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# Temporal Trends in the Frequency of Inducible Myocardial Ischemia During Cardiac Stress Testing

## 1991 to 2009

Alan Rozanski, MD,* Heidi Gransar, MS,†‡ Sean W. Hayes, MD,†‡ James Min, MD,†‡ John D. Friedman, MD,†‡ Louise E. J. Thomson, MBChB,†‡ Daniel S. Berman, MD†‡

*New York, New York; and Los Angeles, California*

**Objectives** This study sought to assess whether the frequency of inducible myocardial ischemia during stress-rest single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) has changed over time.

**Background** The prevalence of cardiac death and other clinical cardiac events have declined in recent decades, but heretofore no study has examined if there has been a temporal change in the frequency of inducible myocardial ischemia during cardiac stress testing.

**Methods** We assessed 39,515 diagnostic patients undergoing stress-rest MPI between 1991 and 2009. Patients were assessed for change in demographics, clinical symptoms, risk factors, and frequency of abnormal and ischemic SPECT-MPI.

**Results** There was a marked progressive decline in the prevalence of abnormal SPECT studies, from 40.9% in 1991 to 8.7% in 2009 ($p < 0.001$). Similarly, the prevalence of ischemic SPECT-MPI declined, from 29.6% to 5.0% ($p < 0.001$), as did the prevalence of severe ischemia. The decline of SPECT-MPI abnormality occurred among all age and symptom subgroups, falling to only 2.9% among recent exercising patients without typical angina. We also noted a progressive trend toward performing more pharmacological rather than exercise stress in all age and weight groups, and pharmacological stress was more likely than exercise to be associated with SPECT-MPI abnormality (odds ratio: 1.43, 95% confidence interval: 1.3 to 1.5; $p < 0.001$).

**Conclusions** Over the past 2 decades, the frequency and severity of abnormal stress SPECT-MPI studies has progressively decreased. Notably, the frequency of abnormal SPECT-MPI is now very low among exercising patients without typical angina. These findings suggest the need for developing more cost-effective strategies for the initial work-up of patients who are presently at low risk for manifesting inducible myocardial ischemia during cardiac imaging procedures. (J Am Coll Cardiol 2013;61:1054–65) © 2013 by the American College of Cardiology Foundation

Cardiac stress tests are widely used for the diagnostic workup of patients with suspected coronary artery disease (CAD). This use is predicated on their ability to signal the presence of hemodynamically significant CAD through the induction of myocardial ischemia during cardiac stress testing. Since the advent of cardiac stress imaging procedures in the 1970s, there has been a progressive decline in the prevalence of cardiac death (1,2), myocardial infarction (3–5), stroke (6), and claudication (7). Furthermore, the prevalence of various CAD risk factors has changed dramatically within society (1,8–10). Nevertheless, heretofore, no study has examined if, and to what extent, the frequency of inducible myocardial ischemia has changed in conjunction with these temporal trends. Accordingly, in this study, we assessed the frequency of test abnormality and inducible myocardial ischemia over the last 2 decades among a large, consecutive cohort of patients undergoing stress-rest single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI).

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## Methods

**Study design.** Our study population consisted of 51,689 consecutive patients who were part of an ongoing prospective registry of SPECT-MPI patients at Cedars-Sinai Medical Center between January 1991 and December 2009.

From the *Division of Cardiology and Department of Medicine, St. Luke's Roosevelt Hospital, New York, New York; †Department of Imaging, Burns and Allen Research Institute, Cedars-Sinai Medical Center, Los Angeles, California; and the ‡Department of Medicine, Burns and Allen Research Institute, Cedars-Sinai Medical Center, Los Angeles, California. Dr. Berman has reported having relationships with Lantheus Medical Imaging, Astellas Pharma US, Inc., GE Healthcare, Siemens, Cardium Therapeutics, Spectrum Dynamics, and Cedars-Sinai. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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From this pool, we excluded 12,174 patients with prior myocardial infarction, percutaneous coronary intervention and/or coronary bypass surgery, or with a history of cardiomyopathy or valvular heart disease. The remaining 39,515 patients constituted our sample and were divided into 4 successive temporal subgroups: 1991 to 1995; 1996 to 2000; 2001 to 2005; and 2006 to 2009. For patients undergoing more than 1 SPECT-MPI study, only the earliest SPECT-MPI study was considered. The study was approved by the Cedars-Sinai Medical Center Institutional Review Board.

