

Exercise and Pharmacologic Stress Testing for Prognosis After Acute Myocardial Infarction

Mario S. Verani

Section of Cardiology, Baylor College of Medicine, Houston, Texas

To evaluate patients after acute myocardial infarction (MI), myocardial perfusion imaging provides prognostic parameters that help identify patients at risk for subsequent cardiac events. In addition, myocardial perfusion imaging can be used to identify functionally important residual stenoses and multivessel disease, even in patients who have received thrombolytic therapy. Three parameters of myocardial perfusion imaging emerge as strong predictors of future cardiac events in post-MI patients: (1) presence of transient defects, (2) the number of transient defects and (3) increased radiotracer uptake in the lung. In addition, radionuclide left ventricular ejection fraction (LVEF) is one of the most powerful predictors of subsequent risk for cardiac events, particularly cardiac death and congestive heart failure. Cardiac catheterization, for the most part, does not add to the prognostic value of radionuclide stress testing. Results of myocardial perfusion imaging studies that employ pharmacologic stress instead of submaximal exercise provide strong predictors of prognosis in post-MI patients.

Key Words: pharmacologic stress testing; exercise stress testing; myocardial perfusion imaging

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After acute myocardial infarction (MI), patients can be risk-stratified using prognostic indicators from stress-testing in combination with radionuclide myocardial perfusion imaging (1-16). Many of these prognostic indicators are the same as those used to predict risk for patients with known or suspected coronary artery disease (CAD).

A review of several studies on post-MI patients (16), including multivariate analysis of results from more than 1,000 patients, indicates that three parameters of myocardial perfusion images are strong predictors of future cardiac events in post-MI patients: (1) presence of transient defects in either the infarct or noninfarct area, (2) number of transient defects and (3) increased radiotracer uptake in the lung. Interestingly, only two of five studies that re-

ported both scintigraphic and angiographic data concluded that coronary angiography adds to the predictive value of myocardial perfusion imaging, whereas three studies concluded that catheterization does not add to the prognostic value of radionuclide stress testing (16).

The excellent study by Gibson et al. demonstrated that submaximal exercise electrocardiography (ECG) in post-MI patients before hospital discharge can separate high-risk and low-risk patients (9). Patients with angina and ST-segment depression on the exercise ECG have significantly worse outcomes than patients without those two variables. On the basis of ²⁰¹Tl scintigraphy, patients in this study were divided into low- and high-risk groups. Patients with transient defects, multiple defects and/or increased lung uptake were assigned to the high-risk group. Although there was also a statistically significant difference in outcome between patients with single-vessel and multivessel disease, the difference was greater when patients were risk-stratified according to myocardial perfusion studies instead of coronary angiography (Fig. 1).

For many post-MI patients, particularly those who cannot exercise at all, or those unable to exercise adequately, pharmacologic stress is often an excellent option. Leppo et al. clearly showed that patients with transient defects on dipyridamole-thallium images were at higher risk than patients with no redistribution (17). The majority of patients without redistribution had no cardiac events. However, since only 33% of patients who had redistribution experienced subsequent cardiac events, it is necessary to refine the prognosis with other clinical and laboratorial predictors of high risk, such as older age, presence of diabetes mellitus, evidence of a large infarct size, Killip Classes III and IV, presence of pulmonary edema, cardiac arrhythmias (ventricular fibrillation or tachycardia, atrial fibrillation), new onset of conduction abnormalities, etc.

RISK STRATIFICATION AFTER THROMBOLYTIC THERAPY

The advent of a thrombolytic therapy capable of opening acutely occluded arteries has dramatically changed the management of MI. How can we predict patients at risk for re-occlusion and subsequent ischemic events? Do the prognostic indicators that worked in the prethrombolytic era

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For correspondence or reprints contact: Mario S. Verani, MD, Section of Cardiology, Baylor College of Medicine, 6535 Fannin F-905, Houston, TX 77030.

