Perfusion Imaging

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The following historical review summarizes an important article on perfusion imaging originally published in JACC in September 1995. This article contributed to the greater understanding of the diagnostic and prognostic applications of exercise myocardial perfusion in patients with suspected or known coronary artery disease.

**Incremental Value of Prognostic Testing in Patients With Known or Suspected Ischemic Heart Disease: A Basis for Optimal Utilization of Exercise Technetium-99m Sestamibi Myocardial Perfusion Single-Photon Emission Computed Tomography**


**ABSTRACT**

A cohort of 1,702 patients was referred for exercise 99mTc-sestamibi single-photon emission computed tomography (SPECT) from January 1, 1991, to January 1, 1993, for whom follow-up could be obtained. Patients were followed for 20 ± 5 months. Of the 1,131 who had normal or equivocal scan results, 1 cardiac death and 1 myocardial infarction occurred (0.2% event rate), and 17 cardiac deaths and 26 nonfatal infarctions were reported in the 571 patients with abnormal scans (7.5% event rate). This low event rate in patients with normal or near-normal scans was similar in patients with a low (<0.15), intermediate (0.15 to 0.85) and high (>0.85) postexercise treadmill test (ETT) likelihood of coronary artery disease (CAD). In contrast, if the scan was abnormal, the hard cardiac event rates were 3.8%, 7.9% and 10.8% in these three groups, respectively. There were 1,282 patients with interpretable exercise electrocardiogram responses, of whom 231 were judged to have a 0% likelihood of CAD. The SPECT had incremental prognostic value in these patients, that in 167 had a normal scan with a 0% event rate and 64 had an abnormal scan with a 6.2% event rate. Of the 503 patients with an intermediate or high post-ETT likelihood of CAD, SPECT also provided incremental prognostic value in the 274 patients with a normal scan who had a 0% event rate, whereas the 229 patients with an abnormal scan had a 7.9% event rate. Risk stratification was also significantly enhanced in the 420 patients with uninterpretable ETT results. No events occurred in those with a normal scan. Finally, the nuclear scan strategy was shown to be cost-effective in patients with intermediate-to-high post-ETT likelihood of CAD if only patients with abnormal scans are referred to catheterization.

Review

Historical perspective. The Cedars-Sinai group has made major contributions to furthering the understanding of the diagnostic and prognostic applications of exercise or pharmacologic stress myocardial perfusion in patients with suspected or known coronary artery disease (CAD). In two studies published in 1986 and 1987, Dr. Berman et al. (1) showed the extent and severity of exercise-induced $^{201}$Tl defects on planar images were independent predictors of future cardiac events (2,3). These reports comprised the largest number of patients ever studied up to that time regarding the assessment of the prognostic value of a noninvasive imaging technique, and the study by Ladenheim et al. (3) was the first to demonstrate the incremental prognostic power of clinical variables, exercise electrocardiographic (ECG) stress test variables and myocardial perfusion imaging data. They extended the important initial observations of Brown et al. (4), who showed that the number of reversible $^{201}$Tl defects on stress scintigrams was the best predictor of death and nonfatal infarction in 100 patients without prior infarction who underwent exercise planar $^{201}$Tl scintigraphy. Using stepwise logistic regression analysis, Ladenheim et al. (3) identified the number of myocardial scan segments with reversible $^{201}$Tl defects and the exercise heart rate as the only independent predictors of subsequent events in 1,689 CAD patients without prior infarction. Other investigators confirmed or extended these findings (5–7), and collectively, these studies published in the 1980s showed that patients with normal perfusion scans had a <1% per year cardiac death or nonfatal infarction rate, whereas those with abnormal scans, particularly those showing a multivessel disease pattern, increased lung $^{201}$Tl uptake or transient ischemic left ventricular cavity dilation had a significantly higher event rate.

Prognostic value of $^{99m}$Tc-sestamibi SPECT. For many years, planar and single-photon emission computed tomography (SPECT) with $^{201}$Tl constituted the only scintigraphic technique available for detecting CAD and determining prognosis. The major limitation of $^{201}$Tl scintigraphy is a high false-positive rate for CAD detection experienced in many laboratories, which is predominantly attributed to image attenuation artifacts (8). In the past decade, new $^{99m}$Tc-labeled perfusion imaging agents were introduced to clinical practice that provided image quality superior to that achieved with $^{201}$Tl because of the more favorable physical characteristics of $^{99m}$Tc for imaging with a SPECT camera. Sensitivity for CAD detection was comparable for $^{99m}$Tc-sestamibi and $^{201}$Tl images, but $^{99m}$Tc-sestamibi yielded enhanced specificity. The Berman article demonstrated the incremental value for determining prognosis over clinical and exercise treadmill test (ETT) data utilizing a dual-imaging protocol (rest $^{201}$Tl/exercise $^{99m}$Tc-sestamibi) in 1,702 patients who were followed after testing for 20 ± 5 months. In this study, patients were divided into low, intermediate and high pretest likelihood of CAD on the basis of clinical and exercise ECG stress test data. $^{99m}$Tc-sestamibi scan results further separated patients into lower and higher risk subgroups. One very important finding in this landmark study was that the cardiac event rate for patients with normal scans was low for all levels of prescan likelihood of CAD. For example, of the 90 patients who were classified as having a >85% likelihood of CAD after the ETT, and who had a normal scan, none had a cardiac event during follow-up. Thus, the cardiac event rate in patients with a normal $^{99m}$Tc-sestamibi SPECT study was very low, even when clinical and exercise stress test variables suggested a high risk of CAD. The rates of referral to catheterization after $^{99m}$Tc-sestamibi SPECT imaging were also low in patients with normal perfusion studies, even if they had a high likelihood of CAD when analyzing only the clinical and ETT results.