**Data collection.** At the time of testing, patients completed a questionnaire regarding pertinent demographic information, chest pain symptoms, cardiac risk factors, and medication use. Additionally, resting heart rate, blood pressure, height, and weight were recorded. We used the responses from 3 questions regarding patients' chest pain (its location, precipitants, and relief with rest or nitroglycerin) to classify each patient into 1 of 4 chest pain categories: asymptomatic, nonanginal chest pain, atypical angina, and typical angina (11). Asymptomatic patients complaining of dyspnea were considered separately (12). A family history of premature CAD was considered present if a primary relative had diagnosed CAD or cardiac event at <55 years of age; current smoking was defined as either currently smoking cigarettes or having stopped smoking for <1 year. Hypertension, hypercholesterolemia, and diabetes were defined on the basis of history and/or taking antihypertensive, lipid-lowering, or diabetic medications, respectively. A Bayesian pre-test likelihood of CAD was calculated for each patient based on age, sex, risk factors, and chest pain symptoms using a validated commercial program (13). Information regarding baseline medications was not recorded before 1999.

Patients either underwent treadmill exercise (55.2%, n = 21,830) or pharmacological stress using either adenosine or dipyridamole (42.4%, n = 16,735) or dobutamine infusion (2.4%, n = 950). Exercise testing was performed using the symptom-limited Bruce protocol. Patients who began exercise but who could not achieve 85% of their maximal predicted heart rate were generally converted into adenosine or dobutamine studies. Heart rate, blood pressure, and electrocardiographic tracings were obtained at rest, at the end of each stress stage, peak stress, and for each of 5-min after stress. Dual isotope SPECT-MPI imaging was performed, using thallium Tl 201 (3 to 4.5 mCi) for rest SPECT-MPI and technetium Tc 99m sestamibi (25 to 40 mCi) for stress SPECT-MPI studies (14). In June 2007, the protocol was changed to same-day rest/stress sestamibi SPECT-MPI (rest dose: 7 to 9 mCi, stress dose: 32 to 40 mCi). Resting thallium Tl 201 SPECT-MPI was initiated 10 min after resting radionuclide injection. For exercise and dobutamine studies, the radioisotope was injected at near maximal stress and SPECT-MPI was begun 15 to 30 min after testing. For adenosine testing, technetium Tc 99m sestamibi was injected at the end of the second minute or at the end of the third minute of 5-min or 6-min adenosine infusions, respectively (140 μg/kg/min for both) (15). In 1996, our adenosine protocol was modified to include an "adeno-walk" protocol, involving concomitant low-level treadmill exercise. In the patients not undergoing the adeno-walk, SPECT imaging was delayed to ~60 min after adenosine infusion. Beginning in 1995, routine 8-/16-frame gated MPI was also incorporated into our post-stress acquisition protocol (16).

**Abbreviations and Acronyms**

**CAC** = coronary artery calcium

**CAD** = coronary artery disease

**MPI** = myocardial perfusion imaging

**SPECT** = single-photon emission computed tomography

Throughout, patients were instructed to withhold beta-blocking medication for 48 h and calcium blockers for 24 h prior to testing, but 5.0% of patients were tested under the influence of beta-blocking medication and 3.8% were tested under the influence of calcium-blocking medications.

SPECT-MPI was performed using multidetector scintillation cameras according to elliptical 180° acquisition of 60 to 64 projections, with 20-s acquisition time per projection. For thallium Tl 201, 2 energy windows were used: a 30% window centered on the 68- to 80-keV peak; and a 10% window centered on the 167 keV peak. For technetium Tc 99m sestamibi, a 15% window centered on the 140-keV peak was used. Between 1991 and 1993, images were obtained in the supine position; in 1994 to 1995, additional prone images were obtained if needed after viewing the supine images; and after 1995, images were routinely obtained in both the supine and prone positions (17). No attenuation correction was applied to our images.

**SPECT-MPI interpretation.** Semiquantitative visual interpretation was performed by experienced observers using a 5-point score (0 = normal to 4 = absence of detectable tracer uptake) for each of either 20 myocardial segments before February 2005 or 17 segments after February 2005, and summed stress, rest, and difference scores were then generated. These indices were converted to percentages of abnormal and ischemic myocardium by dividing the summed scores by 80, the maximal potential score for 20-segment analysis, and by 68 for 17-segment analysis, and then multiplying by 100. Normal, mild, moderate, and severe abnormal and ischemic myocardium were defined as scores <5%, 5% to 9%, 10% to 14%, and ≥15%, respectively. SPECT studies were also assessed visually for the presence of transient ischemic dilation of the left ventricle.

**Follow-up.** Follow-up for all-cause mortality was conducted using the social security death index. The last date of access was May 20, 2011. The mean follow-up was for 9.3 ± 4.7 years (median: 9.0 years; range 0.01 to 20.4 years), with the patients in the earliest epoch followed for the longest duration (15.4 ± 3.9 years) and the patients in the last epoch followed for the shortest duration (3.5 ± 1.1 years). We then compared annualized mortality rates among the 4 temporal groups. Follow-up data was available in 36,727 (92.9%) of our patients.

