Long-Term Outcome of Patients With Intermediate-Risk Exercise Electrocardiograms Who Do Not Have Myocardial Perfusion Defects on Radionuclide Imaging

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Background—The appropriate management of patients with intermediate-risk Duke treadmill scores is not established. The purpose of this study was to determine the long-term risk of subsequent cardiovascular events in patients with an intermediate-risk treadmill score who do not have myocardial perfusion defects on radionuclide imaging.

Methods and Results—The existing databases of the nuclear cardiology laboratories of 4 academic institutions were searched retrospectively. A total of 4649 patients were identified who had intermediate-risk Duke treadmill scores (10 to 4), normal or near-normal exercise single photon-emission computed tomographic myocardial perfusion images using either thallium-201 or technetium-99m sestamibi, and no previous coronary revascularization. Follow-up was 95% complete. Cardiovascular survival was 99.8% at 1 year, 99.0% at 5 years, and 98.5% at 7 years. Cardiac survival free of myocardial infarction was similarly high at 96.6% at 7 years. Cardiac survival free of myocardial infarction or revascularization was 87.1% at 7 years. Near-normal scans and cardiac enlargement were independent predictors of time to cardiac death. Seven-year cardiac survival was still high at 97.0% in the 357 patients with near-normal scans and normal cardiac size and somewhat lower, at 89.0%, in the 167 patients with cardiac enlargement.

Conclusions—Patients with an intermediate-risk treadmill score but with normal or near-normal exercise myocardial perfusion images and normal cardiac sizes are at low risk for subsequent cardiac death and can be safely managed medically until their symptoms warrant revascularization. The appropriate management of patients with cardiac enlargement will remain a matter of clinical judgment. (Circulation. 1999;100:2140-2145.)

Key Words: exercise radioisotopes coronary disease

Although patients with severe angina are customarily referred for cardiac catheterization, the decision to proceed with cardiac catheterization in patients with mild or moderate symptoms is often based on a noninvasive assessment of their risk for future cardiac events.1,2 The exercise treadmill score developed on inpatients at Duke University,3 and subsequently tested prospectively on outpatients,4 is the single most well-validated approach to noninvasive risk stratification. It has been featured in several clinical practice guidelines.1,2,5

Approximately 60% of outpatients will have a low-risk treadmill score, with an anticipated 4-year cardiovascular survival rate of 99%.4 Given this low risk of future events, referral for coronary angiography is certainly debatable. In the small percentage (<5%) of outpatients with a high-risk score and a reported 4-year cardiovascular survival of only 79%, early coronary angiography would seem to be warranted. The remaining third of patients with an intermediate-risk Duke treadmill score have an expected 4-year cardiovascular survival of 95%. The appropriate management of such patients is not well established.

Patients with a normal exercise myocardial perfusion test have a very low subsequent cardiac event rate, as has been demonstrated in multiple studies.6,7 The purpose of this multicenter study was to test the hypothesis that a normal or near-normal exercise myocardial perfusion test in a patient with an intermediate-risk treadmill test would be associated with a very low long-term risk of subsequent cardiovascular events.

Study Group

The study group was identified retrospectively by searching the existing databases of the nuclear cardiology laboratories at 4 institutions: Allegheny University of the Health Sciences (Hahmemann), Cedars-Sinai Medical Center, Columbia University, and the Mayo Clinic (R.J.G., D.O.H., K.R.B), Rochester, Minn; Cedars Sinai Medical Center (D.S.B., R.H.), Los Angeles, Calif; Allegheny University of the Health Sciences (J.H., A.E.I.), Philadelphia, Pa, and Columbia University (O.O.A.), New York, NY.

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Clinic. Patients who underwent exercise myocardial perfusion imaging for the evaluation of known or suspected coronary artery disease after January 1, 1985, and before January 1, 1995, and had a calculable Duke treadmill score (see below) were eligible for the study. The following were grounds for exclusion: (1) previous coronary angioplasty, (2) previous coronary artery bypass surgery, (3) significant valvular heart disease, (4) congenital heart disease, (5) known cardiomyopathy, and (6) an uninterpretable exercise test on the basis of left bundle branch block, paced rhythm, or preexcitation syndrome.

Of the 15,352 eligible patients identified at the 4 participating centers, 8,775 had an intermediate-risk treadmill score. Of these, 4,649 patients (53.0%) had normal or near-normal myocardial perfusion images (see below).

