeine intake is proscribed for 24 hours before the test, including caffeine-containing medications. Likewise, all methylxanthine-containing medications (eg, theophylline and pentoxifylline) are withheld for 24 hours before testing. Medications containing dipyridamole and verapamil are discontinued 48 hours before the test. Of note, combination medications such as Aggrenox (Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT), frequently prescribed for patients with cerebrovascular disease, contain dipyridamole. Medication lists must therefore be examined carefully and exhaustively. Unless specified by the referring physician, β -blockers and nitrates are withheld for 24 hours.¹⁹ A list of all of these relevant medications is included in the written instructions given to each patient. If a question arises as to the safety of short-term discontinuation of a medication, the referring physician and nuclear cardiologist are contacted by the scheduler or nurse for specific instructions.

Patients scheduled for exercise stress MPI are given a similar set of instructions, as the testing of some of them will actually be converted to pharmacologic stress testing at the time of examination, usually because of an inability to perform adequate exercise stress testing, determined either before or during the treadmill test.

Upon arrival to the laboratory, patient height and weight are recorded by self-report and, if unknown, by direct measurement. Intravenous access is obtained, preferably in an antecubital vein, and the line is repeatedly flushed to ensure patency. Intravenous catheter placement in the hand is avoided, because the patient's handgrip while holding onto the handrail during low-level treadmill exercise often causes occlusion of the line during drug infusion. For 1-day imaging protocols, resting MPI is then performed (Figure 1).

PERFORMANCE OF PHARMACOLOGIC STRESS TESTING

After completion of resting imaging, patients go to the treadmill room and electrocardiographic (ECG) monitoring equipment is applied. The blood pressure cuff is placed on the arm without the intravenous catheter. Infusion pumps, loaded with premixed syringes containing adenosine or dobutamine, are connected via flexible tubing to the patient's intravenous catheter, with the patient lying supine (adenosine or dobutamine) or standing on the treadmill if low-level exercise is anticipated (adenosine).

After the patient's weight is entered into the infusion pump, adenosine is infused at a standard rate of $140 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for a total of 4 minutes (total volume infused for a 75-kg patient, 14 mL).^{20,21} Vital signs are measured and recorded every minute for the duration of the infusion. The nurse performing the infusion also elicits and records any symptoms that may occur. The most commonly reported side effects include flushing, shortness of breath, chest pressure, and leg heaviness. Generally, these symptoms are mild and resolve quickly after completion of the infusion. Although it is not our practice to reduce the rate of adenosine infusion, this may be easily done, simply by entering the new desired dose rate into the pump. More serious adverse reactions include bronchospasm and sustained significant (type II second-degree or third-degree) atrioventricular block, which usually necessitate immediate discontinuation of the adenosine infusion. Rarely, intravenous aminophylline infusion (50-100 mg) is required, usually because of bronchospasm. However, as patients are carefully selected for adenosine stress testing in our ambulatory setting, the incidence of serious side effects is low. Of the 1171 adenosine stress MPI studies performed in our laboratory in 2006, only 2 cases (0.17%) required intravenous aminophylline administration, both for respiratory symptoms. In laboratories with a higher proportion of acutely ill, hospitalized inpatients, the rate of serious adverse events may be expected to be somewhat higher.

Two minutes into the adenosine infusion, the stress isotope is injected through a side port in the same intravenous catheter. The line is not separately flushed, as the "dead space" is negligible and the continuous adenosine infusion is sufficient to infuse the small amount of radiopharmaceutical remaining in the intravenous catheter. Because the isotope injection may result in a small bolus of adenosine being administered through the line, transient atrioventricular block at this point is not uncommonly observed. This is usually short-lived and self-limited, however, not requiring any specific corrective measures, and it is generally not significant enough to warrant the use of 2 separate intravenous catheters.

Given the very low incidence of significant complications of vasodilator stress MPI, even in patients later determined to have significant coronary artery disease, testing is generally supervised by registered nurses with specialized training, with immediate physician backup available for emergencies.²² However, personal physician supervision is performed for patients thought to be at higher risk for potential complications of vasodilator stress, such as those with pulmonary disease or baseline conduction system abnormalities. ECG and hemodynamic monitoring is generally continued for 8 minutes after termination of adenosine infusion.

