Exercise Single-Photon Emission Computed Tomography Provides Effective Risk Stratification of Elderly Men and Elderly Women

Uma S. Valeti, MD; Todd D. Miller, MD; David O. Hodge, MS; Raymond J. Gibbons, MD

Background—In a recent study, we reported that the Duke treadmill score was unable to effectively stratify elderly patients according to risk. The purpose of this study was to evaluate the prognostic value of exercise single-photon emission computed tomography (SPECT) in this same population and to examine results by gender.

Methods and Results—A cohort of 247 elderly (age ≥75 years) patients (108 women, 139 men, age 77 ± 3 years) who underwent exercise thallium-201 SPECT were followed up for a median duration of 6.4 years. SPECT variables were significantly associated with cardiac death: summed stress score (SSS) χ² = 19.5, P < 0.001; summed difference score χ² = 12.3, P < 0.001; increased lung uptake χ² = 9.6, P = 0.002; and left ventricular enlargement χ² = 8.3, P = 0.004. The Duke score was not significantly associated with cardiac death (χ² < 1, P = NS). The SSS classified most patients as low risk (49%) or high risk (35%); the Duke score classified the majority (68%) as intermediate risk. Annual cardiac mortality rates for patients categorized by SSS as low risk and high risk were 0.8% and 5.8%, respectively. Cardiac survival rates according to SSS risk categories were significantly different for both women (P = 0.012) and men (P = 0.003).

Conclusions—SPECT classified most elderly patients into clinically useful low- and high-risk categories and accurately predicted outcomes in both genders. If these results can be validated in future studies, exercise SPECT rather than standard treadmill testing may emerge as the initial noninvasive testing strategy in elderly patients who are able to exercise. (Circulation. 2005;111:1771-1776.)

Key Words: aging ■ exercise ■ prognosis ■ radioisotopes ■ scintigraphy

The elderly aged ≥75 years constitute 6% of the US population. They account for two thirds of cardiovascular deaths. American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend treadmill exercise testing as the initial noninvasive method for evaluating coronary artery disease (CAD) in patients with a normal or near-normal resting ECG who can adequately exercise regardless of age. The guidelines acknowledge that the elderly and women represent special populations in whom treadmill testing may be less accurate, but there are insufficient data to recommend stress imaging over standard treadmill testing in these groups. We recently reported that the Duke treadmill score failed to stratify elderly patients according to risk. Although single-photon emission computed tomography (SPECT) generally is more accurate for prognostic purposes than standard treadmill testing, there are few published data on the prognostic value of exercise myocardial perfusion imaging in the elderly, especially elderly women. The purposes of the present study were 2-fold: (1) to examine whether exercise SPECT could provide risk stratification for elderly patients for whom the Duke treadmill score could not and (2) to compare clinical and exercise SPECT results stratified by gender.

Methods

Study Population

The study cohort has been described previously. Our initial study was designed to compare the prognostic value of the Duke treadmill score in the elderly (≥75 years old) versus younger patients. A retrospective analysis of the Mayo Clinic nuclear cardiology database was performed to identify all patients who underwent exercise treadmill thallium (Tl)-201 SPECT between January 1989 and December 1991 who met the same criteria originally used in the development of the Duke score: (1) symptomatic with chest pain or dyspnea; (2) no recent (<3 months) myocardial infarction (MI); (3) no prior percutaneous coronary intervention (PCI) or CABG; (4) no clinical evidence of congenital or cardiomyopathic heart disease; and (5) interpretable ECG during exercise (left bundle-branch block, paced rhythm, preexcitation, or digoxin use excluded). Patients were included regardless of peak exercise heart rate attained. A total of 2551 patients were identified, of whom 247 were ≥75 years old (the study population for the present study). Chest pain was coded according to the criteria of Diamond. Clinical, exercise, and SPECT imaging variables were collected at the time of SPECT into a computer database. Resting ECGs were stored in a separate
Exercise 201Tl SPECT

These methods have been described previously. Patients underwent treadmill exercise using the Bruce protocol. A conversion factor was applied to approximate time on the Naughton protocol to time on the Bruce protocol. The Duke score was calculated as previously described.