Treadmill Exercise Testing
All patients underwent treadmill exercise using a variety of different protocols. For patients who had exercise tests using protocols other than the standard Bruce protocol, a conversion factor was applied to equate exercise duration with the duration of exercise on the Bruce protocol. Electrocardiographic monitoring was performed continuously. Twelve-lead ECGs and blood pressure were obtained at each level of exercise. Exercise was continued to 1 of the following endpoints: severe fatigue, moderate to severe angina, sustained ventricular tachycardia, a decline in systolic blood pressure from baseline, or ≥2 mm horizontal or downsloping ST segment depression. Angina that forced termination of the test was termed “limiting.”

The maximal degree of horizontal or downsloping ST segment change 80 ms after the J point was measured to the nearest 0.5 mm in any lead (except AVR) during exercise or recovery.

Calculation of the Duke Treadmill Score
The treadmill score was calculated as described by Mark et al:

Score = Duration of exercise (min; Bruce protocol) – (5 × maximal ST-segment change [mm]) – (4 × angina index)

The angina index was 0 if the patient had no angina during exercise, 1 if the patient had angina that did not limit exercise, and 2 if the patient had limiting angina. Patients were eligible for the study if they had an intermediate-risk (moderate-risk) score of −10 to 4.4

Myocardial Perfusion Imaging
At peak exercise, either thallium-201 (3.0 to 4.0 mCi) or technetium-99m sestamibi (20 to 30 mCi) was injected; exercise was continued for 60 to 90 s.

Single photon-emission computed tomographic (SPECT) imaging was performed by each center according to its usual routine. Allegheny (n = 526) used a previously described thallium protocol in 452 patients and a 1-day stress-rest sestamibi protocol in 74 patients. Columbia (n = 563) used thallium, and Cedars-Sinai (n = 2345) used a previously reported dual-isotope protocol. Mayo (n = 1215) employed previously described thallium protocols in 1036 patients and a 2-day sestamibi protocol in 179 patients.

All images were reconstructed using standard filters and reconstruction algorithms. The images were reviewed visually by 1 or 2 experienced observers and categorized as normal, near-normal, or abnormal. Near-normal scans were those with nonspecific abnormalities (usually small fixed defects consistent with breast or diaphragmatic attenuation) that were judged subjectively not to represent evidence of coronary artery disease. Cardiac enlargement was judged subjectively at 3 of the 4 centers on the poststress image, and therefore presumably included both fixed and transient left ventricular dilatation; Allegheny did not record this parameter. The interpretations were performed at the time of the clinical study.

Follow-up
Patient follow-up was performed by each of the 4 laboratories by letter or telephone. Events were confirmed by physician contact or hospital records. Significant events consisted of death, nonfatal myocardial infarction, coronary angioplasty, or coronary artery bypass surgery. Deaths were classified as either cardiac or noncardiac. Deaths that could not be classified were considered cardiac. Coronary angiography was assessed separately as a measure of the need for subsequent diagnostic testing.

Follow-up was >97% at 3 of the 4 centers, but only 88% at Columbia University, which reflects its enrollment of an urban, minority, socioeconomically disadvantaged population. Overall, 4,473 patients (95%) had follow-up; subsequent data analysis and presentation focused on this group. Of the 2,345 patients from Cedars Sinai, short-term follow-up for 834 patients was previously reported.

Data and Statistical Analysis
The Section of Biostatistics at the Mayo Clinic coordinated the study and analyzed the data. Each participating center provided 45 clinical and follow-up variables for each patient. Analysis of 3 end points was performed: (1) cardiac death, (2) cardiac death or nonfatal myocardial infarction, and (3) cardiac death, nonfatal myocardial infarction, or late (after 90 days) coronary angioplasty or coronary artery bypass grafting. Survival free of these events was estimated by the Kaplan-Meier method. Patients who died from noncardiac causes (n = 86) were censored from analysis at the time of death. Patients who underwent revascularization after 90 days were censored at the time of revascularization from analysis of the end points of (1) cardiac death or (2) cardiac death or nonfatal myocardial infarction. Patients who underwent revascularization before 90 days were censored from analysis of all 3 endpoints. Upper and lower confidence intervals were computed using Greenwood’s formula, Simple and multiple associations of risk factors and other stratification variables with end point rates were tested using Cox proportional hazards models. Variables of interest included sex, age, traditional atherosclerotic risk factors, symptoms, previous myocardial infarction, high likelihood of coronary artery disease (men with typical angina and patients with previous myocardial infarction), cardiac enlargement, increased lung uptake (thallium scans only), image interpretation (normal or near-normal), the Duke treadmill score, and center where the study was performed.