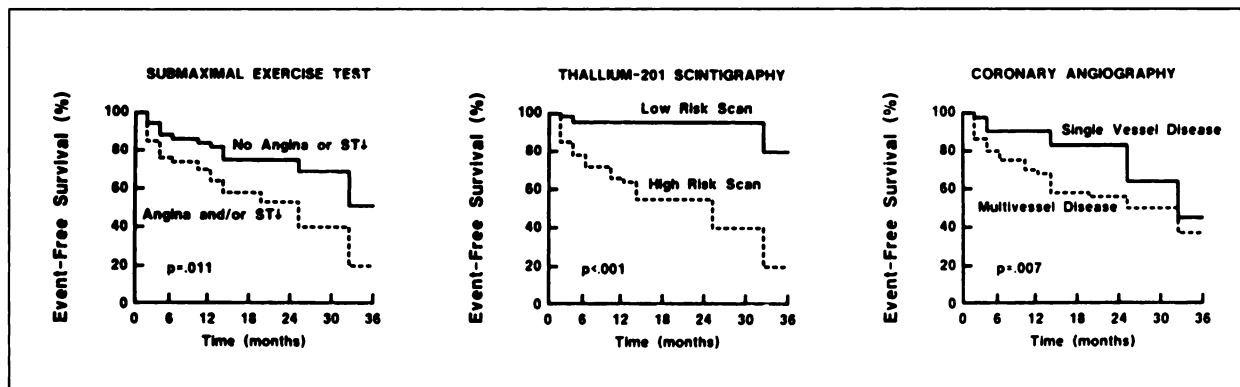


FIGURE 1. Event-free survival according to the results of tests performed before hospital discharge. The best separation between high- and low-risk patients is provided by exercise ^{201}Tl scintigraphy. Reprinted with permission from the American Heart Association (*Circulation* 1991;84(Suppl 1):148).

still apply? A number of clinical studies have attempted to answer these questions (11–15).

Touchstone et al. identified infarct-related arteries in 73% of patients with fixed defects on ^{201}Tl images and in 80% of patients with transient defects (11). Myocardial perfusion images therefore could not predict whether vessels were open or occluded.

Tilkemeier et al. concluded from a retrospective study that patients treated with thrombolytic therapy cannot be risk-stratified on the basis of ^{201}Tl perfusion studies (12). Increased lung uptake was the only predictor in the 107 patients treated with conventional therapies, whereas left ventricular dilatation was the only predictor in the 64 patients treated with thrombolytic agents. The positive predictive value for myocardial perfusion imaging was reported as 33%–36%.

This study has been quoted widely, but there are several factors that raise doubts about conclusions derived from this study:

1. This was a retrospective study addressing two different groups of patients.
2. The ^{201}Tl images were interpreted without quantifying the defects.
3. Many of the events were actually bypass surgery or percutaneous transluminal coronary angioplasty (PTCA), only five patients reached the hard endpoints of MI or death.
4. The thrombolytic group had only a 6% rate of acute MI and a 1% rate of cardiac death.

In another retrospective study of 56 patients, 53 received thrombolytic therapy, 42 of whom underwent coronary angioplasty on Day 1 of MI (13). SPECT imaging with ^{201}Tl and radionuclide angiography were performed 1 wk post-MI. For detection of stenosis in noninfarct-related arteries, ^{201}Tl SPECT had a sensitivity of 57% and a specificity of 46%. The investigators concluded that myocardial perfusion imaging had a low accuracy for detecting the presence of multivessel CAD. However, this study did not address the question of prognostic indicators later on.

More recently, a study by Haber et al. was designed to determine whether exercise ECG or perfusion imaging before hospital discharge in post-MI patients treated with thrombolytic therapy could detect multivessel disease (14). The sensitivity of ST-segment depression on ECG for this diagnosis was only 29%. The sensitivity of perfusion imaging to localize a perfusion defect in a region remote from the infarction was only 35%.

Although these sensitivities are low, it should be noted that the patients were tested with submaximal exercise while most were on anti-ischemic medication, including beta-blockers. Submaximal exercise may not stress the heart sufficiently; hence, multivessel disease will not always be apparent on perfusion images from these patients, particularly those who are heavily medicated. It may also be relatively difficult to detect additional lesions in other vessels because they may seem relatively normal compared to the most severely hypoperfused area of an MI.

Residual Stenosis

In a study of 101 patients with uncomplicated infarction, all had >70% residual stenosis in the infarct-related artery after thrombolytic therapy (15). Myocardial perfusion imaging with ^{201}Tl showed exercise-induced transient defects in 52 (51%) patients and fixed defects in 49 (49%) patients. Although the investigators concluded that ^{201}Tl was not reliable to detect residual stenosis in these patients, there are several factors to consider before accepting this conclusion. It may be more difficult to detect superimposed ischemia if the patient already has a scar. In addition, a stenosis that appears significant on the angiogram may not be functionally critical and may not significantly compromise myocardial perfusion.

It is obvious that many patients with residual stenoses and multivessel disease do not have subsequent events. Thus, the emphasis in future studies must shift from attempts to detect residual stenoses and multivessel disease to patient stratification according to risk of future events.

PHARMACOLOGIC STRESS

Substituting pharmacologic stress agents, such as dipyridamole, adenosine and dobutamine, for submaximal exercise can possibly improve the value of ^{201}Tl myocardial perfusion imaging in post-MI patients.

