Women with High Exercise Tolerance and the Role of Myocardial Perfusion Imaging

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Summary

Background: Myocardial perfusion imaging (MPI) provides incremental diagnostic and prognostic information, even in patients with high exercise tolerance.

Hypothesis: Myocardial perfusion imaging provides significant diagnostic value, specifically in women with high exercise tolerance.

Methods: Our study population consisted of all women who underwent exercise MPI in our Department from January 1992 to June 1996 and reached at least Stage IV in the Bruce protocol. Patients were divided into those with known and those with possible coronary artery disease (CAD). All patients were followed for 3 years from the performance of MPI.

Results: Of 4,803 women who underwent myocardial perfusion imaging, 3,183 had exercise stressing, and of those, 311 reached at least Stage IV in the Bruce protocol. Of these 311 MPI scans, only 23 (7.4%) were abnormal (reversible, fixed, or mixed) and the remaining 288 (92.6%) were normal. Of the 82 patients with known CAD, 13 (15.8%) had an abnormal MPI, while only 10 (4.4%) of the 229 patients with possible CAD. No myocardial infarction or cardiac death occurred within 3 years; one patient with normal MPI needed revascularization.

Conclusion: In women with high exercise tolerance, especially in those without already known CAD, the yield of MPI is very low. Women with high exercise tolerance have an excellent prognosis.

Key words: women, myocardial perfusion imaging, exercise

Introduction

Ischemic heart disease is the leading cause of death in women in the United States.¹ Myocardial perfusion imaging (MPI) has incremental diagnostic and prognostic value over exercise stress testing alone in women with coronary artery disease (CAD).^{2,3} In general, patients with normal MPI have an excellent prognosis, despite the presence of CAD in a large percentage of those tested,^{5–9} and specifically women with normal MPI have an excellent prognosis.^{2–4}

Similarly, high exercise tolerance alone is associated with an excellent prognosis, even in patients with known CAD.^{10–13} Although MPI helps in overall risk stratification of patients with high exercise tolerance,¹⁴ its diagnostic value in women with high exercise tolerance has not been established.

In the present study we evaluate the diagnostic value of MPI in women with high exercise tolerance.

Patients and Methods

Patients

Our study population consisted of a consecutive group of female patients who reached at least Stage IV in the Bruce protocol. From January 1992 until June 1996, there were 4,803 women who underwent MPI in our Department. Treadmill exercise MPI was performed in 3,183 and pharmacologic stress MPI was performed in 1,620. Of those who underwent treadmill exercise, 311 reached at least stage IV in the Bruce protocol.

Of these 311 patients, 82 had known CAD. They had had previous coronary artery revascularization, angiographic evidence of at least one coronary artery stenosis involving > 50% of the luminal diameter, a myocardial infarction (MI), or a combination of these events. The remaining 229 patients had symptoms suggesting possible CAD.

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Methods

Exercise Protocol

Exercise testing was performed after the patient had fasted for at least 4 h. If possible, beta-blocking agents were discontinued for 24 to 48 h before the study, and long-acting nitrate agents were withheld for at least 4 h. All patients underwent maximal symptom-limited exercise testing according to the standard Bruce protocol.¹⁵ Heart rate and blood pressure were measured, and a 12-lead electrocardiogram (ECG) was obtained before exercise, at the beginning of each stage of exercise, during the first min of the recovery period, and then every min for at least 5 min or (in the presence of ST-segment changes or arrhythmias) until the ECG returned to baseline. Exercise endpoints included physical exhaustion, claudication, angina pectoris, dyspnea, ST-segment depression ≥ 2 mm, ST-segment elevation, sustained ventricular tachycardia, or exertional hypotension (≥ 10 mm decrease in systolic blood pressure).

