Long-term prognosis after a normal exercise stress Tc-99m sestamibi SPECT study

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Background. **Patients with a normal stress technetium 99m sestamibi study were shown to have a favorable outcome at intermediate-term follow-up. However, long-term survival has not been studied. The aim of this study was to evaluate the incidence and predictors of mortality and cardiac events at long-term follow-up after a normal exercise stress sestamibi study.**

Methods and Results. **We studied 218 patients (mean age, 53 ± 10 years, 108 men) who had normal myocardial perfusion assessed by Tc-99m sestamibi single photon emission computed tomography at rest and during symptom-limited bicycle exercise stress test. Endpoints during a follow-up period of 7.4 ± 1.8 years were hard cardiac events (cardiac death and nonfatal myocardial infarction) and all-cause mortality. During follow-up, 13 patients died of various causes (cardiac death in 1 patient). Ten patients had nonfatal myocardial infarction (a total of 11 hard cardiac events). By multivariate analysis, independent predictors of cardiac events were history of coronary artery disease ($\chi^2 = 5$, $P = .03$) and lower exercise heart rate ($\chi^2 = 12$, $P = .001$). Independent predictors of all-cause mortality were age ($\chi^2 = 4$, $P = .05$) and exercise heart rate ($\chi^2 = 5$, $P = .03$). The annual mortality rate was 0.6% in the first 5 years and 1.8% between the sixth and eighth years. The annual hard cardiac event rate was 0.7% in the first 5 years and 1.5% between the sixth and eighth years. Receiver operating characteristic curves identified an exercise heart rate lower than 130 beats/min as the cutoff value that separated patients with regard to their risk for mortality and hard cardiac events.**

Conclusions. **It is concluded that the annual mortality and cardiac event rate is less than 1% during 5-year follow-up after a normal exercise sestamibi study. Therefore repeated testing would not be required unless there is a change in symptoms. Follow-up should be closer in patients with a history of coronary artery disease and in those who fail to achieve an exercise heart rate of 130 beats/min or greater. (J Nucl Cardiol 2003;10:261-6.)**

Key Words: Exercise stress test • sestamibi single photon emission computed tomography • prognosis • mortality • coronary artery disease

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Identification of patients at low risk of cardiac events has an important impact on management by avoiding the risk and cost related to further diagnostic and therapeutic approaches, which are unlikely to improve the outcome in low-risk patients.[1-3] Stress technetium 99m sestamibi single photon emission computed tomography (SPECT) imaging is a useful technique for the diagnosis and prognostic stratification of patients with known or suspected coronary artery disease (CAD).[4-23] Patients with a normal stress sestamibi myocardial perfusion study were reported to have a low event rate at short- and intermediate-term follow-up.[9,19] However, the long-term outcome after a normal study is unknown. Because of the lack of long-term follow-up data, it is not known whether patients with a normal study may require repeated testing, and if so, what the duration of a low-risk status is in a patient with a previously normal study. In addition, data regarding overall mortality after a normal sestamibi study are scarce. The aim of this study was to evaluate the incidence and predictors of mortality and cardiac events at long-term follow-up after normal exercise stress Tc-99m sestamibi SPECT results.

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METHODS

Patient Selection

The study population comprised consecutive patients referred for exercise stress testing in conjunction with Tc-99m sestamibi SPECT between 1988 and 1995, who had normal

myocardial perfusion at rest and during exercise stress testing. Patients with significant valvular heart disease were excluded from this study. Patients with unstable chest pain were generally excluded from stress testing. Follow-up data were collected in the year 2000 and could be completed in all patients. The mean follow-up duration was 7.4 ± 1.8 years (range, 5.2-11.7 years in patients without events).

Exercise Stress Test

All patients underwent a symptom-limited upright bicycle ergometry test with a stepwise increment of 20 W each minute.[24] An ischemic response was defined as horizontal or downsloping ST-segment depression of 1 mm or greater persisting 80 milliseconds after the J point.

