Myocardial Perfusion Profile in a Young Population With and Without Known Coronary Artery Disease: Comparison by Gender

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ABSTRACT

Background: More and more young people are being referred for evaluation or screening for coronary artery disease (CAD). However, the value of myocardial perfusion imaging (MPI) in this population is unclear, especially in the absence of symptoms.

Methods: The study sample included 1765 consecutive patients less than 51 years old who were referred to a major medical center for stress/rest MPI study. Clinical and MPI variables were compared between patients with and without known CAD, by gender.

Results: There were 1346 (76%) men and 419 (24%) women of mean age 44 ± 6 years; 461 (26%) had known CAD. Stress-induced ischemia was detected in 321 patients (18.2%) and significant ischemia in 131 (7.4%); there was no difference in the rate or severity of ischemia by presence of symptoms. Among those without known CAD, the rate of stress-induced ischemia by MPI was significantly lower in women than men. On logistic regression analysis, the independent predictors of ischemia in men were high cholesterol, diabetes, angina during stress testing, ST depression, and smoking ($P < .0001$); and in women, the independent predictors were diabetes and high cholesterol.

Conclusion: Known CAD and stress-induced ischemia are significantly more prevalent in young men than in young women, irrespective of risk factors. The independent predictors of ischemia differ between men and women.

Introduction

Although the use of stress myocardial perfusion imaging (MPI) is well established in various populations, by gender and by clinical status,^{1–3} its value in detecting coronary artery disease (CAD) in young people, especially in the absence of cardiac symptoms, remains unclear.

In one study of exercise electrocardiogram findings in 2500 asymptomatic young men undergoing routine screening, 2.1% had abnormal scans suggesting CAD.⁴ Others reported little diagnostic value for thallium exercise myocardial scintigraphy (planar imaging) in asymptomatic young men, with a high rate of false positives, in accordance with Bayesian probability theory.⁵ However, this study was performed in 1993, and the data may be less accurate than the data obtainable today with highly sensitive and specific single photon emission computed tomography (SPECT) and gated SPECT.^{6,7}

The increase in the number of young people undergoing evaluation or screening for CAD has led to an increase in referrals for MPI or echocardiographic stress test. The aim of this study was to determine the rates of detection

of ischemia by MPI in a young population with or without symptoms or known CAD, by gender.

Methods

Study Sample

The sample consisted of 1765 consecutive patients less than 51 years old who were referred to a major medical center for stress/rest MPI study between March 2002 and September 2005. Our database review showed that this group represented 13% of all 13 576 patients who underwent MPI at our center during this period.

The data were reviewed for patient age, gender, and cardiovascular history.

Stress Myocardial Perfusion Imaging

Stress testing was performed by treadmill (Bruce protocol) in 1478 (84%) patients and with dipyridamole in 287 (16%). Cardiac imaging was done with thallium-201 in 70% of patients and with technetium-99m (Tc-99m)-sestamibi in 30%. Patients were instructed to discontinue β -blocker agents 48 hours before testing and antianginal medications 24 hours before testing.

Stress testing was performed under fasting conditions. An intravenous line was inserted. Heart rate, blood pressure, and electrocardiographic tracings were recorded prior to and at each stage of exercise, and at peak of symptoms or maximal predicted heart rate. For the treadmill test, thallium-201 (3–4 mci) was injected, and exercise was continued for 30–60 seconds. In the dipyridamole protocol, thallium was injected 4 minutes after termination of dipyridamole infusion. SPECT imaging was performed about 10 minutes after thallium injection and again 3–4 hours later, at rest. Additional thallium reinjection imaging was performed in patients with fixed defects. In the patients who underwent MPI with Tc-99m-sestamibi, we used the 1 or 2 day protocol, as accepted.⁷

SPECT acquisition was performed with a large-field digital gamma camera (SP-6, Elscint Ltd., Haifa, Israel), over 180-degrees, starting at the 45-degree right anterior oblique and positioning at 6-degree intervals for 30 seconds per image. Redistribution images were repeated 3 to 4 hours after exercise using the same parameters. After the images were reconstructed, 2-dimensional polar plot maps were generated to assess the extent of the perfusion abnormality in each of the 3 coronary artery territories. The total extent of myocardial ischemia was expressed as a percentage of global perfusion of the left ventricle. Perfusion defects were analyzed visually and semiquantitatively. Filling defects were diagnosed as ischemia when the 2 contiguous slices showed reversibility or when bull's-eye mapping showed a decrease of more than 10% in the intensity of the perfusion defects in the redistribution phase.⁸

For purposes of the study, we recorded the stress variables (including symptoms during the stress test), ST depression on the electrocardiogram, amount of exercise in metabolic equivalents (METs), and percentage of maximal heart rate at peak exercise. The total amount of ischemia (including severity and extent) was classified as mild, moderate, or severe (1 to 3) according to the number of vascular territories affected.⁹

Statistical Analysis

The data were compared between patients with and without symptoms and with and without known CAD by sex.

