Risk Stratification Soon After Acute Infarction

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Two decades ago, exercise testing “soon after acute myocardial infarction” meant that stress testing was performed 3 weeks after the acute event. It was conventional wisdom that patients recovering from acute myocardial infarction should avoid physical activities exceeding a workload of 3 METs for some time. Formal physical rehabilitation was not commenced before 10 weeks after infarction. In 1979, Theroux et al challenged this concept by submitting patients with recent and uncomplicated acute infarction to submaximal exercise electrocardiography at the time of hospital discharge, which at that time was \( \approx 11 \) days after infarction. Not only was submaximal exercise testing shown to be safe in such patients, it also provided important prognostic information concerning the occurrence of future cardiac events. Although this landmark study set the stage for the use of exercise testing to evaluate patients with recent myocardial infarction, the prognostic power of exercise electrocardiography in later studies was found to be limited. This was probably due to difficulties in interpreting exercise ECGs in patients with abnormal resting ST-T segments. A few years later, Gibson et al showed that the addition of \( {}^{201} \text{Tl} \) myocardial perfusion imaging to submaximal predischARGE exercise electrocardiography significantly enhanced the power of the test for predicting future cardiac events compared with that of exercise electrocardiography alone. More recently, Mahmarian et al demonstrated that quantitative single photon emission computed tomography (SPECT) myocardial perfusion imaging with either exercise or pharmacological vasodilation in patients with recent myocardial infarction allowed patients to be stratified into low-, intermediate-, or high-risk groups. Cardiac events after infarction have been noted to occur predominantly during the 4 to 6 weeks after the acute event, after which time the cardiac event rate is considerably lower. Thus, risk stratification by stress testing should be performed before the patient is discharged from the hospital. When exercise testing is postponed until several weeks after infarction to achieve maximal exercise effort, there is substantial risk that some patients will already have suffered the cardiac events about which one wished to prognosticate. The 1996 “Guidelines for Management of Patients with Acute Myocardial Infarction” recommend submaximal exercise testing at 4 to 6 days after infarction and symptom-limited exercise at 10 to 14 days after infarction.

Early Dipyridamole Myocardial Perfusion Imaging

In the present issue of Circulation, Brown et al report the results of a multicenter trial in patients with their first acute myocardial infarction. They provide important and compelling data indicating that in selected patients, risk stratification can be performed much earlier. In 1990, Brown et al reported in a limited number of patients that early risk stratification without physical exercise was feasible with pharmacological vasodilation and planar \( {}^{201} \text{Tl} \) myocardial perfusion imaging on day 1 to 4 after acute myocardial infarction. In that study, abnormal dipyridamole \( {}^{201} \text{Tl} \) myocardial perfusion imaging was found to be a predictor of in-hospital and late cardiac events. Since this publication, there have been important changes in the healthcare environment such that early noninvasive risk assessment has become an attractive strategy to reduce the cost of hospitalization. In addition, there have been substantial technical advances in nuclear cardiology with the current widespread availability of multiheded, high-resolution SPECT gamma cameras, improvements in image and data processing, and the clinical availability of \( {}^{99m} \text{Tc} \)-labeled imaging agents.

The present report by Brown et al extends and confirms their previous observations in a larger number of patients with acute myocardial infarction from multiple clinical sites using state-of-the-art dipyridamole \( {}^{99m} \text{Tc} \)-sestamibi SPECT imaging. Of a total of 451 patients with first acute myocardial infarction enrolled in the study, 339 were randomized to early (2 to 4 days) dipyridamole \( {}^{99m} \text{Tc} \)-sestamibi SPECT imaging followed by predischarge (6 to 12 days) submaximal exercise SPECT, and 112 patients were randomized to submaximal predischarge exercise SPECT alone. The 3:1 randomization procedure was chosen to assess the relative safety of early dipyridamole infusion in patients with acute infarction. No adverse effects attributable to dipyridamole infusion were observed. An important aspect of the study was that the results of the early dipyridamole myocardial perfusion imaging study were not made available to the responsible physicians and thus could not influence patient management. The predischarge SPECT study was regarded as part of routine clinical care, and its results were available to those caring for the patient.

There were 29 in-hospital events (cardiac death, recurrent infarction, and revascularization) and 68 late cardiac events.
(cardiac death and recurrent infarction). Early dipyridamole myocardial SPECT was predictive of both in-hospital and late cardiac events and most importantly was a more powerful predictor than predischarge submaximal exercise SPECT. The extent and severity of the dipyridamole myocardial perfusion defects and the degree of defect reversibility were multivariate predictors for in-hospital events, as was the peak creatine kinase level. With respect to late cardiac events after hospital discharge, again, the extent and severity of dipyridamole defects, the degree of defect reversibility, the size of the rest defect, and anterior location of infarction were multivariate predictors. Although the extent and severity of the exercise myocardial perfusion defect were multivariate predictors of late cardiac events, they were less powerful predictors than early dipyridamole myocardial perfusion imaging. The larger the vasodilator-induced myocardial perfusion defect, the larger the defect reversibility, and the larger the rest defect, the higher the cardiac event rate. The extent of defect reversibility was a particularly powerful predictor in patients with intermediate-sized stress defects. In patients with large stress defects, regardless of the degree of defect reversibility, the event rate was high. An important observation in this prospective trial was that the prognostic value of stress myocardial perfusion imaging was not influenced by whether or not the patients received thrombolytic therapy. This is of importance in view of previous publications that questioned the usefulness of predischarge SPECT risk stratification in patients who had undergone thrombolysis.