Imaging Protocol

Myocardial perfusion imaging was performed with technetium-99m (^{99m}Tc) sestamibi using a single day, "rest-stress" protocol.¹⁶ For rest imaging, 9 to 10 mCi (333–370 MBq) of ^{99m}Tc sestamibi was injected intravenously. One h later, single photon emission computed tomography (SPECT) was performed with (1) a triple-headed detector camera (Prism 3000 XP; Picker International, Cleveland, Ohio, USA); a low-energy, high-resolution collimator; a 20% symmetrical window at 140 keV; a 64×64 matrix; elliptical orbit with 120 projections, using step and shoot acquisition at 3° degree intervals with 20 s dwell time per stop; or (2) a single-headed detector camera (General Electric 3000; General Electric, Waukesha, Wisconsin, USA); a low-energy, high-resolution collimator; a 20% symmetrical window at 140 keV; 64×64 matrix; a circular orbit with 64 projections, using step and shoot acquisition at 3° degree intervals, with a 20 s dwell time per stop.

After the completion of rest imaging, the patient exercised on the treadmill as described above. Technetium-99m sestamibi 27–30 mCi (999–1110 MBq) was injected intravenously at peak exercise and the patient continued to exercise for 1 min. Stress imaging was begun 15 to 30 min after the end of exercise according to the same protocol used for the rest MPI. All stress acquisitions (except those involving significant arrhythmias) were gated, using eight frames per cycle and a 20% window for the RR interval.

Image Interpretation

All studies were interpreted by a nuclear medicine specialist who was blinded to the patient's clinical information except for gender, weight, height, and breast size. The static tomographic perfusion images were displayed in the short-axis, vertical long-axis, and horizontal long-axis views. By modifying the alignment of the images as well as the window and

intensity, the interpreter could select the most appropriate display of slices and was able to choose from all the gated slices in these three axes.

The static tomographic images were reviewed first, followed by the gated slices. Unprocessed data were reviewed last to identify soft tissue attenuation or motion during image acquisition, which could cause artifacts.

Defects were described as mild, moderate, or marked. Those present only on stress images were considered reversible perfusion defects; those present on both stress and rest images, with decreased motion or thickening in the gated images, were considered fixed perfusion defects; and defects that were worse during stress than at rest, with decreased wall motion in the gated images, were considered mixed (reversible and fixed) defects. Those present both during stress and at rest, with normal wall motion in the gated images, were attributed to soft tissue attenuation and were considered normal.^{17, 18}

Each MPI study was classified overall as either normal or abnormal. Abnormal MPI studies consisted of one or more reversible, fixed, or mixed defects.

Diagnosis/Indication for Myocardial Perfusion Imaging

Patients with known CAD: Patients with prior coronary artery bypass graft (CABG), prior nonsurgical revascularization, or prior MI were identified (Table I). Sixteen patients had a combination of surgical and nonsurgical revascularizations and/or prior MI.

Patients with possible CAD: Review of the inpatient or outpatient charts was performed for identification of the main indication for the performance of MPI. Table I demonstrates the indications identified. When there was a prior diagnostic test (resting or exercise ECG) that was suspicious for CAD, the test results were considered to be the main indication for the performance of MPI.

TABLE I Diagnosis/indications for the patients undergoing myocardial perfusion imaging for patients with known and with possible coronary artery disease

Known CAD (n = 82)	Possible CAD (n = 229)
1. CABG	1. Arrhythmia
2. MI	2. MVP
3. PTCA	3. TMT+
	4. CP
	5. Pre-op
	6. ECG+
	7. Dyspnea
	8. Syncope
	9. Hypercholesterolemia

Abbreviations: CABG = coronary artery bypass graft, CAD = coronary artery disease, CP = chest pain, ECG+ = positive baseline electrocardiography, MI = myocardial infarction, MPI = myocardial perfusion imaging, MVP = mitral valve prolapse, TMT+ = positive exercise electrocardiography, Pre-op = preoperative evaluation, PTCA = percutaneous transluminal coronary angioplasty.