Near peak exercise, 3 to 4 mCi of 201Tl were injected. Patients were imaged in the supine position beginning 10 minutes after exercise. An anterior planar image was obtained for 5 minutes to assess cardiac size and pulmonary activity. Tomographic imaging was then performed over a 180° arc with the “step-and-shoot” method. Filtered back projection was performed with a Ramp-Hanning filter. Resting images were acquired 3 to 4 hours later. Patients tested after January 1, 1990, were reinjected with 1 mCi of 201Tl. Image interpretation was done by consensus of 2 experienced observers using a 14-segment short-axis model and a 5-point scoring system (0 = absent uptake; 1 = severely decreased uptake; 2 = moderately decreased uptake; 3 = mildly decreased uptake; and 4 = normal uptake). Because most mild fixed defects represent soft tissue attenuation, these segments (scores of 3 on both images) were considered to be normal and recoded to scores of 4. Summed stress attenuation, these segments (scores of 3 on both images) were calculated from the 14 short-axis segments as originally described by the Cedars-Sinai group.19 SSS and SDS risk categories (0 to 1) were adapted to our scoring system. SDS risk categories included low (48 to 52), intermediate risk (43 to 47), and high risk (48 to 52).

Follow-Up

Patient follow-up was conducted with mailed questionnaires, scripted telephone interviews, review of medical records, or physician contacts. Defined events included death, nonfatal MI, PCI, and CABG. Stated events were confirmed by review of the hospital chart, a death certificate, or a clinician’s report. A reviewer blinded to other data coded the cause of death. MI was diagnosed on the basis of chest pain, ECG changes, and cardiac enzymes. Revascularization procedures were defined as early (≤3 months) or late (>3 months) after SPECT. Follow-up was 95% complete at a median duration of 6.4 years.

Statistical Analysis

Differences between women and men were compared with the rank sum test for continuous variables and the χ² test for categorical variables. Three end points were analyzed: cardiac death, cardiac death/MI, and cardiac death/MI/late PCI or CABG. Patients with PCI/CABG at any time were censored from the first 2 end points. Patients with early PCI/CABG were censored from the death/MI/late PCI or CABG end point. Associations between exercise SPECT variables and outcome were tested with proportional hazards models. Multivariate models were created by the stepwise method. Survival curves were generated by the Kaplan-Meier method. Differences between survival curves were tested with the log-rank test. Once it was determined that the SPECT SSS was associated with outcome (see Results), multivariate models were created post hoc to determine the independent prognostic value of SPECT imaging in relation to clinical variables and the Duke score. The clinical variables considered for these models included age, gender, prior MI, chest pain classification, diabetes, smoking, hypertension, and hyperlipidemia. Statistical significance was defined as P < 0.05.
Results

Clinical Characteristics
The study group consisted of 108 women and 139 men (Table 1). Mean age was similar. Notable differences between groups included a higher percentage of typical angina and smoking in men and more hypertension and hyperlipidemia in women. Only 42 patients (17%) had an established clinical history of CAD on the basis of old (>3 months) MI. Of the 126 patients with ST-T abnormalities on the resting ECG, only 7 had major (>1 mm) ST-segment deflection.

Exercise SPECT Results
Exercise duration was shorter in women, but more men developed angina and had an ischemic ECG (Table 2). There was no difference in Duke score risk categories. A normal SPECT scan (SSS = 56) was present in 56% of women versus 22% of men (P < 0.001). All 4 SPECT imaging variables (SSS, SDS, increased lung uptake, and left ventricular enlargement) were worse in men.

Risk Classification by Duke Score and SPECT
The Duke score classified most patients (68%) as intermediate risk and only 26% as low risk and 6% as high risk (Figure 1); in contrast, the SSS categorized substantially more patients as low risk (49%) or as high risk (35%) and only 16% as intermediate risk. Figure 2 shows examples of 2 patients with similar intermediate-risk Duke scores, but one with low-risk and the other with high-risk SPECT images.