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**Table 1** Comparison of Clinical Characteristics Among the Temporal Patient Groups

| Parameters | 1991–1995 (n = 6,335) | 1996–2000 (n = 10,264) | 2001–2005 (n = 14,089) | 2006–2009 (n = 8,827) | p Values (Trend) |
|---|---|---|---|---|---|
| Age, yrs | 64.1 ± 12.6 | 63.9 ± 13.2 | 60.7 ± 13.7 | 59.1 ± 13.7 | 0.0001 (<0.001) |
| <55 | 1,534 (24.2) | 2,698 (26.3) | 4,949 (35.1) | 3,403 (38.6) | |
| 55–64 | 1,408 (22.2) | 2,288 (22.3) | 3,526 (25.0) | 2,403 (27.2) | |
| ≥65 | 3,393 (53.6) | 5,278 (51.4) | 5,614 (39.9) | 3,021 (34.2) | <0.001 (<0.0001) |
| Sex | | | | | |
| Male | 3,487 (55.0) | 5,502 (53.6) | 7,257 (51.5) | 4,531 (51.3) | |
| Female | 2,848 (45.0) | 4,762 (46.4) | 6,832 (48.5) | 4,296 (48.7) | <0.001 (<0.0001) |
| Ethnicity | | | | | |
| Caucasian | 5,015 (79.2) | 7,431 (72.4) | 9,336 (66.3) | 5,305 (60.1) | |
| African American | 506 (8.0) | 991 (9.7) | 2,170 (15.4) | 1,767 (20.0) | |
| Asian/Pacific Islander | 213 (3.4) | 325 (3.2) | 633 (4.5) | 560 (6.3) | |
| Hispanic/Latino | 123 (1.9) | 384 (3.7) | 1,059 (7.5) | 982 (11.1) | |
| Other/Unknown | 478 (7.6) | 1,133 (11.0) | 891 (6.3) | 213 (2.4) | <0.001 (<0.0001) |
| Patient status | | | | | |
| Outpatient | 4,558 (72.0) | 7,371 (71.8) | 8,846 (62.8) | 5,029 (57.0) | |
| Inpatient | 1,777 (28.1) | 2,890 (28.2) | 4,724 (33.5) | 3,000 (34.0) | |
| Emergency department | — | — | 519 (3.7) | 798 (9.0) | <0.001 (<0.0001) |
| Chest pain symptoms | | | | | |
| Asymptomatic | 2,028 (32.0) | 2,799 (27.3) | 3,207 (22.8) | 2,002 (22.7) | |
| Nonanginal chest pain | 1,642 (25.9) | 1,706 (16.6) | 1,509 (10.7) | 468 (5.3) | |
| Atypical angina | 1,569 (24.8) | 3,632 (35.4) | 7,737 (54.9) | 5,260 (59.6) | |
| Typical angina | 803 (12.7) | 1,126 (11.0) | 476 (3.4) | 164 (1.9) | |
| Dyspnea only | 292 (4.6) | 1,001 (9.8) | 1,160 (8.2) | 932 (10.6) | <0.001 (<0.0001) |
| Coronary disease risk factors | | | | | |
| Family history | 1,433 (22.6) | 2,398 (23.4) | 1,647 (11.7) | 1,229 (13.9) | <0.001 (<0.0001) |
| Hypertension | 2,953 (46.6) | 5,313 (51.8) | 8,238 (58.5) | 5,549 (62.9) | <0.001 (<0.0001) |
| High cholesterol | 2,570 (40.6) | 4,606 (44.9) | 6,397 (45.4) | 4,386 (49.7) | <0.001 (0.0001) |
| Smoking | 1,055 (16.7) | 1,208 (11.8) | 1,026 (7.3) | 747 (8.5) | <0.001 (<0.0001) |
| Diabetes | 871 (13.8) | 1,102 (10.7) | 2,190 (15.5) | 1,712 (19.4) | <0.001 (<0.0001) |
| Weight | 165.7 ± 35.3 | 171.1 ± 39.9 | 177.3 ± 46.6 | 181.1 ± 51.2 | 0.0001 (<0.001) |
| Body mass index, kg/m$^2$ | 26.3 ± 4.7 | 27.2 ± 5.5 | 28.0 ± 6.5 | 28.6 ± 7.1 | 0.0001 (<0.001) |
| Normal, <25 | 2,676 (42.7) | 3,786 (37.1) | 4,781 (34.0) | 2,886 (32.8) | |
| Overweight, 25–29.9 | 2,481 (39.5) | 4,068 (39.8) | 5,270 (37.5) | 3,119 (35.4) | |
| Obese, ≥30 | 1,117 (17.8) | 2,364 (23.1) | 3,996 (28.5) | 2,807 (31.9) | <0.001 (<0.0001) |
| Resting hemodynamics | | | | | |
| Heart rate, beats/min | 70.0 ± 13.0 | 71.8 ± 13.9 | 70.5 ± 13.1 | 69.2 ± 12.8 | 0.0001 (<0.001) |
| Systolic blood pressure, mm Hg | 143.9 ± 24.8 | 141.7 ± 23.8 | 138.9 ± 20.1 | 139.3 ± 20.4 | 0.0001 (<0.001) |
| Diastolic blood pressure, mm Hg | 83.6 ± 11.4 | 81.6 ± 11.3 | 78.0 ± 10.7 | 78.5 ± 10.8 | 0.0001 (<0.001) |
| Rest electrocardiogram | | | | | |
| Abnormal rest electrocardiogram | 4,114 (64.9) | 5,644 (55.0) | 6,342 (45.0) | 3,876 (43.9) | <0.001 (<0.0001) |
| Left ventricular hypertrophy | 736 (11.6) | 1,194 (11.6) | 662 (4.7) | 387 (4.4) | <0.001 (<0.0001) |
| Left bundle branch block | 173 (2.7) | 261 (2.6) | 252 (1.8) | 136 (1.5) | <0.001 (<0.0001) |
| Atrial fibrillation | 151 (2.4) | 259 (2.5) | 303 (2.2) | 180 (2.0) | 0.09 (0.03) |