Results are given as mean±SD. To compare mean continuous parameters between groups, a Student *t* test or Duncan's multiple comparison option was used. To analyze statistically significant relationships in the distribution of categorical variables, a χ^2 test was performed, as appropriate.

Pearson correlation coefficient (*r*) and its significance (*P*) were calculated between variables. *P* values ≤ .05 were considered statistically significant.

To predict myocardial ischemia, a series of multivariate stepwise logistic regression models were fitted to the data.

Results

Background and Clinical Factors

The sample included 1346 (76%) men and 419 (24%) women of mean age 44±6 years; 395 (22%) were less than 40 years old. The age distribution of the subjects is presented in Figure 1. Cardiovascular history revealed CAD in 461 patients (26%), myocardial infarction in 278 (16%), coronary artery bypass grafting in 98 (6%), and percutaneous coronary intervention in 401 (23%).

Reasons for referral for MPI were angina in 124 patients (7%), any sort of chest pain other than angina in 997 (56%), other symptoms such as fatigue or shortness of breath in 90 (5%), abnormal resting electrocardiogram (without symptoms) in 41 (2%), nondiagnostic exercise test in 59 (3%), positive exercise test in 187 (11%), and CAD risk factors in 267 (15%).

MPI Results

Reasons for terminating exercise was typical angina in 124 patients (7%), mean maximal predicted heart rate during exercise was 91.2%±7.5%, and mean METs was 11.8±5.8. Significant ST depression (horizontal of 2 mm or more or down sloping) was noted in 345 patients (20%). Ischemia on MPI, in 321 patients (18%): mild in 190 (11%), moderate in 113 (6.4%), and severe in 18 (1%). Mean left ventricular ejection fraction was 55±14; left ventricular dilatation (fixed or transient) was found in 242 patients (14%), and increased lung uptake, in 209 (12%). A total of 10% of scans (*n* = 186) yielded false-positive results; this category included women with breast attenuation, and obese patients with diaphragmatic attenuation especially in presence of normal wall motion. This group of patients had low to intermediate probability of CAD, and no clinical features for CAD during stress study. As such most of them did not have coronary catheterization. This group was not classified with the abnormal scan group.

Patients with known CAD were characterized by a higher rate of older age, diabetes mellitus, high cholesterol, smoking, and positive family history than patients without known CAD (Table 1). No risk factors were found in 24% of the patients without CAD compared to 5.6% of those with CAD. Both these groups had similar workload, percent

Figure 1. Age distribution of study population.

Table 1. Cardiac Risk Factors and MPI Results in Young Patients (<51 Years) With or Without Known Coronary Artery Disease

	No CAD (n = 1304)	CAD (n = 461)	P Value
Clinical			
Age (yr)	43.5±6.2	45.3±4.8	<.0001
Sex (female)	376 (28.6%)	42 (9.3%)	NS
Diabetes mellitus	158 (12.2%)	89 (19.3%)	<.0001
Hypertension	351 (26.9%)	137 (29.7%)	NS
High cholesterol	352 (27%)	261 (57%)	<.0001
Smoking	314 (24%)	179 (39%)	<.0001
Family history	265 (20%)	117 (25.4%)	.02
Obesity	291 (22.3%)	90 (21%)	NS
No risk factors	315 (24.2%)	26 (5.6%)	<.0001
Stress test			
PPHR (%)	91.6±6.8	87.5±7.8	NS
METs	11.6±6.2	11.1±2.6	NS
ST depression	263 (20%)	82 (18%)	NS
Presence of Ischemia	138 (10.6%)	183 (39.7%)	<.001
Mild ischemia	78 (6%)	112 (24.3%)	<.001
Moderate ischemia	45 (3.5%)	68 (14.7%)	<.001
Severe ischemia	15 (1.1%)	3 (0.7%)	NS
EF (%)	56.2±8.5	44.2±12.5	NS
TID	117 (10%)	127 (27.5%)	NS
Lung uptake	102 (7.8%)	102 (22.1%)	NS

Abbreviations: CAD, coronary artery disease; EF, ejection fraction; METs, metabolic equivalents; NS, not significant; PPHR, predicted peak heart rate; TID, transient ischemic dilatation. All values are n (%) unless otherwise indicated.

predicted peak heart rate, and rate of ST depression, although the prevalence of ischemia was 4 times higher in the patients with CAD (Table 1).