When near-normal scan interpretation proved to be a significant predictor of multiple end points, post hoc analysis was performed to determine if any of the following parameters predicted a near-normal scan: radiopharmaceutical used, age, sex, duration of exercise, angina during exercise, ST change during exercise, or Duke score.

Results
Overall Results
The clinical and exercise characteristics of the study population are shown in Table 1. The mean age was 61 ± 11 years, and 54.3% of the participants were women. The patients exercised for 4.7 ± 3.8 minutes on the Bruce protocol; many of the patients had intermediate-risk treadmill scores because of poor exercise capacity. However, 57.3% had either angina or ≥1 mm of horizontal or downsloping ST depression during exercise.

During a mean follow-up of 3.2 years (minimum, 1 year; median, 2 years), a total of 26 cardiac deaths, 57 nonfatal myocardial infarctions, and 75 coronary revascularizations occurred. A total of 45 of these revascularizations (60%) used percutaneous approaches; the remaining 30 (40%) consisted of coronary artery bypass grafting. During follow-up, 285 additional patients underwent coronary angiography without subsequent revascularization.
Cardiovascular Survival

Cardiac survival (Figure 1; Table 2) was 99.8% at 1 year, 99.0% at 5 years, and 98.5% at 7 years. The 95% lower confidence limit for cardiac survival at 1 year was 99.7%; at 5 years, 98.5%; and at 7 years, 97.8%. No discernible increase in cardiac mortality occurred over time; the average annual cardiac mortality during 7 years of follow-up was 0.21%.

Cardiac survival free of myocardial infarction was similarly high, at 99.7% for 1 year, 97.8% for 5 years, and 96.6% for 7 years (Figure 2). Cardiac survival free of myocardial infarction or revascularization was 98.2% at 1 year, 91.1% at 5 years, and 87.1% at 7 years (Figure 2). The curves for both cardiac survival free of myocardial infarction and cardiac survival free of myocardial infarction or revascularization were both linear over time and did not suggest any change in the annual event rate.

The cumulative incidence of coronary angiography (before or without revascularization) was 3.2% by 1 year, 11.8% by 5 years, and 17.1% by 7 years (Figure 3). The annual rate of coronary angiography also appeared to be linear over time after an initial small number of angiograms.

Predictors of Cardiac Mortality

On a univariate basis, previous myocardial infarction and high likelihood of coronary artery disease did not predict cardiac death or myocardial infarction, but they did predict subsequent revascularization (Table 3). Of the exercise parameters, failure to achieve 80% of maximum predicted heart rate was significantly associated with all end points. Of the imaging parameters, both near-normal images and cardiac enlargement were significantly associated with all end points. Increased lung uptake (thallium studies only) was not significant by itself, but it was highly significant in the presence of cardiac enlargement.

On a multivariate basis, a near-normal perfusion scan (odds ratio, 9.3; 95% confidence limits, 3.0 to 28.7) and cardiac enlargement (odds ratio, 9.3; 95% confidence limits, 1.5 to 12.2) demonstrated a significant (P<0.01), independent association with time to cardiac death. The 3463 patients with normal perfusion scans and normal heart sizes had a 5-year cardiac survival of 99.6% and a 7-year cardiac survival of 99.4% (Figure 4). In contrast, the 357 patients with near-normal scans and normal heart sizes had a 7-year cardiac survival of 97.0%, and the 167 patients with cardiac enlargement had a 7-year cardiac survival of only 89.0%. Only 23 patients had both cardiac enlargement and near-normal scans, which precluded analysis of this subgroup.

No evidence of heterogeneity of event rates between centers (P=0.83) existed on formal analysis. The results did not change significantly if the patients from Columbia University (the center with the lowest rate of complete follow-up) were excluded from the analysis. No association between treadmill score and cardiac mortality existed on either a univariate or multivariate basis.