*Continued on the next page*

**Statistical analyses.** Stata software (version 11.2, StataCorp., College Station, Texas) was used to analyze the data. Continuous variables were compared across four groups using the Kruskal-Wallis test, and for ordered groups, Cuzick test for trend was added. Categorical variables were compared using Pearson chi-square test, and the chi-square test for trend added for ordered groups as well. Annualized mortality rates were calculated by dividing the number of events by person-years and were compared using the log-rank test and test for trend for ordered groups.

Logistic regression was done to obtain the risk-adjusted odds ratio of clinical factors predicting abnormal SPECT in each temporal period.

A propensity matching score was developed to match 1,000 randomly selected patients from the earliest epoch (1991 to 1995) to 1,000 patients of each of the other 3 epochs based on age, sex, symptom class, stress mode, body mass index, cholesterol, diabetes, hypertension, smoking, and family history. The propensity score was generated from the resulting predicted probabilities of 3 logistic regression

**Table 1 Continued**

| Parameters | 1991–1995 (n = 6,335) | 1996–2000 (n = 10,264) | 2001–2005 (n = 14,089) | 2006–2009 (n = 8,827) | p Values (Trend) |
|---|---|---|---|---|---|
| Pre-test likelihood of CAD | | | | | |
| Mean CAD likelihood | 40.1 ± 30.2 | 44.7 ± 30.8 | 46.8 ± 30.3 | 49.2 ± 30.6 | 0.0001 (<0.001) |
| Low CAD likelihood, <15% | 1,871 (29.5) | 2,602 (25.4) | 3,181 (22.6) | 1,871 (21.2) | |
| Intermediate likelihood, 15%–84% | 3,630 (57.3) | 6,035 (58.8) | 8,610 (61.1) | 5,296 (60.0) | |
| High CAD likelihood, ≥85% | 833 (13.2) | 1,627 (15.9) | 2,298 (16.3) | 1,659 (18.8) | <0.001 (<0.0001) |
| Medication use | | | | | |
| Lipid-lowering medications | — | 481/2,553 (18.8) | 3,714 (26.4) | 3,010 (34.1) | <0.001 (<0.0001) |
| Statins | — | 460 (18.0) | 3,541 (25.1) | 2,726 (30.9) | <0.001 (<0.0001) |
| Ezetimibe | — | 0 (0) | 69 (0.5) | 380 (4.3) | <0.001 (<0.0001) |
| Other lipid medications | — | 25 (1.0) | 219 (1.6) | 437 (5.0) | <0.001 (<0.0001) |
| Antihypertensive medications | — | 631/2,553 (24.7) | 6,466 (45.9) | 4,689 (53.1) | <0.001 (<0.0001) |
| Beta-blockers | — | 333 (13.0) | 2,753 (19.5) | 2,158 (24.5) | <0.001 (<0.0001) |
| ACE inhibitors | — | 181 (7.1) | 2,443 (17.3) | 1,619 (18.3) | <0.001 (<0.0001) |
| ARBs | — | 40 (1.6) | 953 (6.8) | 1,314 (14.9) | <0.001 (<0.0001) |
| Calcium blockers | — | 170 (6.7) | 1,544 (11.0) | 1,178 (13.4) | <0.001 (<0.0001) |
| Diuretics | — | 137 (5.4) | 1,907 (13.5) | 1,468 (16.6) | <0.001 (<0.0001) |
| Oral diabetic medications | — | — | — | 714 (8.1) | — |
| Aspirin | — | 207 (8.1) | 3,502 (24.9) | 2,613 (29.6) | <0.001 (<0.0001) |
| Stress test mode | | | | | |
| Exercise | 4,454 (70.3) | 6,014 (58.6) | 7,173 (50.9) | 4,189 (47.5) | |
| Pharmacological | 1,881 (29.7) | 4,250 (41.4) | 6,916 (49.1) | 4,638 (52.5) | <0.001 (<0.0001) |
| Use of pharmacological testing by subgroups of age and BMI | | | | | |
| <55 yrs | 192 (12.5) | 601 (22.3) | 1,705 (34.5) | 1,300 (38.2) | <0.001 (<0.0001) |
| 55–64 yrs | 305 (21.7) | 708 (30.9) | 1,457 (41.3) | 1,216 (50.6) | <0.001 (<0.0001) |
| ≥65 yrs | 1,384 (40.8) | 2,941 (55.7) | 3,754 (66.9) | 2,122 (70.2) | <0.001 (<0.0001) |
| Normal, <25 kg/m$^2$ | 790 (29.5) | 1,578 (41.7) | 2,343 (49.0) | 1,496 (51.8) | <0.001 (<0.0001) |
| Overweight, 25–29.9 kg/m$^2$ | 661 (26.6) | 1,528 (37.6) | 2,321 (44.0) | 1,453 (46.6) | <0.001 (<0.0001) |