### Caveats Concerning the Present Study

Because the results of early vasodilator SPECT imaging were not made available to the attending physicians, the study design makes it possible to assess the true predictive value for in-hospital events without the confounding effect of interventions consciously or subconsciously driven by the results of imaging. On the other hand, the predictive value of submaximal exercise imaging at discharge may have been reduced because of revascularizations triggered by the results of imaging that were available to responsible physicians. This constitutes one of the unavoidable limitations of evaluating the prognostic value of clinically well-accepted diagnostic methodologies. High-risk studies will trigger interventions designed to prevent imminent cardiac events. These immediate interventions may limit subsequent “hard” events in patients with the most abnormal studies. Thus, paradoxically, the diagnostic modality may appear to have lost its prognostic power.

All patients enrolled in this study had experienced their first myocardial infarction. It is therefore unclear whether the excellent results of this study can be extrapolated to infarct patients with prior infarction without additional research. In patients with prior infarction, it is conceivable that the extent of the resting defect or myocardial scar rather than defect reversibility may be the important predictor of cardiac events.

The study by Brown et al. was conducted at a time when angioplasty for acute infarction was not yet common practice. The same strategy of early risk stratification used in this study will also have to be tested in a patient population in which primary angioplasty is performed.

In the present study, SPECT imaging was not acquired with ECG gating. It is conceivable that the combined assessment of myocardial perfusion and function would have further enhanced the prognostic power of testing.

### Vasodilation Myocardial Perfusion SPECT

Vasodilation with dipyridamole is an attractive pharmacological procedure in patients with very recent acute infarction, because it does not produce myocardial ischemia in the majority of patients but rather increases myocardial blood flow by recruiting coronary flow reserve. Differences in coronary flow reserve due to significant residual coronary artery disease can be visualized after injection of a radiotracer. A potential disadvantage of dipyridamole is its relatively long effective half-life. In some patients with severe coronary artery disease, coronary steal may occur owing to reversal of blood flow in collateral circulation and may create true and undesirable myocardial ischemia. Although this usually can be reversed with intravenous aminophylline, the effect of dipyridamole may last for 20 to 45 minutes. In many nuclear cardiology laboratories, adenosine infusion is presently used instead of dipyridamole. In particular, in patients with recent acute infarction, adenosine has the substantial advantage of a 30-second half-life. Adverse effects of adenosine can be reversed quickly by discontinuation of the infusion. In the study by Brown et al., 12% of patients had ECG ST-T segment depression, presumably due to coronary steal. In the first days after acute myocardial infarction, dobutamine is a less attractive pharmacological stressor, because infusion will cause increased metabolic demand and may provoke undesirable supraventricular and ventricular arrhythmias and alterations in blood pressure.

### Early Hospital Discharge Strategy

This study provides compelling data for early risk stratification with vasodilator SPECT in patients with an uncomplicated early clinical course after acute infarction. In recent years, there has been considerable pressure to discharge infarct patients as early as possible. Indeed, some patients can be discharged earlier than others. With the advent of early revascularization for acute myocardial infarction, the natural history of infarction has changed dramatically. The size of infarction can be limited successfully in appropriate patients by thrombolysis or primary angioplasty. Not only do these patients have smaller infarcts, but the precise extent of coronary artery disease and/or the size of myocardial damage may be known, allowing for aggressive discharge clinical pathways. However, in many patients who are cared for in hospitals without direct access to coronary angiography, such detailed information is generally not available. There are proponents for the position that it is more convenient and cost-effective to perform early elective coronary angiography to assess the extent of coronary artery disease and then revascularize appropriate coronary stenoses rather than delay such management decisions by waiting for the results of predischarge exercise testing.

The important results of the study by Brown et al. should serve as evidence that patients who appear to recover well from acute infarction can be evaluated safely and effectively...
by vasodilator myocardial perfusion imaging as early as 2 to 4 days after admission. In particular, in smaller hospitals without immediate access to angiography and angioplasty, vasodilator myocardial perfusion SPECT can be used as an effective gatekeeper for discriminating between those patients who require transfer to larger centers for revascularization and those who are at low risk and can be managed conservatively in the hospital where they are initially hospitalized. In 1999, “soon after myocardial infarction” means the second or third day. If this management strategy of early postinfarction risk stratification is widely adopted, substantial cost savings can be realized in appropriate patient populations.

References


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