Follow-Up

For identification of adverse cardiac events, all patients were followed for 3 years from the day of the performance of MPI by a review of outpatient and inpatient records. Cardiac events included (1) cardiac death (related to arrhythmia, known or suspected MI, or pulmonary edema or unexpected death without an identifiable noncardiac cause), (2) nonfatal MI, and (3) myocardial revascularization by means of CABG or percutaneous transluminal coronary angioplasty (PTCA) resulting from progressive angina after MPI. Myocardial infarction and cardiac death were considered hard cardiac events. Revascularization was considered a soft event.

Statistical Analysis

Intergroup comparisons were performed with the Student's *t*-test for continuous variables and Fisher's exact test for categorical variables. All continuous variables are described as mean $\pm$ standard deviation (SD). *P* values <0.05 were considered significant.

Results

Of the entire cohort, only 23 patients (7.4%) had abnormal MPI and the remaining 288 (92.6%) had normal MPI. Clinical, exercise, and myocardial perfusion variables of those with normal and abnormal MPI are compared in Table II. Abnormal MPI was more frequent in patients with known CAD. Significant intergroup differences between patients with normal and abnormal MPI were found in age, baseline and peak heart rates, and percentage of the maximum age-predicted heart rate attained.

Demographic, exercise and myocardial perfusion variables of the patients with known and possible CAD are demonstrated in Table III. There were significant intergroup differences in the age, duration of exercise, baseline and peak heart rates, and percentage of the maximum age-predicted heart rate attained. Of the patients with known CAD, 15.8% had an abnormal MPI compared with only 4.4% of those with possible CAD ($p < 0.001$).

Table IV demonstrates the distribution of the frequency of different indications for the performance of MPI in patients with normal and abnormal scans. It was surprising that there were no abnormal MPI scans in patients who were referred for MPI because of arrhythmia or prior positive resting ECG. Similarly, the vast majority of the patients who were referred for MPI for evaluation of chest pain or because of a prior abnormal treadmill exercise ECG had also a normal MPI scan (94 and 93%, respectively).

To address the issue of referral bias for performance of MPI in women with overall very low likelihood of significant CAD, the frequency of abnormal MPI scans in the entire population of women who had MPI was examined in our laboratory during the same period as the study group. Of the 3,183 women who underwent treadmill exercise with MPI (includ-

TABLE II Clinical, exercise, and myocardial perfusion variables in patients with normal and abnormal myocardial perfusion imaging

Variables	Abnormal MPI (n = 23)	Normal MPI (n = 289)	p Value
Clinical variables			
Age	57.9 $\pm$ 9.3	51.7 $\pm$ 10.5	0.006
% CAD	14/23	69/289	<0.001
Exercise parameters			
Duration	610 $\pm$ 75	612 $\pm$ 75	NS
Baseline HR	64 $\pm$ 11	71 $\pm$ 11.8	0.008
Peak HR	136 $\pm$ 17	154 $\pm$ 17	<0.0001
% of MPHR	84 $\pm$ 8.5	91.5 $\pm$ 9	<0.001
Baseline SBP	140.5 $\pm$ 17	136 $\pm$ 20	NS
Peak SBP	188 $\pm$ 50	193 $\pm$ 36	NS
Change in SBP	47 $\pm$ 46	67 $\pm$ 35	NS
Baseline DBP	76 $\pm$ 11	77 $\pm$ 13	NS
Peak DBP	74 $\pm$ 15	75 $\pm$ 18	NS
Change DBP	-1.2 $\pm$ 18	-2.7 $\pm$ 17	NS
MPI results			
% Reversible	35	—	—
% Fixed	22	—	—
% Mixed	43	—	—

Abbreviations: CAD = coronary artery disease, HR = heart rate, DBP = diastolic blood pressure, MPI = myocardial perfusion imaging, SBP = systolic blood pressure, MPHR = maximum predicted heart rate, NS = not significant.