Prognostic Comparison of Duke Score and SPECT
During follow-up, there were 33 cardiac deaths (11 women, 22 men) and 17 nonfatal MIs (10 women, 7 men). Revascularization procedures included 17 early PCIs (5 women, 12 men), 10 early CABGs (5 women, 5 men), 26 late PCIs (8 women, 18 men), and 18 late CABGs (8 women, 10 men). Table 3 shows the univariate associations between the 4 SPECT imaging variables and the Duke score with clinical outcome. As reported previously, the Duke score demonstrated a statistically significant association only with the combined end point of cardiac death/MI/late PCI or CABG. SPECT imaging variables were strongly associated with all end points. In multivariate analyses, the SSS was the only variable predictive of cardiac death (χ² = 19.5, P < 0.001) or cardiac death/MI (χ² = 14.4, P < 0.001). A post hoc analysis demonstrated that the SSS was also associated with cardiac death (χ² = 4.1, P = 0.04) in the subset (48%) of patients who failed to reach 85% of predicted maximal heart rate. Figure 3 shows cardiac survival according to SSS risk categories. Differences between survival curves were highly significant (P < 0.001). For cardiac mortality, the Duke score appeared to be able to identify high-risk patients (estimated annual cardiac mortality 4.8%), but the differences between risk categories were not statistically significant, primarily because of the limited number of patients in the high-risk category. Additionally, patients categorized as low risk by the Duke score had an annual cardiac mortality rate of 2.0%. In contrast, prediction of annual cardiac mortality by SSS categories was more useful (low risk 0.8%, high risk 5.8%).

Prediction of Outcome by Gender
Overall, cardiac survival was better in women than men (P = 0.009). Cardiac survival was significantly different according to SSS risk categories in both women (Figure 4) and men (Figure 5). Annual cardiac mortality was 4.6% in women and 6.0% in men in high-risk patients and 0.6% in women and 1.4% in men in low-risk patients. Outcome by SSS risk categories was also significantly different for each gender for the other end points of cardiac death/MI (women P < 0.001, men P = 0.008) and cardiac death/MI/late PCI or CABG (women P = 0.010, men P = 0.051).

Multivariate Models
Post hoc models were created for the end points of cardiac death, cardiac death/MI, and cardiac death/MI/late PCI or...
CABG. For the end point of cardiac death, the model \( \chi^2 \) for clinical variables was 14.05. Independent variables were prior MI (adjusted \( \chi^2 7.73, P = 0.005 \)) and gender (adjusted \( \chi^2 4.74, P = 0.03 \)). The addition of the SSS increased the model \( \chi^2 \) to 19.09 (\( P = 0.02 \)). The only independent variable in this model was the SSS (adjusted \( \chi^2 5.03, P = 0.02 \)). Gender (\( P = 0.12 \)) and prior MI (\( P = 0.27 \)) were no longer significant once the SSS was entered into the model. The SSS was also an independent variable in the models for cardiac death/MI (\( P = 0.008 \)) and for cardiac death/MI/late PCI or CABG (\( P = 0.002 \)).

**Discussion**

This study demonstrates that exercise SPECT was both more efficient and more accurate than standard treadmill testing for risk stratification of patients aged \( \geq 75 \) years who were able to exercise. ACC/AHA guidelines recommend medical therapy for patients categorized as low risk and coronary angiography (with revascularization if warranted) for high-risk patients.4 A test that is efficient for risk stratification should classify most patients as low risk or high risk. Treatment of intermediate-risk patients is less certain, and these patients frequently require additional testing to refine risk status. In the present study, the percentage of the population classified as intermediate risk decreased from 68% by the Duke score to 16% by SPECT. ACC/AHA guidelines also recommend an annual cardiac mortality threshold <1% to correctly identify a population as low risk and >3% to identify a population as high risk. The Duke score classified one fourth of the population as low risk with observed annual cardiac mortality of 2.0%; SPECT classified one half of the population as low risk with an observed annual cardiac mortality of 0.8%. Substantially more patients were classified as high risk by SPECT than by the Duke score (35% versus 6%), with an observed mortality rate of 5.8%. Inspection of the survival curves (Figures 3 through 5) reveals little to no difference in survival for low- and intermediate-risk patients by SSS. This finding might simply be due to the small numbers of patients in the SSS intermediate-risk category, but the possibility exists that a more abrupt threshold occurs in elderly patients between those in the low- and intermediate- versus high-risk categories than the more gradual escalation of risk across categories in younger patients.10,11

**Potential Explanations for the Study Results**

Exercise duration is a major component of risk classification by the Duke score. Elderly patients with limited exercise...
capacity (<5 minutes with the Bruce protocol) will be categorized as intermediate or high risk depending on the presence and severity of angina and ECG changes. These manifestations of ischemia are less common in the elderly.20 Conversely, the SSS is a scintigraphic measure of the extent and severity of both ischemic and infarcted myocardium. Patients without CAD will be classified as low risk regardless of workload achieved. SSS high-risk classification only requires scan evidence of extensive and severe ischemia, a finding that appears to be easier to demonstrate in these patients than the more "stringent" combination of abnormal variables required for high-risk classification by the Duke score.