SPECT Imaging

Approximately 1 minute before the termination of the exercise stress test, an intravenous dose of 370 MBq of Tc-99m sestamibi was administered.[24] Stress images were acquired 1 hour after termination of the exercise test. For resting studies, 370 MBq of sestamibi was injected 24 hours after the stress study. Image acquisition was performed with a Siemens Gammasonics single-head Rota Camera (Orbiter; Siemens Corp, Iselin, NJ). Thirty-two projections were obtained, from the left posterior oblique to the right anterior oblique over 180°. The semiquantitative interpretation of the scan was performed by visual analysis assisted by the circumferential profiles analysis as previously described.[25] A normal study was defined as absence of perfusion abnormalities.

Follow-up

Follow-up was obtained by mailed questionnaires and scripted telephone interviews. Events were verified by contacting primary physicians and reviewing medical records and death certificates. The endpoints considered were all-cause mortality and hard cardiac events, defined as nonfatal myocardial infarction and cardiac death. Myocardial infarction was defined according to usual clinical, electrocardiographic, and enzymatic criteria. Patients who had coronary revascularization before other events were censored at the time of revascularization.

Statistical Analysis

The χ^2 test was used to compare differences between proportions. The Student *t* test was used for analysis of continuous data. Logistic regression models were used to identify independent predictors of follow-up events. $P < .05$ was considered statistically significant. Parameters included in the multivariate analysis model were those found to be significant (or of borderline significance, $P < .1$) in the univariate analysis.

RESULTS

Clinical Features

The patients' mean age was 53 ± 10 years. There were 108 men and 110 women. Forty-seven patients (twenty-two percent) had a history of CAD (previous non–Q-wave myocardial infarction in 14 patients and previous coronary angioplasty in 33 patients studied 1.2 ± 2.1 years after the intervention). None of the patients had previous coronary artery bypass surgery. In the remaining patients, the pretest probability of CAD based on the classification of Diamond and Forrester[25] was low in 57 patients and intermediate or high in 114 patients. Medications on the day of the test included β-blockers in 68 (31%) patients, calcium channel blockers in 59 (27%), and angiotensin-converting enzyme inhibitors in 27 (12%). Chest pain was the main complaint in 158 (72%); this was classified as atypical of angina in 114 and typical in 44. Risk factors for CAD were diabetes mellitus in 14 patients (6%), cigarette smoking in 58 (27%), hypercholesterolemia in 53 (24%), and hypertension in 71 (33%).

Hemodynamic Response

There was a significant increase in heart rate (78 ± 15 beats/min vs 148 ± 24 beats/min, $P < .0001$) and systolic blood pressure (137 ± 21 mm Hg vs 188 ± 25 mm Hg, $P < .0001$) from rest to peak exercise, respectively. The target heart rate (85% of the maximal predicted heart rate) was reached in 161 patients (74%). The mean working capacity was 144 ± 42 W. Nine patients (four percent) had ST-segment depression, and 25 (11%) had angina induced by exercise.

Follow-up

During follow-up, 13 patients died of various causes (cardiac death in 1 patient). Ten patients had nonfatal myocardial infarction (a total of 11 hard cardiac events). Revascularization procedures were performed in 15 patients (5 underwent coronary artery bypass surgery and 10 underwent coronary angioplasty). All patients had a change in symptoms that necessitated referral for coronary angiography according to the discretion of the treating physician. Univariate predictors of myocardial revascularization were history of CAD (hazard ratio = 4.6; 95% confidence interval [CI], 2-11), lower exercise heart rate (hazard ratio = 0.9; 95% CI, 85-94), and exercise-induced angina (hazard ratio = 2.6; 95% CI, 1.01-7.2). By multivariate analysis, a history of CAD was the only independent predictor (hazard ratio = 4.6; 95% CI, 1.8-9).