| Obese, ≥30 kg/m$^2$ | 403 (36.1) | 1,121 (47.4) | 2,236 (56.0) | 1,676 (59.7) | <0.001 (<0.0001) |
| SPECT results | | | | | |
| Sum stress score ≥5% | 2,046 (32.3) | 1,666 (16.2) | 1,638 (11.6) | 829 (9.4) | <0.001 (<0.0001) |
| Sum difference score ≥5% | 1,620 (25.6) | 1,372 (13.4) | 1,328 (9.4) | 530 (6.0) | <0.001 (<0.0001) |
| Sum stress score ≥10% | 1,233 (19.5) | 1,013 (9.9) | 822 (5.8) | 416 (4.7) | <0.001 (<0.0001) |
| Sum difference score ≥10% | 927 (14.6) | 775 (7.6) | 600 (4.3) | 216 (2.5) | <0.001 (<0.0001) |
| % with TID of the left ventricle | 244 (3.9) | 276 (2.7) | 330 (2.3) | 56 (1.6)* | <0.001 (0.008) |
| Deaths | | | | | |
| All patients | 2,749 (43.4) | 3,067 (30.5) | 2,290 (18.5) | 685 (8.7) | <0.001 (<0.0001) |
| Exercise patients | 1,436 (32.2) | 987 (16.7) | 399 (6.3) | 69 (1.8) | <0.001 (<0.0001) |
| Pharmacologic patients | 1,313 (69.8) | 2,080 (49.9) | 1,891 (31.2) | 616 (15.1) | <0.001 (<0.0001) |
| Annual mortality rates, %/yr (95% CI) | | | | | |
| All patients | 3.3 (3.2–3.4) | 3.0 (2.9–3.1) | 2.6 (2.5–2.7) | 2.6 (2.4–2.8) | 0.002 (0.0003) |
| Exercise patients | 2.2 (2.1–2.3) | 1.5 (1.4–1.6) | 0.8 (0.7–0.9) | 0.5 (0.4–0.6) | <0.001 (<0.0001) |
| Pharmacologic patients | 7.2 (6.8–7.6) | 5.9 (5.7–6.2) | 4.8 (4.6–5.0) | 4.7 (4.4–5.1) | <0.001 (<0.0001) |

Values are mean ± SD or n (%) unless otherwise indicated. — = data were unavailable. *Data analyzed until June 2007.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; CI = confidence interval(s); SPECT = single-photon emission computed tomography; TID = transient ischemic dilation.

models that predicted being in each of the latter 3 epochs versus being in the earliest epoch, with the aforementioned risk factors in the models. Thus, 3 separate propensity score-matchings were done; that is, every epoch was matched to the first epoch, separately. The resulting propensity scores were then used to match every patient from a latter epoch to a similar patient in the first epoch (1:1) using Mahalanobis nearest-neighbor matching algorithm (18). This matching resulted in 4,000 patients (1,000 in each epoch) with similar clinical profiles as patients seen in the 1991 to 1995 epoch.

## Results

The clinical characteristics of our patient population are shown in Table 1. There was a progressive decrease in the mean age of our patient population, a mild increase in the percentage of women studied, an increase in nonwhite

groups, a decrease in the percent of outpatients, and a decline in both the percentage of asymptomatic and typical angina patients referred for testing. There was a decrease in the percentage of patients with a family history of premature CAD and in those who were current smokers, but an increase in the percentage who had hypertension, high cholesterol, diabetes, and obesity. However, mean resting systolic and diastolic blood pressure measurements were lower for the 2006 to 2009 cohort versus the 1991 to 1995 cohort. Concomitantly, there was a progressive increase in the use of aspirin and lipid-lowering and antihypertensive medications. There was also a temporal decline in the percentage of patients with an abnormal resting electrocardiogram or left ventricular hypertrophy. Overall, the mean pre-test Bayesian likelihood of CAD rose from 40.1% to 49.2% during the 4 temporal periods, and the majority of patients tested had an intermediate (15% to 84%) pre-test likelihood of CAD.