Whenever possible, adjunctive treadmill exercise is used. Low-level exercise is effective in ameliorating vasodilator-related side effects and improves imaging characteristics.¹¹⁻¹³ For most patients, this involves walking on the treadmill at 1 mph at a 0% grade, initiated and performed simultaneously with the adenosine infusion. The adenosine infusion and exercise are terminated simultaneously. Depending on the patient's functional capacity, higher levels of exercise (eg, first stage of the Bruce protocol) or simple marching in place may be used. If the patient is noted to have a long stride, the treadmill speed may be increased in increments of 0.1 mph, until a comfortable gait is achieved. The ultimate level of exercise performed is determined by the subjective assessment of the supervising personnel. Those patients who are unable to perform exercise in the standing position may swing their legs in the seated position or lift light weights with the arm contralateral to the arm with the intravenous catheter.²³ With even very low levels of exercise, vasodilator side effects appear to be minimized. Only a small minority of patients are unable to perform any degree of adjunctive low-level exercise. According to the conventional wisdom of our nursing staff, if a patient can walk into the laboratory, he or she will be able to perform some level of exercise during adenosine stress.

A complete lack of even mild vasodilator symptoms such as flushing, however, may raise the possibility of unrecognized or unreported caffeine intake or of faulty adenosine administration. This observation should be recorded and reported to the interpreting physician, who may include this as a consideration when the final perfusion images are reviewed. The intravenous site should be frequently monitored for signs of infiltration. Whereas the adequacy of exercise stress may be estimated by parameters such as heart rate and double product at peak stress, the adequacy of vasodilator stress is more difficult to assess. Given the consistent coronary vasodilator effect produced by the standard adenosine dose, in the absence of antagonists of adenosine action, the adequacy of vasodilator stress is most often presumed.

In our laboratory, for patients with left bundle branch block or ventricular pacing, adjunctive treadmill exercise is not generally performed, so as to minimize the possibility of perfusion defects occurring related to an elevated heart rate and an abnormal sequence of myocardial activation. In our clinical experience, however, these patients tolerate stationary low-level arm and leg exercise, without significant heart rate increases.

To allow time for diminution of splanchnic tracer activity, image acquisition is initiated approximately 45 to 60 minutes after isotope injection. In addition, patients are encouraged to eat a snack, to increase gut blood flow and facilitate subdiaphragmatic tracer washout. For patients who performed a higher degree of adjunctive exercise, imaging may be performed slightly earlier (20-45 minutes).

During dobutamine stress, supine positioning of patients is maintained throughout. Dobutamine is administered at an initial rate of $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and increased in increments of $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ every 3 minutes, to a maximum of 40 to $50 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Occasionally, as for dobutamine stress echocardiography, intravenous atropine, at a dose of 0.5 to 1 mg, may be administered for additional heart rate augmentation. The dobutamine infusion is continued for 1 minute after injection of the stress isotope. Early termination of the drug infusion may be necessary when dobutamine infusion is complicated by significant arrhythmia, severe hypertension, or marked ischemic ST-segment changes or other clinical evidence of significant myocardial ischemia. Milder symptoms such as flushing, palpitations, chest "fullness," and nausea generally do not necessitate discontinuation of the dobutamine stress protocol.

The determination of the adequacy of dobutamine stress may be problematic. Unlike during dobutamine stress echocardiography, the contractile response of the left ventricle cannot be visualized during dobutamine infusion for MPI. Real-time assessment of endpoints for dobutamine stress echocardiography such as the development of regional wall motion abnormalities and left ventricular cavity obliteration are not available during dobutamine infusion for MPI studies. Furthermore, there is no clear evidence that target heart rate responses for exercise are applicable to dobutamine stress. Generally, a heart rate target of 85% of predicted maximum is used, which not uncommonly requires adjunctive leg-raising exercise or intravenous atropine administration (or both). As the dobutamine stress protocol generally requires more active decision making and carries a higher potential risk for adverse effects, direct physician supervision is routine in our laboratory.

As for adenosine stress, image acquisition is delayed for 45 to 60 minutes after isotope injection, again to allow for washout of splanchnic tracer uptake.

INTERPRETATION OF PHARMACOLOGIC STRESS MPI STUDIES

Clinical observations from pharmacologic stress testing differ from those from exercise stress testing. Symptoms associated with vasodilator stress, in particular, are often nonspecific; chest discomfort or dyspnea occurring with adenosine infusion, for example, may be related to medication effect, myocardial ischemia, or both. Whereas coronary vasorelaxation is mediated by stimulation of adenosine A_{2A} receptors, other side effects such as atrioventricular block and bronchospasm are mediated by other adenosine receptor subtypes (A_1 and A_{2B} receptors, respectively). Adenosine nonselectively activates these receptors, so symptoms occurring during vasodilator stress may simply reflect drug effect.

The lack of an ischemic ECG response to vasodilator stress is not a reliable negative predictive indicator. With the addition of low-level exercise, the occurrence of an ischemic ECG response may be more frequent.⁹ Perhaps reflecting the generally higher-risk patient population referred for adenosine stress testing, patients with normal perfusion imaging studies but an ischemic ECG response to adenosine stress, though uncommon, have a higher cardiac event rate and a higher incidence of multivessel coronary artery disease.²⁴

Dobutamine infusion often gives rise to symptoms related to the positive chronotropic and inotropic actions of the drug. These may be variously described as chest discomfort or a sensation of heart "pounding," making interpretation of symptoms related to this mode of stress difficult. In the setting of a normal resting electrocardiogram, ischemic ECG responses to dobutamine administration should generally raise the level of suspicion of inducible myocardial ischemia.