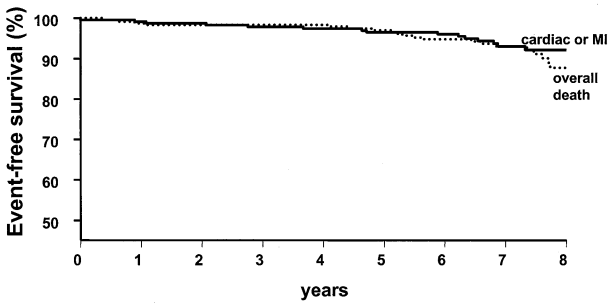

Figure 1. Kaplan-Meier survival curves after a normal exercise sestamibi study. *MI*, Myocardial infarction.

Clinical and exercise stress test variables associated with hard cardiac events in the Cox regression model are presented in Table 1. Independent predictors in the multivariate analysis were a history of CAD and lower exercise heart rate. Predictors of all-cause mortality are presented in Table 2. Age and exercise heart rate were independent predictors of mortality. The annual mortality rate was 0.6% in the first 5 years and 1.8% between the sixth and eighth years. The annual hard cardiac event rate was 0.7% in the first 5 years and 1.5% between the sixth and eighth years. The annualized hard cardiac event rate was 0.5% in patients without a history of CAD and 1.5% in patients with a history of CAD. Figure 1 demonstrates survival curves for both endpoints in the entire population.

Receiver operating characteristic curves identified an exercise heart rate lower than 130 beats/min as the cutoff value that separated patients with regard to risk for mortality and hard cardiac events. Kaplan-Meier survival curves based on ability to achieve an exercise heart rate of 130 beats/min or greater are shown in Figure 2 (hard cardiac events) and Figure 3 (all-cause mortality). The incidence of hard cardiac events showed a statistically significant difference by 2 years between patients who achieved an exercise heart rate of 130 beats/min or greater versus those who did not. Survival curves (endpoint of hard cardiac events) in patients with and without a history of CAD are presented in Figure 4. The difference between both groups was statistically significant at 5 years of follow-up.

Table 1. Predictors of hard cardiac events (cardiac death and nonfatal myocardial infarction) in a Cox regression analysis

Variable	χ^2	*P*	Hazard ratio	95% CI
Univariate analysis				
Hypertension	5	.03	3.8	1.1-13.9
History of CAD	6	.009	4.6	1.3-15.7
Exercise heart rate	8	.003	0.96	0.94-0.99
ST depression	9	.002	15	1.5-32
Multivariate analysis				
History of CAD	5	.03	4.8	1.2-19.8
Exercise heart rate	12	.001	0.95	0.92-0.98

Table 2. Predictors of all-cause mortality in a Cox regression analysis

Variable	χ^2	*P*	Hazard ratio	95% CI
Univariate analysis				
Age	14	.0001	1.13	1.05-1.21
History of CAD	7	.005	4.5	1.4-14.2
Exercise heart rate	16	.0001	0.96	0.94-0.98
Target heart rate achieved	6	.01	4.1	1.2-13
ST depression	2	.1	4.6	0.6-41
Multivariate analysis				
Age	4	.05	1.08	1.00-1.17
Exercise heart rate	5	.03	.97	0.95-1.00

DISCUSSION

In this study we assessed the long-term outcome of 218 patients with suspected or known CAD who were followed up for a mean of 7.4 years after a normal exercise stress Tc-99m sestamibi study. The annual mortality rate was 0.6% in the first 5 years and 1.8% between the sixth and eighth years. The hard cardiac event rate was 0.7% in the first 5 years and 1.5% between the sixth and eighth years. Therefore the study demonstrated that the low-risk warrantee of a normal exercise sestamibi study exists during the 7 years after the test with a particularly low event rate in the first 5 years. In a multivariate analysis of clinical and exercise stress test data, independent predictors of mortality were age and exercise heart rate. Independent predictors of hard cardiac events were history of CAD (previous myocardial infarction or coronary angioplasty) and exercise heart rate. Failure to achieve a maximal exercise heart rate of 130 beats/min or greater identified patients with a higher risk of death and hard cardiac events.