In a series of 126 patients studied with adenosine-thallium SPECT five days (average) post-MI, approximately 50% were treated with thrombolytic agents and 50% underwent early bypass surgery or PTCA (18). Results showed that the SPECT study could detect infarct-related arteries in 97%, and multivessel disease in 70%, of patients (Table 1). These results are higher than detection rates reported in studies using submaximal exercise (9-15). To identify residual stenoses and additional lesions in early post-MI patients with myocardial perfusion studies, pharmacologic stress agents may offer a substantial improvement over submaximal exercise.

With regard to predicting subsequent cardiac events, this study indicated that patients with smaller perfusion defects were at lower risk. Patients who later died had much larger defects, involving about half of the left ventricle, with half of the defect being reversible and half being fixed. Patients who suffered heart failure also had large perfusion defects on adenosine-thallium scans. Patients who experienced recurrent infarction showed more ischemia than scar tissue on perfusion images (Table 2).

These data provide some guidelines for using myocardial perfusion images to risk-stratify post-MI patients on thrombolytic therapy. In this study (18), patients were also grouped according to perfusion defect characterization. Patients with defects <20% of the left ventricle had a low event rate, whereas patients with defects involving >20% of the left ventricle had a much higher risk for subsequent cardiac events over a 1.5-yr follow-up. If >10% of the left ventricle showed reversibility, indicating an ischemic defect, the prognosis was much worse than if <10% of the left ventricle was ischemic overall (in both the infarction and noninfarction region). Thus, the total amount of ischemia

TABLE 1
Sensitivities of Adenosine-Thallium SPECT for Detection of Individual Coronary Artery Stenoses

Stenosis	All vessels	Infarct-related artery	Noninfarct-related artery
Moderate (51% to 69%)	65 (28/43)	100 (17/17) [†]	42 (11/26)
Severe (≥70%)	95 (111/117) [*]	100 (83/83) [‡]	82 (28/34) [*]
All stenoses	87 (139/160)	100 (100/100) [†]	65 (39/60)

^{*}p = 0.0001 vs. moderate stenosis.

[†]p = 0.0001 vs. noninfarct-related artery.

[‡]p = 0.002 vs. noninfarct-related artery.

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TABLE 2

Cardiac Events Correlated with Perfusion Defect Size on Adenosine-Thallium SPECT Images

	No complications (n = 52)	Chest pain (n = 14)	CHF/death VT (n = 25/12)	Total complications (n = 41)
PDS total	22% ± 15%	33% ± 19% [*]	51% ± 14%	45% ± 18% [‡]
PDS ischemia	10% ± 10%	21% ± 16% [†]	18% ± 14% [§]	19% ± 14% [¶]
PDS scar	12% ± 10%	12% ± 8%	33% ± 10% [‡]	26% ± 16% [‡]

^{*}p = 0.047 vs. no complications.

[†]p = 0.01 vs. no complications.

[‡]p = 0.0001 vs. no complications.

[§]p = 0.004 vs. no complications.

[¶]p = 0.001 vs. no complications.

PDS = perfusion defect size; CHF = congestive heart failure; VT = ventricular tachycardia.

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was a potent predictor of future cardiac events. In addition, left ventricular ejection fraction (LVEF) was a strong indicator of survival. However, the number of diseased vessels did not make a statistically significant difference in predicting outcome (19).

PROGNOSTIC MODELS

All of these prognostic indicators can be combined to create models that predict outcomes with greater accuracy than predictions based on one variable. By plotting the total amount of ischemia in the left ventricle versus the LVEF measurement, one can determine whether an individual patient fits into a low- or high-risk category (19).

Sophisticated Versus Simplistic Image Interpretation

A recent multicenter study by Moss et al. concluded that detection of silent (asymptomatic) ischemia after acute MI or unstable angina is not useful in stratifying patients at risk for subsequent coronary events (20). This report has received considerable attention, but there are several flaws in the study design.

Of the 8500 patients screened for this study, 1800 were excluded because they underwent bypass graft shortly after MI, and 5700 other patients were excluded for unexplained reasons. Finally, less than 1000 patients were studied with submaximal exercise perfusion imaging. Patients did not undergo routine coronary angiography, and very few patients reached the hard end-point events of MI or cardiac death.

In addition, the interpretation of planar ^{201}Tl images was extremely simplistic; these studies were interpreted as either positive or negative. In today's clinical world of cardiovascular nuclear medicine, we can no longer expect to adequately stratify patients on the basis of a positive or negative ^{201}Tl study. Perfusion image interpretation must

be more sophisticated and must include an evaluation of the extent and severity of ischemia, not merely its presence.

RADIONUCLIDE ANGIOGRAPHY

Radionuclide angiography remains a powerful predictor of prognosis in post-MI patients (1–8). LVEF and end-systolic volume are strong predictors of mortality and congestive heart failure. Measurements that reflect residual ischemia during exercise, such as decreasing LVEF and deteriorating wall motion, are useful predictors of subsequent nonfatal MI and unstable angina.