TABLE III Clinical, exercise, and myocardial perfusion parameters in patients with known and possible coronary artery disease

Variable	Known CAD	Possible CAD	p Value
Clinical			
Age	55 $\pm$ 8.6	51 $\pm$ 11	0.007
Exercise parameters			
Duration	597 $\pm$ 64	618 $\pm$ 75	0.005
Baseline HR	86 $\pm$ 9.6	71 $\pm$ 12	0.05
Peak HR	145 $\pm$ 18	155 $\pm$ 17	<0.001
% MPHR	88 $\pm$ 10	92 $\pm$ 9	0.001
Baseline SBP	141 $\pm$ 20	134 $\pm$ 20	0.01
Peak SBP	191 $\pm$ 37	193 $\pm$ 38	NS
Change in SBP	50 $\pm$ 33	58 $\pm$ 37	NS
Baseline DBP	77 $\pm$ 12	77 $\pm$ 13	NS
Peak DBP	74 $\pm$ 16	75 $\pm$ 18	NS
Change in DBP	-2 $\pm$ 18	-3 $\pm$ 17	NS
MPI results			
% Abnormal	15.8	4.4	<0.001
% Reversible	2.4	2.6	NS
% Fixed	3.6	0.9	NS
% Mixed	9.8	0.9	<0.001

Abbreviations as in Table II.

ing our study group), 835 (26%) had abnormal MPI, which was significantly higher than the frequency of abnormal MPI in our study group ($p < 0.001$). Similarly, of the 1,620 women

TABLE IV Frequency of differences in diagnosis in patients with normal and abnormal MPI

Diagnosis	Abnormal MPI (n = 23)	Normal MPI (n = 289)	p Value
Known CAD			
CABG (%)	9 (31)	20 (69)	<0.001
MI (%)	5 (16)	27 (84)	NS
PTCA (%)	3 (19)	34 (81)	NS
Possible CAD			
Arrhythmia	0	45	NS
MVP	0	3	NS
TMT+	3	43	NS
CP	7	103	NS
Pre-op	0	5	NS
ECG+	0	13	NS
SOB	0	1	NS
Syncope	0	3	NS
Hypercholesterolemia	0	3	NS

Abbreviations: CABG = coronary artery bypass graft, CAD = coronary artery disease, CP = chest pain, ECG+ = positive baseline electrocardiography, MI = myocardial infarction, MPI = myocardial perfusion imaging, MVP = mitral valve prolapse, Pre-op = preoperative evaluation, PTCA = percutaneous transluminal coronary angioplasty, TMT+ = positive exercise electrocardiography, SOB = shortness of breath, NS = not significant.

who underwent pharmacologic stress (dipyridamole or dobutamine) MPI, 814 (50.2%) had abnormal MPI ($p < 0.001$). Overall, 34% of the women who underwent MPI in our Department in the same period as our study group had abnormal scans compared with 7.3% of our study group ($p < 0.001$).

Follow-Up

No hard events occurred within 3 years from the performance of MPI. One patient with normal MPI underwent revascularization secondary to progressive angina 14 months following MPI.

Discussion

The incidence of nonfatal CAD in women has doubled during the last decade in the USA;¹ however, CAD continues to remain underdiagnosed and untreated in women.¹⁹⁻²² The initial manifestation of symptomatic CAD in women is an average of 10 years later than in men.²³ Physicians evaluating women with known or suspected CAD need to know when they should order a noninvasive diagnostic test and which diagnostic test to use in each patient. Bayes' theorem indicates that in patients with a low likelihood of significant disease, the positive predictive value of a diagnostic test is poor. Although MPI has an incremental value in the prognosis of women in general,²⁻⁴ its incremental value in women with high exercise tolerance has not been demonstrated previously.

Nonetheless, patients with high exercise tolerance are considered a low risk group. Dagenais *et al.*,¹⁰ who studied patients with painless positive exercise ECG results, showed that survival correlates strongly with exercise tolerance and that patients who reached Stage IV in the Bruce protocol had a 100% 6-year survival rate. Similarly, McNeer *et al.*¹¹ showed that patients who reach Stage IV in the Bruce protocol with a normal ST-segment response had a 100% survival rate at 12 months.

We have recently shown that MPI helps in overall risk stratification of patients with high exercise tolerance, and that patients with abnormal MPI have an 8-fold higher risk for cardiac events than do those with normal MPI.¹⁴ However, these results relate mainly to men since the vast majority of the patients in that group were men (87% men vs. 13% women). In the present study we evaluated the value of MPI in women with high exercise tolerance.