Near-Normal Images

The location of the minor abnormality of the near-normal images was anterior in 23%, inferior in 42%, and other (primarily apical) in 35%. On post hoc analysis, increasing age (P<0.001), male sex (P<0.001), ST change with exercise (P=0.003), and a lower treadmill score (P=0.005) were all associated with an increased likelihood of near-normal images, but duration of exercise (P=0.93), angina during exercise (P=0.73), and radiopharmaceutical used (P=0.63) were not.

Discussion

One of the major goals of the clinical and noninvasive assessment of patients with known or suspected coronary artery disease is to identify a group of patients who have such a low risk of subsequent cardiovascular mortality that they...
need not undergo coronary angiography in an effort to improve their subsequent survival. Patients with a low-risk treadmill test (Duke treadmill score $\geq 5$) are such a group. The results of this study demonstrate that patients with an intermediate-risk treadmill score (10 to 4) but normal exercise myocardial perfusion images and cardiac size are also a very low-risk group. The 5-year cardiac survival reported here for patients with normal perfusion scans and no cardiac enlargement (99.6%) exceeds the 4-year cardiac survival rate (99%) reported for patients with a low-risk treadmill test. Because the reported mortality risk of coronary revascularization is $\geq 1\%$, it is highly unlikely that revascularization will improve the survival of patients with an intermediate-risk treadmill score, normal exercise myocardial perfusion images, and normal cardiac size. Such patients can, therefore, presumably be safely managed medically until their symptoms warrant revascularization.

Patients with intermediate-risk treadmill scores constitute a significant subset of all patients undergoing exercise testing, although the exact percentage varies widely between studies. Many patients with intermediate-risk treadmill scores have positive ST segment changes (1 mm horizontal or downsloping ST segment depression), but some patients qualify on the basis of angina during exercise and/or a limited exercise duration. In the original inpatient population used to validate the treadmill score, Mark et al found that 62% of inpatients had intermediate-risk treadmill scores. In their subsequent prospective study in a lower risk outpatient population, the percentage of patients with an intermediate-risk treadmill score was only 34%. Previous reports from 2 of the laboratories participating in this study included a mixture of both inpatients and outpatients. Hachamovitch et al reported that intermediate-risk treadmill scores occurred in 54% of patients referred for exercise myocardial perfusion imaging; Iskandrian et al reported a similarly high percentage of 46%. Thus, the prevalence of intermediate-risk treadmill scores in the literature ranges from 33% to 66% of all patients undergoing treadmill testing. In this study, 57% of all patients with a calculable treadmill score had an intermediate risk score. About half of the patients with an intermediate-risk score will have normal myocardial perfusion images and normal cardiac size and, therefore, an excellent prognosis. This large cohort of patients need not undergo early coronary angiography in an effort to improve their cardiac survival.

The laboratories participating in this study all performed SPECT myocardial perfusion imaging but used different radiopharmaceutical approaches and observers. No detectable difference existed between centers on formal testing, suggesting that the specific radiopharmaceutical approach used did not affect the results. We did not test interobserver or intraobserver variability. Our results are consistent with many

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LCL95 indicates 95% lower confidence limit; UCL95, 95% upper confidence limit; and MI, myocardial infarction.

Figure 2. Cardiac survival free of myocardial infarction (solid line) and cardiac survival free of myocardial infarction or revascularization (dashed line) for 4473 patients with follow-up. Number of patients eligible at each interval, and the 95% confidence limits, are provided in Table 2.

Figure 3. Cumulative incidence of coronary angiography (either before or without revascularization) for 4473 patients with follow-up. The cumulative incidence of angiography was only 17.1% by 7 years.
previously reported studies, demonstrating that a normal exercise myocardial perfusion image is associated with very low subsequent cardiac mortality.\(^6,7\) Although the majority of this literature was based on the use of planar or SPECT thallium studies, more recent studies have described similar results using technetium-99m sestamibi\(^15\) and dual isotope protocols.\(^7\) Our results should apply, regardless of the specific radiopharmaceutical protocol used. However, all of the laboratories participating in this study are high-volume laboratories with expert observers who interpreted the images. Our results should not be extrapolated to low-volume laboratories with less expert observers without further study.