Impairment of heart rate response to exercise has been associated with an increased risk of mortality and incident CAD. The associated risk was reported to be persistent after adjustment to the qualitative presence of perfusion abnormalities.[26] One possible explanation of the association between lower heart rate response and events in our study is the reduced sensitivity of exercise stress myocardial perfusion imaging at a lower heart rate,

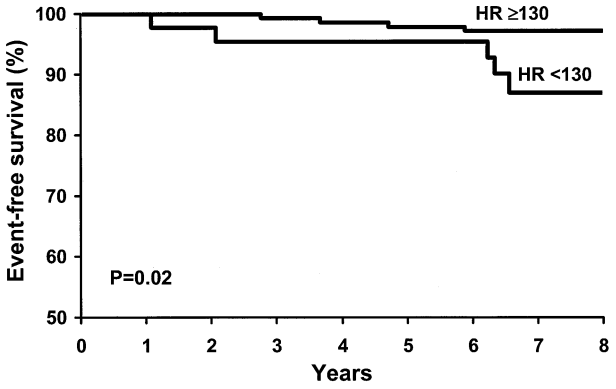

Figure 2. Kaplan-Meier event-free survival for the endpoint of cardiac death and nonfatal myocardial infarction according to the ability to achieve an exercise heart rate (*HR*) of 130 beats/min or greater.

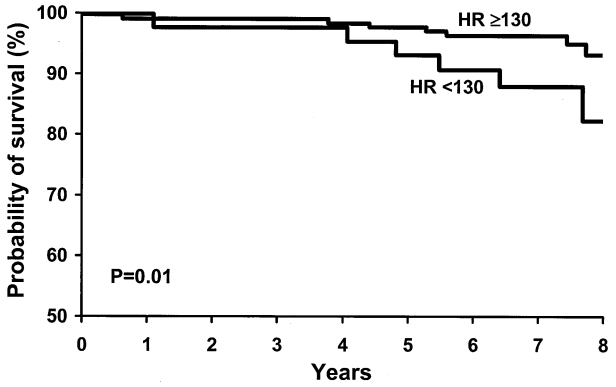

Figure 3. Kaplan-Meier survival for the endpoint of all-cause mortality according to the ability to achieve an exercise heart rate (*HR*) of 130 beats/min or greater.

reflecting the inability to induce myocardial ischemia with exercise. Therefore patients who fail to achieve a heart rate of 130 beats/min or greater may profit from another stress testing study after 1 to 2 years, as event-free survival curves showed significant diversion by 2 years (Figure 2). Perhaps a pharmacologic stress study may overcome the potential limitation of reduced sensitivity of exercise myocardial perfusion imaging in patients with low exercise heart rate.

There were 11 hard cardiac events among the 218 patients in this study during follow-up. These consisted mainly of nonfatal myocardial infarction (10 patients), whereas only 1 patient had cardiac death. A history of CAD was an independent predictor of hard events. The occurrence of nonfatal myocardial infarction in these patients does not necessarily indicate failure of the technique to predict functionally significant CAD, as these patients may have had no flow-limiting lesion by the time of stress testing. In addition, patients studied

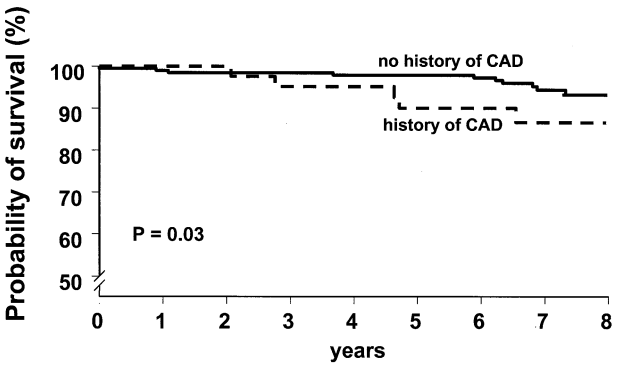

Figure 4. Kaplan-Meier event-free survival for the endpoint of cardiac death and nonfatal myocardial infarction in patients with and without a history of CAD.

after angioplasty may have a normal study with late progression to restenosis and myocardial infarction. The event-free survival rate was significantly different between patients with and without a history of CAD by 5 years of follow-up. Therefore we recommend that the stress test should be repeated after 4 years of a normal exercise perfusion study in patients with a history of CAD.