There was also a progressive decline in the frequency of patients who were tested with exercise as opposed to pharmacological stress. During the 1991 to 1995 epoch, 70.3% of patients underwent stress SPECT-MPI using exercise testing but by the 2006 to 2009 epoch, only 47.5% of the patients underwent exercise testing. The increasing use of pharmacological testing was noted both among younger and older patients and among normal weight, overweight, and obese patients. Annualized all-cause mortality rates declined during each epoch between both patients undergoing exercise and patients undergoing pharmacological stress testing.

**Temporal change in the frequency of abnormal and ischemic SPECT-MPI studies.** As shown in Figure 1, there was a marked progressive temporal decline in the prevalence of abnormal stress SPECT-MPI studies, ranging from 40.9% in 1991 to only 8.7% in 2009 ($p < 0.0001$), and a parallel decline in the prevalence of ischemic SPECT-MPI studies, ranging from 29.6% in 1991 to only 5.0% in 2009 ($p < 0.0001$). The prevalence of moderately to severely abnormal SPECT studies also declined progressively, from 20.6% in 1991 to 4.6% in 2009 ($p < 0.0001$), as did the prevalence of transient ischemic dilation of the left ventricle.

Table 2 shows the decline in the prevalence of abnormal SPECT-MPI studies according to patients' relevant clinical parameters. There was a progressive decline in the prevalence of abnormal SPECT studies in all age groups; both sexes; all ethnicities; both outpatients and inpatients; all symptom, risk factor, and medication subgroups; and among both patients referred for exercise and patients referred for pharmacological stress. Similarly, the prevalence of ischemic SPECT studies also declined significantly in each of these clinical subgroups ($p < 0.001$ for each clinical parameter; data not shown).

When the 1,000 randomly selected patients in the first epoch were compared with the propensity matched subsets from the subsequent 3 epochs, there were no significant differences between the patients in each epoch for the matching variables: age ($p = 0.93$); sex ($p = 0.66$); chest pain symptoms ($p = 0.65$); hypertension ($p = 0.49$); hypercholesterolemia ($p = 0.83$); smoking ($p = 0.32$); diabetes ($p = 0.52$); family history of premature CAD ($p = 0.11$); body mass index ($p = 0.54$); and type of stress test ($p = 0.79$). Within this propensity-matched cohort, the temporal decline in the frequency of abnormal SPECT studies persisted over our 4 epochs: 31.5%, 14.8%, 12.5%, and 10.7%, respectively (Table 3).

Figure 2 shows the prevalence of observing an abnormal SPECT study for the most current temporal subgroup of patients (2006 to 2009) among exercise versus pharmacological patients, after excluding the 247 exercise patients (5.9%) who did not achieve >85% of maximal predicted heart rate. Among exercising patients without typical an-

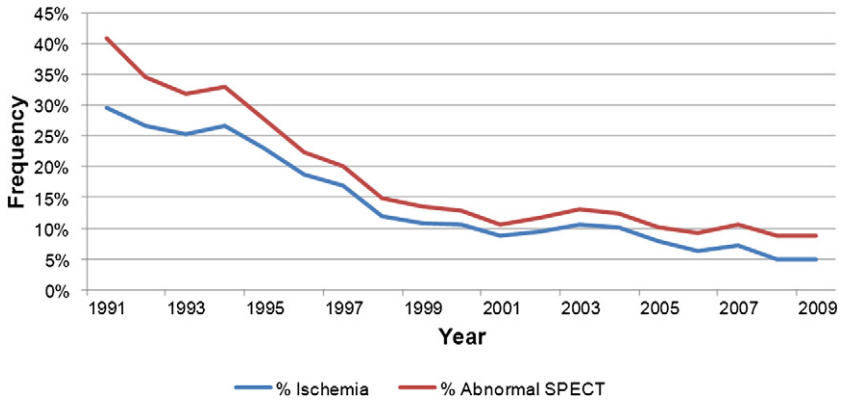


**Figure 1** Yearly Frequency of Abnormal and Ischemic SPECT-MPI

The frequency of abnormal and ischemic single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) studies are shown by year from 1991 to 2009. A progressive decline was noted in both frequencies.

gina, the prevalence of an abnormal SPECT-MPI study was only 2.9%.