The patients without CAD were further divided into 2 subgroups by presence/absence of symptoms (Table 2). Significantly more symptoms that led to referral for MPI were found in the patients with hypertension and obesity and in the smokers. The asymptomatic subgroup had a high rate of ST depression during exercise that was related to referral bias. Workload and maximal predicted heart rate were similar in both subgroups. Interestingly, the prevalence of ischemia was also similar (10.7% vs 10.4%, $P =$ not significant [NS]) and was unrelated to symptoms (Table 2).

Table 2. Cardiac Risk Factors and MPI Results in Symptomatic and Asymptomatic Young Patients (<51 Years) Without Known Coronary Artery Disease

	Symptomatic (n = 851)	Asymptomatic (n = 453)	P Value
Clinical			
Diabetes mellitus	115 (13.5%)	43 (9.5%)	NS
Hypertension	252 (29.6%)	99 (21.8%)	.002
High cholesterol	247 (29.0%)	105 (23.2%)	NS
Family history	164 (19.3%)	101 (22.3%)	NS
Smoking	236 (27.7%)	78 (17.2%)	<.0001
Obesity	212 (24.9%)	79 (17.4%)	.002
No risk factors	176 (20.7%)	139 (30.7%)	<.0001
Stress test			
ST depression	135 (15.9%)	128 (28.3%)	<.0001
PPHR	91.4±6.8	91.7±6.5	NS
METs	11.4±6.5	11.7±5.4	NS
Ischemia	91 (10.7%)	47 (10.4%)	NS
Lung uptake	144 (16.9%)	65 (14.3%)	NS

Abbreviations: METs, metabolic equivalents; NS, not significant; PPHR, predicted peak heart rate. All values are n (%) unless otherwise indicated.

The comparison by gender is shown in Table 3. The women had higher rates of diabetes and hypertension, but lower rates of smoking. The prevalence of CAD was significantly lower in women (10% vs 30%, $P < .0001$) as well as the rate of ischemia by MPI (9% vs 21%, $P < .0001$). Among those with no known CAD, the rate of stress-induced ischemia was much lower in women than in the men (5.6% vs 12.6%, $P = .0002$). However, the rate of ischemia in CAD women was similar to those in men (40% vs 41%, $P =$ NS).

In the univariate analysis, all the clinical and risk factors and stress variables that showed significant correlation with ischemia by MPI, were included in logistic regression analysis, for men and women.

The independent predictors for detecting ischemia by gender are summarized in Table 4. In men, significant predictors of silent ischemia were diabetes, high cholesterol, smoking, angina during stress, and significant ST depression; in women, only diabetes and cholesterol significantly predicted silent ischemia.

Discussion

The results of this large population of young people (age <51 years) show that the rates of known CAD as well as

Table 3. Comparison of Cardiac Risk Factors and MPI Results in Young People (<51 Years) by Sex

	Women (n = 419)	Men (n = 1346)	P Value
Clinical			
Age	45±5	44±6	NS
Known CAD	42 (9%)	408 (30%)	<.0001
Diabetes mellitus	75 (18%)	172 (13%)	.008
Hypertension	151 (36)	337 (25%)	<.0001
High cholesterol	128 (31%)	485 (36%)	.04
Family history	88 (21%)	294 (22%)	NS
Smoking	76 (18%)	417 (31%)	<.0001
Obesity	109 (26%)	279 (21%)	.02
No risk factors	87 (21%)	254 (19%)	NS
Stress test			
ST depression	97 (23%)	248 (18%)	.03
MPI-ischemia	38 (9%)	283 (21%)	<.0001
LVEF	57±11	52±11	<.0001
Abbreviations: CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MPI, myocardial perfusion imaging; NS, not significant. All values are n (%) unless otherwise indicated.			

