Editorial Comment

Which Pharmacological Stress Is Optimal?
A Technique-Dependent Choice

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Pharmacological stress is in widespread use for the noninvasive evaluation of patients suspected of having coronary artery disease. This alternative form of stress is used either in conjunction with radionuclide myocardial perfusion imaging or with two-dimensional echocardiography.

Reasons for using pharmacological stress as a substitute for physical exercise may vary. In the nuclear cardiology laboratory, patients generally perform physical exercise on treadmill or bicycle. Pharmacological stress is used in selected patients who are incapable of performing adequate physical exercise because of orthopedic, neurologic, peripheral vascular, or other medical problems.1 On the other hand, in the echocardiography laboratory, the performance of physical exercise in conjunction with two-dimensional echocardiography is a challenging task, and an alternative mode of non-physical stress may be preferred in most patients.2,3

The first pharmaceutical to be employed for simulating cardiac stress was intravenously administered dipyridamole.4 Dipyridamole has been used in combination with 201Tl scintigraphy for more than a decade. Recently, new agents for pharmacological stress have been introduced—adenosine5 and dobutamine.6,7

The technology of radionuclide imaging and echocardiography has evolved considerably in recent years. Although planar radionuclide imaging remains an adequate imaging modality, single-photon emission computerized tomography (SPECT), which enables more precise detection of disease in specific coronary arteries, is now used widely. The new 99mTc-labeled imaging agents, such as Sestamibi, now ensure consistently good-quality SPECT images.8,9

Similar to radionuclide images, echocardiographic images are now often acquired on dedicated minicomputers. Selected digitized cardiac cycles can be displayed as an endless loop, analogous to cine display of radionuclide ventriculography, for analysis of regional wall motion. Because of considerable technical difficulties with physical exercise on supine bicycle, stress two-dimensional echocardiography is increasingly performed in conjunction with either intravenous infusion of high-dose dipyridamole or dobutamine.7,10,11

At the present time, it is not clear which pharmacological stress is best suited for which imaging modality. Therefore, the report by Marwick et al in this issue of Circulation12 is of considerable interest and of importance for the disciplines of nuclear cardiology and echocardiography. The investigators evaluated prospectively in a consecutive series of 97 patients the diagnostic yield of adenosine and dobutamine stress in conjunction with 99mTc-Sestamibi SPECT and digitized two-dimensional echocardiography. This study is unique since each patient underwent four different stress test combinations.

The results and conclusions of this study are important and helpful for clinical practice. Adenosine SPECT-MIBI appeared to be a sensitive method (sensitivity, 86%), comparable to that of dobutamine two-dimensional echocardiography (85%) and dobutamine SPECT-MIBI (80%). However, these three combinations were substantially superior compared with adenosine two-dimensional echocardiography, which had a sensitivity of only 58%.

In view of the different mechanisms of action of adenosine and dobutamine, these results should not be surprising.

Intravenous infusion of adenosine causes near-maximal dilatation of the coronary resistance vasculature and near-complete recruitment of the coronary blood flow reserve. In patients with significant coronary artery disease, this results in marked heterogeneity of regional myocardial blood flow. Blood flow in regions supplied by normal coronary arteries increases to a greater extent than in regions supplied by arteries with significant stenoses. This heterogeneity of regional myocardial blood flow can be imaged with radioactive myocardial perfusion imaging agents as an area with relatively diminished uptake of radiotracer. In most patients, no myocardial ischemia is created, and therefore regional wall motion remains normal. This explains the relatively low sensitivity of adenosine two-dimensional echocardiography in Marwick et al’s study.

In contrast, the primary effect of dobutamine infusion constitutes an increase in heart rate and systolic blood pressure and thus a direct increase in myocardial oxygen demand, similar to that occurring during moderate physical exercise. To accommodate the increased metabolic demand, regional nutrient myocardial blood flow must increase accordingly. In the presence of a significant coronary stenosis, insufficient increase in regional myocardial blood flow leads to ischemia and abnormal regional wall motion. Thus, both adenosine and dobut-
tamine create heterogeneity of myocardial blood flow. The heterogeneity is probably more pronounced with adenosine than with dobutamine. With dobutamine, this heterogeneity is almost always associated with ischemic wall motion abnormality, whereas this is not necessarily the case with adenosine.