**Temporal predictors of abnormal and ischemic SPECT-MPI studies.** Table 4 compares the adjusted odds ratios for observing an abnormal SPECT-MPI study during each temporal period according to our study parameters. Increased age, male sex, inpatient status, typical angina, dyspnea, hypertension, smoking, diabetes, higher body mass index, an abnormal rest electrocardiogram, the use of cardioprotective medication, and the performance of pharmacological stress testing were consistent predictors of an abnormal SPECT-MPI study during each of our 4 temporal periods.

## Discussion

Our study documents a marked and progressive decline in the frequency of abnormal and ischemic SPECT-MPI studies among diagnostic patients over the last 2 decades. Whereas the frequency of abnormal studies was 40.9% in 1991, by 2009, the frequency of abnormal SPECT-MPI studies among our diagnostic patients decreased to only 8.7% and the frequency of myocardial ischemia decreased from 29.6% to only 5.0%. We also observed a substantive and progressive decrease in the frequency of moderate to severely abnormal and ischemic SPECT-MPI studies. Notably, the declining frequency of abnormal and ischemic SPECT-MPI studies was broad-based, occurring among both younger and older patients, in men and women, within all ethnicities, among inpatients and outpatients, in both asymptomatic and symptomatic patients, within each CAD risk factor subgroup, and among both patients undergoing exercise or pharmacological SPECT-MPI. Of further note, the incidence of positive MPI-SPECT studies continued to decrease in our most recent study group even following the release of American College of Cardiology/American Heart Association guidelines in 2003 (19) and appropriate use criteria in 2005 (20), which were introduced to reduce inappropriate use of MPI-SPECT as an initial test in low-risk and intermediate-risk subjects.

**Temporal trends in baseline clinical parameters.** The declining frequency of abnormal SPECT-MPI was accompanied by a progressive change in a variety of baseline clinical parameters. These included a temporal decline in patient age; a mild increase in the percentage of women tested; less typical angina patients; a decline in smoking; and increasing weight, obesity, and diabetes. In addition, the frequency of hypertension rose during each successive temporal period, but baseline systolic and diastolic blood pressure levels were lower in the 2006 to 2009 epoch, probably due to the progressively greater use of antihypertensive medications in our patient population. Lipid-lowering medications and aspirin use also increased progressively. Due to the changing pattern of risk factors over time, we also performed a propensity analysis that resulted in subgroups of similar age, sex, symptom class, and risk factor profiles across our 4 epochs. Our observed temporal decline in the frequency of SPECT-MPI abnormality was maintained within these propensity-matched subgroups.

**Predictors of SPECT-MPI abnormality and ischemia.** Despite the temporal decline in SPECT-MPI abnormality and changing characteristics of our referred patient population, the clinical predictors of SPECT-MPI abnormality and ischemia remained highly consistent over time. Predictors included increasing age, male sex, inpatient status, typical angina, dyspnea, hypertension, smoking, diabetes, increasing body mass index, pharmacological stress, and an abnormal resting electrocardiogram. The prevalence of abnormality was also elevated among those patients taking cardioprotective medications compared with those who did, probably reflecting higher risk among such patients.

**Prior studies.** Even though our current database began in 1991, we had previously studied patients who had undergone exercise thallium planar MPI studies in the late 1970s and 1980s (21). At that time, the frequency of abnormal exercise MPI studies was 50% among 1,689 diagnostic patients, which was nearly twice the frequency noted for exercise SPECT-MPI abnormality in the earliest temporal period of our study (i.e., 27.5%), and other studies conducted during that time also noted a similarly high frequency of abnormal MPI studies (22). Thus, consideration of this earlier literature suggests that the temporal decline in stress MPI abnormality since the late 1970s may be even greater than that documented in our study.

**Potential explanations.** A number of mechanisms may account for our findings. First, reduction in risk factors, as observed in our study, could have served to reduce ischemia by retarding the progression of atherosclerosis and/or by favorably influencing pathophysiological determinants of myocardial ischemia, such as endothelial dysfunction (23). In our referral population, there was a mixed pattern of temporal CAD risk factor change. Favorable changes included progressive decline in smoking, family history of premature CAD, and resting blood pressure measurements. In addition, though not measured in our study, there have also been declining cholesterol levels (1) and transfat ingestion among Americans (24), and these trends may also have been applicable in our patients as well. However, we noted progressive rise in obesity and diabetes. Of note, in an analysis that included similar change of CAD risk factor change, including rise in obesity and diabetes, Ford et al. (3) still attributed 44% of an observable national decline in cardiovascular deaths to risk factor reduction and similar findings have been noted by others (25).