Our data clearly show that the diagnostic value of MPI in women who reach and/or exceed Stage IV of the Bruce protocol is low. Only 7.4% of the entire cohort had abnormal MPI. When the patients were separated into those with known and those with possible CAD, it was not surprising to see that patients with known CAD were more likely to have abnormal MPI than those with suspected CAD (15.8 and 4.4%, respectively). Similarly, patients with possible CAD who were referred for MPI because of arrhythmia, positive baseline ECG, or even positive exercise ECG were found to have a negligible chance of having an abnormal MPI.

In addition, it was shown that the prognosis of women with high exercise tolerance, with or without known CAD, was excellent, even with positive MPI. Therefore, in women with high exercise tolerance, the combination of the limited diagnostic information with the limited prognostic information of MPI strongly suggests that women who reach Stage IV of the Bruce protocol need not undergo MPI.

Clinicians are aware that diagnostic tests, including MPI, have the greatest value in groups with intermediate pretest probability of disease.^{24, 25} The intermediate range of pretest probability extends from 10 to 90%.²⁶⁻²⁸ It is well known that a diagnostic test provides maximal information when the probability of disease before testing is near 50% and that the test has very little diagnostic value if the pretest probability is near 0% or 100%.²⁵

Another way to define the useful range of probability of disease, outside of which a diagnostic test should not be performed, is based on recognizing that there is a threshold level below which the number of false positive responses will exceed the true positives, and a second threshold level above which the number of false negative responses will exceed the true negatives.²⁴

If we consider, for example, a 92.2% specificity of myocardial perfusion in women as derived from the work of Taillefer *et al.*²⁹ (the major prospective study to evaluate these values for MPI in women and therefore the main study present in the literature, where the estimated values of sensitivity and specificity are not influenced by the selection bias usually present in a retrospective evaluation of those), then it is important to emphasize that the number of positive tests in a population with

0% prevalence of disease is equal to $100\% - \text{specificity}$, that is, all positive cases are false positives. Given a specificity of 92.2%, in the group of women with high exercise tolerance we see almost exactly the same positive rate (7.4%) that we would expect from false positives alone (7.8%). If we separate the group in those with known and those with possible CAD, it is evident that the same conclusion applies definitely to women with possible CAD. In women with known CAD, the positive rate is slightly higher than the expected false positive rate, but it is still in the range where the false positive results are approximately half of all positive results.

In our department we have been routinely using ^{99m}Tc sestamibi as the radiopharmaceutical for MPI. It has been shown that ^{99m}Tc sestamibi provides improved specificity compared with thallium for the detection of CAD in women, and that the addition of gating increases the specificity even further.²³ However, even with these techniques it is unlikely to reach a level where the rate of true positive outweighs that of false positive results for CAD in a population with very low likelihood of significant disease, as is the case in our study population. Performance of imaging studies in these clinical situations would probably lead to unnecessary interventional procedures, higher risk of complications, and higher expense.

It is safe to say that it is not beneficial to perform MPI in women with high exercise tolerance, especially when they do not have known CAD. Since the vast majority of these patients would have normal MPI, it would be expected that this group of women would have a good prognosis.²

Limitations of the Study

Although our data strongly suggest that MPI has no diagnostic value in women with high exercise tolerance, there may be isolated cases in which patients would benefit from MPI. The low overall percentage of women who reached at least Stage IV of the Bruce protocol did not allow the evaluation of MPI in subgroups of patients with specific clinical characteristics (i.e., multiple risk factors, diabetes, etc.). However, the very low number of abnormal studies in women with high exercise tolerance indicates that it would require a very large number of procedures for the possible benefit of very few.

Conclusion

The yield of myocardial perfusion imaging in women who demonstrate high exercise tolerance is very low. In addition, women with high exercise tolerance demonstrate excellent prognosis even with abnormal myocardial perfusion imaging.

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