It should be noted that in Marwick et al's study the administered doses of both pharmacological stresses were relatively high compared with those commonly used in clinical practice (180 μg/kg/min for adenosine and 40 μg/kg/min for dobutamine). Therefore, both tests were evaluated at their full potential. In this regard, it is relevant to examine the clinical feasibility of reaching an adequate end point with both modalities. Infusion of the pharmaceutical had to be stopped prematurely in 36% of patients using dobutamine and in 28% of patients using dipyridamole. With dobutamine, the test was most often terminated by the physician, e.g., because of marked change in blood pressure, while the patient was asymptomatic. On the other hand, with adenosine it was frequently the patient who complained about side effects, necessitating premature termination of infusion. The majority of the patients whose test was terminated prematurely had positive tests and therefore sensitivity was most likely not significantly affected. The percentage of patients with nondiagnostic tests, i.e., negative results and premature termination of infusion, was 12% for dobutamine and 18% for adenosine. It is in the latter group of patients that coronary artery disease might have been missed. Therefore, although side effects were relatively frequent with both agents, the prevalence of potentially false-negative tests was acceptable. From a practical point of view, both adenosine and dobutamine have a rapid onset of action and a short plasma half-life—30 and 120 seconds, respectively. Thus, adverse side effects usually can be easily controlled by stopping the infusion.

It is important to note that Marwick et al intentionally excluded patients with prior myocardial infarction. The focus was on the detection of stress-induced ischemia (transient changes in myocardial perfusion or regional wall motion) rather than on identification of coronary artery disease. It should be realized that in clinical practice, a substantial number of patients are referred for evaluation of residual stress-induced ischemia after a recent myocardial infarction. It is in the latter group of patients that radionuclide myocardial perfusion imaging may have a considerable advantage over two-dimensional echocardiography. Interpretation of two-dimensional echocardiography is generally based on qualitative visual analysis of regional wall motion. In contrast, interpretation of SPECT myocardial perfusion images is frequently performed using computer quantification of images. In general, with visual analysis, it is relatively easy to appreciate a change from normal to abnormal (ischemia in a patient without prior myocardial infarction). However, it is more difficult to identify reliably a change from abnormal to “more abnormal” (ischemia in a patient with prior myocardial infarction). Image quantification, as routinely performed in many nuclear cardiology laboratories, allows for objective comparison of the size and change in size of myocardial perfusion defects, particularly in the presence of prior myocardial infarction. Quantification of the amount of stress-induced ischemia is also of prognostic import-

ance. An extensive body of literature documents the functional and prognostic significance of (semi)quantitative analysis of myocardial perfusion imaging. The greater the extent and severity of myocardial perfusion abnormalities, the poorer the patient’s prognosis.13 Such (semi)quantitative information appears (as yet) not to be obtainable with the use of digitized two-dimensional echocardiography.

Can pharmacological stress completely replace physical exercise?14? The answer is negative. Much useful clinical information is lost by employing pharmacological stress alone. For complete evaluation of the patient with coronary artery disease, physical exercise in combination with an imaging technique is preferred. During physical exercise, a number of clinical parameters, such as duration of exercise,15 increase in heart rate,16 reproduction of symptoms, blood pressure response,17 and ECG ST segment changes, provide invaluable complementary functional data that should be considered and incorporated with cardiac imaging results. Pharmacological stress should be considered a surrogate and second choice, to be reserved for patients in whom physical stress can be expected to be inadequate.

The results of Marwick et al’s study are important and indicate that, depending on the imaging modality used, a particular form of pharmacological stress is preferred. If two-dimensional echocardiography is used, dobutamine pharmacological stress is the stress agent of choice, whereas if myocardial perfusion SPECT is used, either adenosine or dobutamine is an appropriate agent. With the dosage and protocols described by Marwick et al, the diagnostic yield for detecting myocardial ischemia in patients without prior myocardial infarction is comparable for either imaging modality.

References


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