Rationale for Risk Stratification in the Elderly

Average life expectancy at age 75 is 10 years for men and 12 years for women.21 A major reason to perform risk stratification is to identify those patients with left main/3-vessel CAD in whom CABG improves life expectancy.2 The 7 randomized, controlled trials comparing medical therapy versus CABG performed 2 decades ago enrolled primarily men between the ages of 40 and 60 years.22 Age >65 years and female gender were exclusion criteria in many of these trials. The recent Trial of Invasive versus Medical therapy in Elderly patients (TIME)23,24 compared medical therapy to coronary angiography followed by revascularization (if feasible) in 282 CAD patients aged ≥75 years (42% women). At 1 year, there were no differences in rates of death or MI, but there were fewer major adverse cardiac events (which included hospitalization for unstable angina) in patients assigned to angiography. Observational studies also suggest that survival in octogenarians is prolonged with revascularization.25,26 More data are necessary to determine which elderly patients benefit from an aggressive strategy. Until such data become available, extrapolation of results from studies of middle-aged men to elderly patients will continue. In the United States, one fourth of PCI/CABG procedures are performed in patients aged ≥75 years, and one third are performed in women.27 Accurate risk stratification of these patients is important.

Prior Studies

Although previous studies of stress testing have included elderly patients, few have specifically focused on the elderly, especially women. A small number of studies that involved “younger” elderly patients (mean ages 65 to 72 years) suggest that exercise testing and myocardial perfusion imaging can predict outcome.14–16,28 Results were not presented separately by gender. Several studies have examined women,29–35 but the ages of the women in these studies were substantially younger. The unique aspects of the present study are inclusion of the “older” elderly (≥75 years old) and demonstration of the risk stratification value of exercise SPECT in both genders.

Study Limitations

The major limitation relates to selection bias. The study population represents a group of elderly patients who were referred to a nuclear cardiology laboratory at a tertiary-care medical center and were judged to be “healthy” enough to perform adequate exercise. Other elderly patients with different clinical characteristics might be more effectively evaluated with different testing strategies. Elderly patients referred for pharmacological SPECT may be “sicker,” and the results of this study may not apply to them. The radioisotope was 201TI rather than one of the technetium-based isotopes that are more commonly used at the present time. SPECT perfusion images are usually similar with these different isotopes.3 Measurements of gated SPECT regional wall motion and ejection fraction were not performed. Patients in the present study underwent SPECT imaging nearly 15 years ago. Owing to advances in medical therapy, event rates might be lower if this study were performed at the present time.

Implications

With the aging of the population, there will be a shift in disease burden from younger to older patients, especially older women, because life expectancy is greater in women than in men. The elderly and women have been underrepresented in studies of CAD for a number of years.36,37 Evaluation and management of these patients is commonly performed by extrapolation of studies in middle-aged men. ACC/AHA guidelines recommend treadmill testing as the initial noninvasive method for assessment of CAD in patients with a normal or near-normal resting ECG, regardless of age or gender. Most patients (97%) in the present study met these ECG criteria. SPECT was both more efficient and more accurate for risk stratification of this population. If these results can be confirmed in futures studies, exercise SPECT rather than standard treadmill testing may emerge as the initial exercise testing modality in both women and men aged ≥75 years who are able to exercise.

Acknowledgments

We thank Pam McCabe and Tamie Tiedemann for secretarial preparation of the manuscript and Tammy Hudson for assistance with collection of follow-up data.

References


Exercise Single-Photon Emission Computed Tomography Provides Effective Risk Stratification of Elderly Men and Elderly Women
Uma S. Valeti, Todd D. Miller, David O. Hodge and Raymond J. Gibbons

Circulation. 2005;111:1771-1776; originally published online April 4, 2005; doi: 10.1161/01.CIR.0000160862.36124.8E
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
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:
http://circ.ahajournals.org/content/111/14/1771

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/