CAUTIONARY FACTORS

There are several cautionary factors to remember when attempting to risk-stratify post-MI patients with myocardial perfusion imaging techniques.

Sicker patients often do not receive thrombolytic therapy. When reviewing a clinical trial of patients on thrombolytic therapy, it should be noted that these patients are not as sick as patients from past trials before thrombolytic agents were available.

Sicker patients often are not studied with noninvasive techniques. Their status directs them toward an invasive strategy (i.e., catheterization), and they often are not included in clinical trials designed to determine the value of myocardial perfusion imaging.

Fewer patients (20% to 35%) in the thrombolytic clinical trials have double- or triple-vessel disease; in many of the prethrombolytic trials, a majority of patients (about 66%) had multivessel disease. Moreover, after thrombolytic therapy, many patients are treated with beta-blockers or aspirin, which may further decrease the rate of subsequent cardiac events.

For the most part, thrombolytic trials include low-risk patients, who are difficult to stratify. According to a survey of all post-MI patients in the 1990 U.S. Medicare population, “all comers,” provided the patients are at least 65 yr of age, the majority of whom do not receive thrombolytic therapy, the 1-mo mortality was 23%, and the 1-yr mortality was 36% (21). These mortalities are severalfold higher than those for typical thrombolytic trials.

In light of these cautionary factors, it is still appropriate to risk-stratify post-MI patients who received thrombolytic therapy according to myocardial perfusion results and radionuclide angiography.

There are additional cautionary factors, unrelated to thrombolytic therapy, to consider when predicting outcomes in post-MI patients. Although stress testing is used to determine risk of subsequent cardiac events, recurrent infarctions usually occur at rest and may have a different mechanism. A 30% stenosis, for example, may not cause visible ischemia on a myocardial perfusion image, but it may cause a subsequent infarct due to plaque rupture followed by thrombosis.

Submaximal exercise, particularly when patients are

medicated with beta-blockers, may not be sufficient to elicit detectable ischemia. Pharmacologic stress agents should be used more widely to risk-stratify post-MI patients.

CONCLUSION

Myocardial perfusion imaging with radiotracers provides a noninvasive method of risk-stratifying post-MI patients for subsequent cardiac events. In addition, these studies can be used to help identify residual stenosis and multivessel disease, even in patients who received thrombolytic therapy. The results of several published studies concluding that perfusion imaging provides limited value in risk stratification and evaluation of diseased arteries may be influenced by low-risk study populations, submaximal exercise and unsophisticated interpretation of ^{201}Tl images.

Three parameters of myocardial perfusion imaging emerge as strong predictors of future cardiac events in post-MI patients: (1) presence of transient defects, (2) the number of transient defects and (3) increased radiotracer uptake in the lung. Catheterization, for the most part, does not add to the prognostic value of radionuclide stress testing.

The use of pharmacologic stress agents instead of submaximal exercise is recommended in post-MI patients for more meaningful myocardial perfusion study results.

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Condensed from 15 Years Ago:

Reproducibility of Ejection-Fraction Determinations by Equilibrium Radionuclide Angiography in Response to Supine Bicycle Exercise: Concise Communication

Matthias E. Pfisterer, Alexander Battler, Susan M. Swanson, Robert Slutsky, Victor Froelicher and William L. Ashburn

University of California Medical Center, San Diego, California

Sixteen patients with stable, chronic coronary artery disease were studied twice within an average of 15 days to evaluate the reproducibility of ejection fraction (EF) determined by equilibrium radionuclide angiography (EQ) at rest, during supine bicycle exercise (ex), and in the recovery period (rec).

Following injection of 20-25 mCi of ^{99m}Tc-tagged human serum albumin, data were analyzed for 2-min periods at rest, during several stages of exercise (submax, max), and during recovery (rec1 = min 2 + 3, rec2 = min 9 + 10). Each patient reached similar (heart rate) × (blood pressure) products in the two studies: 21280 ± 5200 compared with 20390 ± 4140 mmHg/min. Mean EFs for the first and second studies were: at rest (53.0 ± 10.8)%, (52.5 ± 10.4)% (r = 0.95); submax ex (51.4 ± 12.0)%, (52.1 ± 12.8)% (r = 0.91); max ex (50.6 ± 12.6)%, (51.6 ± 12.9)% (r = 0.97); rec1 (62.7 ± 11.6)%, (62.4 ± 12.2)% (r = 0.95); rec2 (55.5 ± 10.8)%, (57.2 ± 11.7)% (r = 0.91). In stable patients, the reproducibility of EF determined by EQ is excellent during rest, supine bicycle exercise, and recovery from exercise.

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