Interpretation of the images from pharmacologic stress MPI is similar to that from exercise stress. Imaging characteristics may be affected by the mode of stress, however. With adenosine infusion, splanchnic tracer activity may be prominent, complicating interpretation of perfusion, particularly of the inferior wall. Adjunctive prone imaging may help in this circumstance. Again, low-level exercise has been demonstrated to help to decrease such extracardiac tracer activity.^{12,13,25} As previously mentioned, initiation of imaging after pharmacologic stress is delayed for 20 to 60 minutes (vs 10 to 30 minutes for exercise stress). Occasionally, when high splanchnic activity is observed to persist despite this delay, another nongated acquisition is performed after an additional delay of 30 to 90 minutes. Importantly, the nuclear technologist plays an important role in initiating such measures, which requires review of image quality before the patient leaves the laboratory.

As for exercise stress, scintigraphic signs of diffuse myocardial ischemia such as transient ischemic dilation of the left ventricle and elevated lung tracer activity are important prognostic signs in vasodilator stress testing. Transient ischemic dilation seen with adenosine stress MPI is associated with higher cardiac risk both with concomitant myocardial perfusion abnormalities²⁶ and without them.²⁷ Increased lung thallium 201 uptake has been demonstrated to be correlated with the presence of significant coronary artery disease with both dipyridamole and adenosine stress MPI.^{28,29} Although these findings are meaningful indicators of a higher coronary artery disease risk when present, the lower likelihood of stress-induced left ventricular dysfunction with pharmacologic stress might limit the negative predictive value of the test in this regard. This observation, coupled with the inherent lack of clinical exercise data associated with pharmacologic stress testing, highlights one of the main potential pitfalls of vasodilator stress MPI, namely, the difficult detection of "balanced" ischemia due to diffuse myocardial hypoperfusion.

Again, the addition of adjunctive low-level exercise stress has been demonstrated to improve the sensitivity of dipyridamole stress^{9,10} and adenosine stress.^{11,13,25,30-32} The prognostic value of an abnormal adenosine study with adjunctive exercise was found to be greater than for adenosine alone in a large community-based study, an effect magnified further when combined with the finding of transient ischemic dilation.²⁶ Potential mechanisms for the improvement in test sensitivity with the addition of low-level exercise include a greater degree of coronary hyperemia achieved with dual stress modalities, reduction in the degree of image artifacts, and exercise-related constriction of the resistance arterioles in ischemic territories resulting in an increase in flow heterogeneity.¹⁴

REPORTING OF PHARMACOLOGIC STRESS MPI FINDINGS

As for exercise stress MPI, symptoms, hemodynamic response to stress, occurrence of arrhythmias, and ECG response to stress are reported for pharmacologic stress MPI. The final report clearly notes the type of pharmacologic stress used and whether adjunctive low-level exercise was performed. Interpretation of perfusion images is performed as for exercise stress MPI, with note made of the presence or absence of transient ischemic dilation, difference in calculated left ventricular ejection fraction between stress and rest (if available), and reversible elevated right ventricular lung tracer uptake, as well as description of the patterns of myocardial perfusion. The presence of significant adjacent extracardiac tracer activity, which may complicate accurate interpretation of

perfusion, is also described. Comparison to the images from prior studies (not simply the report) is routine in our laboratory, as direct comparison provides indispensable information to the referring physician. Importantly, if the study is compared with a prior study, the mode of stress of both studies is reported, as differences in MPI findings may be related in part to different stress modalities.

CONCLUSION

In the substantial proportion of patients in whom exercise stress testing is not possible, pharmacologic stress MPI is an important tool in the detection of ischemic heart disease. With careful attention to patient selection, performance of the pharmacologic stress protocols, addition of adjunctive low-level exercise stress whenever possible, and measures to optimize image quality, important diagnostic and prognostic information can be obtained, comparable to that produced with standard exercise stress testing. Novel vasodilator stress agents, currently under development, such as the selective adenosine A_{2A} receptor agonists regadenoson and binodenoson, may allow for reduced pulmonary and bradycardiac side effects, enhanced ease of administration, and possibly, greater inclusion of patients with pulmonary disease.^{33,34} As older patients with multiple comorbidities are increasingly referred for nuclear cardiology studies, the ability to perform high-quality pharmacologic stress MPI is a basic requirement of the contemporary nuclear cardiology laboratory.

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