Comparison With Previous Studies

To our knowledge, this study provides the longest-term follow-up after stress sestamibi study, with a mean follow-up of 7.4 years as compared with the mean follow-up in previous studies, which ranged between 13 and 28 months. Stratmann et al[7] found that the annualized rate of nonfatal myocardial infarction or cardiac death in 521 patients after exercise sestamibi SPECT was 0.5% with a normal study and 7% with an abnormal study. Brown et al[9] reported a 0.5% annual event rate in 234 patients with normal exercise or dipyridamole planar sestamibi imaging followed up for 10 ± 2 months. In another study of 207 patients with normal exercise planar or SPECT sestamibi studies, none died during a follow-up period of 13.5 ± 2 months, whereas 1 patient (0.5%) had a nonfatal myocardial infarction.[8]

Berman et al[6] used dual-isotope imaging in 1702 patients with known or suspected CAD. Only 2 of 1131 patients with normal or equivocal studies (0.2%) had a nonfatal myocardial infarction or cardiac death during a follow-up of 20 ± 5 months, as compared with 43 of 571 patients with an abnormal study (8%). In 2200 patients without documented CAD followed up for a mean of 1.6 years after exercise testing with dual-isotope SPECT, Hachamovitch et al[5] reported a hard cardiac event rate of 0.3% over the follow-up period in 1623 patients with normal SPECT studies. In 412 patients with intermediate

pretest probability of CAD followed up for 17 ± 13 months, Nallamouthu et al[13] reported only 1 event in 295 patients with normal studies (0.3%; $P < .0001$). Travin et al[21] studied 1226 men and 1151 women who underwent sestamibi SPECT with either exercise or dipyridamole testing. A normal rest-stress sestamibi study was associated with an annual rate of cardiac death or nonfatal myocardial infarction of 1.7% in men and 0.8% in women. Steinberg et al[27] reported a follow-up of 288 patients with normal stress thallium myocardial imaging for a mean of 10.3 years. The cardiac mortality rate was 1% and the total mortality rate was 6.3% at 10 years.

Studies that evaluated the prognostic value of pharmacologic stress sestamibi SPECT have reported a low risk of cardiac events in patients with a normal study. However, the event rate tended to be higher after a normal pharmacologic study as compared with normal exercise stress studies, reflecting the higher risk status of a population unable to perform exercise stress testing.[28]

Evaluation of All-Cause Mortality

Recently, the evaluation of all-cause mortality as a separate follow-up endpoint has gained increasing interest. This is because of the difficulties encountered in determining the actual cause of death[29] and the association of CAD with other comorbid conditions, which are independently predictive of death. This is the first study that evaluates long-term mortality after stress sestamibi studies. We found that patients with normal sestamibi studies have a very low annual mortality rate during a mean of 7.4 years of follow-up. However, the mean age of the study patients was 53 years, which is younger than the ages in most outcome studies. This may explain in part the low overall mortality rate and therefore the results may not apply to an older population.

Conclusion

This study showed that the annual mortality and cardiac event rate is less than 1% during 5-year follow-up after a normal exercise sestamibi study. Therefore, in general, repeated testing should not be required during the 5 years after a normal study, unless there is a change in symptoms. Follow-up should be closer in patients with a history of CAD and in those who fail to achieve an exercise heart rate of 130 beats/min or greater.

Acknowledgment

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