Table 4. Predictors of Ischemia by Myocardial Perfusion Imaging in Young Women Vs Young Men (<51 Years)

	Odds Ratio	Confidence Limits
Men		
ST Depression	2.00	1.46–2.75
Diabetes mellitus	1.93	1.33–2.78
High cholesterol	1.77	1.34–2.32
Smoking	1.50	1.15–1.95
Angina at stress	1.40	1.21–1.61
Women		
Diabetes mellitus	3.28	1.56–6.88
High cholesterol	2.56	1.24–5.30

stress-induced ischemia were quite high, accounting for about one-quarter of the referrals for MPI. The incidence of stress-induced ischemia rose from 10% in the subjects without known CAD to 4 times that in the subjects with known CAD. The prevalence of ischemia seemed to be

unrelated to the referral symptoms, and it was independently predicted by CAD risk factors and exercise variables.

The majority of referred subjects had at least 1 CAD risk factor (excluding age and sex), which could explain the relatively high prevalence of ischemia, and which was probably unrelated to age.

The prevalence of silent stress-induced ischemia has been examined in several studies of young cohorts. Most focused on asymptomatic subjects.^{4,5,10,11} In 1991, Pedersen et al⁴ screened 2500 asymptomatic male aviators using bicycle exercise testing. Results were abnormal in 55 (2.1%), of whom only 9 (16%) had cardiac disease. The authors concluded that standard exercise electrocardiography is a poor predictor of CAD and cannot serve as a single screening test in asymptomatic young people because it yields too many false-positives when the pre-test likelihood of disease is low. In our study, these young patients referred for stress MPI either because of symptoms, ECG abnormalities, or CAD risk factors, which categorize this population as “intermediate probability” of CAD. In this case the post-test probability, in terms of sensitivity and specificity of MPI to detect ischemia is paramount.

The value of screening asymptomatic subjects to detect occult CAD is still controversial.^{12–15} In their recent review, Goldman et al¹⁶ found the evidence for exercise electrocardiography to be overwhelmingly negative, concluding that it would be cost-ineffective to screen asymptomatic individuals. Others suggested a prognostic value for other variables in asymptomatic patients, such as functional capacity and risk factors of CAD, especially diabetes¹⁴ and, in an earlier study, also calcium score.¹⁷ The reasons for referral for MPI in the present local study were mainly suspected cardiac symptoms, followed by electrocardiographic abnormalities (at rest or stress) or CAD risk factors in the absence of cardiac symptoms. In those with at least 1 risk factor for CAD with or without electrocardiographic abnormalities, the prevalence of ischemia reached 10%. These findings may indicate that in asymptomatic subjects who meet these criteria, MPI may be of diagnostic benefit despite their young age. Moreover, besides its prognostic use, MPI is an accepted tool for making medical or interventional decisions.

Although screening of young, low-risk subjects without symptoms or cardiac risk factors is still not recommended, in men, a positive exercise test by itself may serve as an independent predictor of ischemia by MPI. Thus, the referral of these subjects, regardless of age may be justified given the nonspecific nature of electrocardiographic abnormalities during exercise.

With regard to young women, we showed that the incidence of silent ischemia is low overall and compared to that in young men. It is well recognized that estrogen plays a cardioprotective role in women and that the gradual age-related increase in CAD might represent the gradual process of menopause.¹⁸ Nevertheless, as shown in the

Framingham study,^{19,20} early detection of CAD is important in women because of the worse prognosis of the disease than in men, and the higher mortality rate after myocardial infarction.^{19,20} The present study shows that in young women, ST depression and chest pain during exercise testing are not independent predictors of ischemia by MPI. However, the 2 factors that were found to be independent predictors on regression analysis suggest that in young women MPI should be targeted at those with diabetes or high cholesterol. The same predictors, with the addition of smoking, were reported by De et al²¹ in a coronary angiography study of women less than 45 years old.

Limitations of the Study

Although our study group was large, the figures were based on a local population and may not be applicable to other groups.

We did not assess cardiac events, which could have provided important information on the prognostic yield of MPI.

Conclusions

The prevalence of stress-induced ischemia is substantial in people below age 51 years, regardless of the presence of cardiac symptoms. In men, positive findings on exercise testing or cardiac risk factors may predict ischemia by MPI. In young women, although the rate of silent ischemia is low, the referral for MPI is justified when there are cardiac risk factors, particularly diabetes.

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