Subsequent cardiac death in this low-risk patient population was relatively more frequent in patients with near-normal images, ie, the presence of a nonspecific abnormality on myocardial perfusion imaging, although the absolute event rate remained low in this group. Such abnormalities are often attributed to breast attenuation, diaphragmatic attenuation, or technical artifact. One previous small study using planar thallium imaging reported that such findings were still indicative of an excellent prognosis.\(^16\) Several possible explanations exist for the finding of a higher cardiac event rate in patients with nonspecific abnormalities. These abnormalities may represent prior infarction rather than attenuation. Alternatively, they may represent areas of myocardial ischemia, where the reversibility of the defects was not appreciated. Finally, it is conceivable that they are due to attenuation but that this reduced the sensitivity of the imaging technique for the detection of subtle areas of ischemia in the same region. The post hoc analysis would suggest that near-normal images were more likely in patients who were at greater risk for underlying coronary artery disease on the basis of clinical and exercise parameters. Further technical improvements, such as quantitative methods, gated SPECT imaging,\(^17\) and attenuation correction,\(^18\) which were not used in this study, may help to address this limitation.

Although the 7-year cardiac survival of the patients with nonspecific abnormalities (97.0%) is clearly worse than that of patients with normal images, their annual mortality remains very low (<0.5%). A previous meta-analysis\(^19\) found that coronary artery bypass grafting offered no mortality benefit compared with medical treatment in patients who were classified as low-risk, with a 5-year mortality of 5.5% (annual mortality, 1.1%). Revascularization is, therefore, unlikely to improve the survival of patients with near-normal images and normal cardiac size.

The other imaging parameter that was associated with subsequent cardiac death was the presence of cardiac enlargement, which was interpreted subjectively. Scans with this finding would usually be classified as abnormal in the absence of perfusion abnormalities. Although information about this parameter was only available from 3 of the 4 centers, it was clearly of great prognostic importance. This finding presumably reflected underlying left ventricular dysfunction. Although it is conceivable that this dysfunction was related to ischemic heart disease, the absence of perfusion abnormalities would suggest that these patients more likely had an unrecognized cardiomyopathy. This finding is consistent with a previous study of patients with left
bundle branch block,20 which found that the presence of cardiac enlargement along with other evidence of left ventricular dysfunction identified a high-risk subset of patients. Measurements of left ventricular function were not routinely performed at the time these patients were studied. However, such measurements are now readily available using either first-pass radionuclide angiography or gated SPECT myocardial perfusion imaging.17 The appropriate management of these patients will remain a matter of clinical judgment.

These results do not apply to patients who are unable to exercise, who have undergone prior revascularization, or patients with uninterpretable ECGs. These patients were excluded from the previous validation studies of the treadmill score and from this study. Limited experience exists in the application of the treadmill score to patients >80 years of age. Only 2.6% of the patients in this study were >80 years of age, suggesting that our results should be applied with caution in this group. Our results should not be applied to the far smaller group of patients with high-risk scores. In 90 such patients reported by Hachamovitch et al,22 the prevalence of normal images was lower (31%) and the event rate was higher (3.6%) in the presence of normal images.

Despite these limitations, our results suggest that exercise myocardial perfusion imaging in patients with intermediate-risk treadmill scores may obviate the need for coronary angiography in many patients. The cost of coronary angiography is 4-fold higher than myocardial perfusion imaging.23 If the performance of exercise myocardial perfusion imaging in all patients with intermediate-risk Duke treadmill scores eliminates the need for coronary angiography in many such patients, it would seem to be cost effective for this purpose, without even considering the potential cost of the rare complications (including death) associated with coronary angiography. In the current era, when the cost-effective allocation of health-care resources is a primary concern, our results seem to have important implications for patient management because they suggest that such patients should undergo exercise myocardial perfusion imaging as a first step. Coronary angiography can be avoided in those patients with normal or near-normal exercise myocardial perfusion images and normal cardiac size. We hope that subsequent Clinical Practice Guidelines carefully consider this evidence.

Acknowledgements

Supported by a grant from the American Society of Nuclear Cardiology, Bethesda, Md. The American Society of Nuclear Cardiology solicited funds for this specific project from ADAC Laboratories, Amersham Healthcare, DuPont Pharmaceuticals, Fujisawa Healthcare, Genia Automedics, Mallinckrodt Medical, and Merck & Co.

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_Circulation_. 1999;100:2140-2145
doi: 10.1161/01.CIR.100.21.2140
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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