The Berman study was one of the first to provide data concerning the cost benefit of nuclear testing. The nuclear scan was cost-effective in patients with interpretable exercise ECG responses and an intermediate-to-high post-ETT likelihood of CAD and in those with uninterpretable exercise ECG responses and an intermediate-to-high pre-ETT likelihood of CAD. In contrast, nuclear testing was not cost-effective in patients who had a low likelihood of having CAD after ETT. Going directly to catheterization based on the ETT alone cost $2,089 per patient as compared with $1,729 per patient when only patients with abnormal nuclear scan results were referred to catheterization.

Subsequent prognostic studies. After the publication of the Berman study, the Cedars-Sinai group continued to evaluate the prognostic value of exercise SPECT. In a study by Hachamovitch et al. (9), nuclear testing was found to add significant incremental prognostic value to the Duke treadmill score for risk assessment. There were 834 patients classified as having an intermediate risk of subsequent death infarction on the basis of the Duke treadmill score who had a normal scan. The subsequent hard event rate was 0.4% during follow-up of this group. Multiple logistic regression analysis revealed that scan information from $^{99m}$Tc-sestamibi SPECT contributed 95% of all the information regarding referral to catheterization. In another publication by Hachamovitch et al. (10), the Cedars-Sinai group reported that during exercise $^{99m}$Tc-sestamibi SPECT provided incremental prognostic value for both men and women. In fact, receiver operating characteristic (ROC) analysis demonstrated superior discrimination for the nuclear scan results in identifying high-risk women than men (area under curve: 0.84 in women vs. 0.71 in men; p < 0.0005). In that study, the odds ratio comparing events of patients with abnormal scan results versus those with normal scan results was greater in women than in men, suggesting superior stratification using SPECT imaging in women. When added to the clinical and exercise model in a Cox proportional hazards analysis, nuclear data provided...
17% more prognostic information in men and 37% more in women when compared with clinical and exercise variables alone. That study comprised 2,742 men and 1,394 women who underwent the dual-isotope SPECT protocol and were followed for an average of 20 ± 5 months.

The Cedars-Sinai group went on to demonstrate in a retrospective analysis of their patient cohort that the results of SPECT imaging might assist in deciding which patients with abnormal scans would do well with medical therapy compared with early revascularization (11). They found that the annual cardiac death rate was only 0.8% in patients with mildly abnormal stress perfusion scans who received medical treatment after testing compared with an annual death rate of 0.9% in patients with a mildly abnormal scan who underwent early revascularization after testing. In contrast, patients with moderately abnormal and severely abnormal scans (more extensive defects) benefited from revascularization early after nuclear testing.

Finally, the Cedars-Sinai group, in conjunction with several other institutions, prospectively enrolled 11,372 consecutive stable chest pain patients who had been referred for stress myocardial perfusion imaging or cardiac catheterization (12). The stress imaging patients and the direct catheterization patients were matched by their pretest clinical risk of CAD (low, intermediate and high). The composite three-year cost of care for the two management strategies was compiled. These strategies were an initial stress perfusion SPECT with selective catheterization of high-risk patients (clinically high risk and those with ischemia on SPECT) or direct catheterization as the initial diagnostic approach to diagnosing CAD. The investigators found that diagnostic and follow-up costs of care were 30% to 41% higher for the patients undergoing direct catheterization in all pretest clinical risk subsets. The costs for the direct cardiac catheterization strategy ranged from $2,878 to $4,579 compared with $2,387 to $3,010 (p < 0.001) for the stress perfusion imaging plus selective catheterization strategy.

Influence on the field. These clinical observational studies reported by Berman et al. (1)—describing the supplementary diagnostic and prognostic value, as well as the cost-effectiveness, of stress myocardial perfusion imaging over clinical and exercise ECG stress test data in large numbers of men and women with suspected or known CAD—have had a great influence on the area of clinical decision making. Risk stratification and management strategies were developed based on studies in which known outcome was linked to noninvasive imaging variables, such as the extent of stress-induced hypoperfusion. The concept has thus emerged that stress myocardial perfusion imaging may function as a “gatekeeper” for referral for invasive strategies because it may identify low-risk groups who have an excellent prognosis treated with medical therapy and do not benefit from early revascularization. Conversely, the identification of high-risk patients who would most likely benefit from early revascularization on the basis of an expected high cardiac event rate with medical treatment can also be accomplished. This management approach, in which referral for cardiac catheterization is ischemia driven, is also highly cost-effective.

REFERENCES