Second, our data raise a question as to whether there has been a concomitant trend toward less severe angiographic disease in the presence of cardiac symptoms. Specifically, we noted a progressive decline in the frequency of SPECT-MPI abnormality in each of our chest pain groups, including patients with typical angina. The frequency of SPECT-MPI abnormality was 51.6% among typical angina patients referred

**Table 2 Temporal Prevalence of Abnormal SPECT According to Clinical Parameters**

| Clinical Parameters | 1991–1995 (n = 6,335) | 1996–2000 (n = 10,264) | 2001–2005 (n = 14,089) | 2006–2009 (n = 8,827) | p Values (Trend) |
|---|---|---|---|---|---|
| Age group, yrs | | | | | |
| <55 | 270 (17.6) | 188 (7.0) | 317 (6.4) | 160 (4.7) | <0.001 (<0.0001) |
| 55–64 | 407 (28.9) | 295 (12.9) | 368 (10.4) | 211 (8.8) | <0.001 (<0.0001) |
| ≥65 | 1,369 (40.4) | 1,183 (22.4) | 953 (17.0) | 458 (15.2) | <0.001 (<0.0001) |
| Sex | | | | | |
| Female | 751 (26.4) | 555 (11.7) | 581 (8.5) | 282 (6.6) | <0.001 (<0.0001) |
| Male | 1,295 (37.1) | 1,111 (20.2) | 1,057 (14.6) | 547 (12.1) | <0.001 (<0.0001) |
| Ethnicity | | | | | |
| Caucasian | 1,679 (33.5) | 1,298 (17.5) | 1,128 (12.1) | 513 (9.7) | <0.001 (<0.0001) |
| African American | 160 (31.6) | 136 (13.7) | 271 (12.5) | 184 (10.4) | <0.001 (<0.0001) |
| Asian/Pacific Islander | 61 (28.6) | 51 (15.7) | 63 (10.0) | 33 (5.9) | <0.001 (<0.0001) |
| Hispanic/Latino | 37 (30.1) | 52 (13.5) | 122 (11.5) | 81 (8.3) | <0.001 (<0.0001) |
| Patient status | | | | | |
| Outpatient | 1,400 (30.7) | 1,124 (15.3) | 878 (9.9) | 393 (7.8) | <0.001 (<0.0001) |
| Inpatient | 646 (36.4) | 542 (18.8) | 742 (15.7) | 410 (13.7) | <0.001 (<0.0001) |
| Emergency department | — | — | 18 (3.5) | 26 (3.3) | 0.93 (0.88) |
| Symptom class | | | | | |
| Asymptomatic | 608 (30.0) | 367 (13.1) | 358 (11.2) | 210 (10.5) | <0.001 (<0.0001) |
| Nonanginal chest pain | 385 (23.5) | 199 (11.7) | 180 (11.9) | 57 (12.2) | <0.001 (<0.0001) |
| Atypical angina | 515 (32.8) | 479 (13.2) | 730 (9.4) | 374 (7.1) | <0.001 (<0.0001) |
| Typical angina | 414 (51.6) | 373 (33.1) | 153 (32.1) | 37 (22.6) | <0.001 (<0.0001) |
| Dyspnea only | 124 (42.5) | 248 (24.8) | 217 (18.7) | 151 (16.2) | <0.001 (<0.0001) |
| Coronary risk factors | | | | | |
| Family history | | | | | |
| No | 1,621 (33.1) | 1,321 (16.8) | 1,490 (12.0) | 757 (10.0) | <0.001 (<0.0001) |
| Yes | 425 (29.7) | 345 (14.4) | 148 (9.0) | 72 (5.9) | <0.001 (<0.0001) |
| Hypertension | | | | | |
| No | 933 (27.6) | 634 (12.8) | 471 (8.1) | 164 (5.0%) | <0.001 (<0.0001) |
| Yes | 1,113 (37.7) | 1,032 (19.4) | 1,167 (14.2) | 665 (12.0%) | <0.001 (<0.0001) |
| High cholesterol | | | | | |
| No | 1,199 (31.9) | 897 (15.9) | 814 (10.6) | 367 (8.3) | <0.001 (<0.0001) |
| Yes | 847 (33.0) | 769 (16.7) | 824 (12.9) | 462 (10.5) | <0.001 (<0.0001) |
| Smoking | | | | | |
| No | 1,684 (31.9) | 1,455 (16.1) | 1,507 (11.5) | 747 (9.3) | <0.001 (<0.0001) |
| Yes | 362 (34.3) | 211 (17.5) | 131 (12.8) | 82 (11.0) | <0.001 (<0.0001) |
| Diabetes | | | | | |
| No | 1,644 (30.1) | 1,362 (14.9) | 1,186 (10.0) | 546 (7.7) | <0.001 (<0.0001) |
| Yes | 402 (46.2) | 304 (27.6) | 452 (20.6) | 283 (16.5) | <0.001 (<0.0001) |
| Body mass index, kg/m$^2$ | | | | | |
| Normal <25 | 824 (30.8) | 540 (14.3) | 499 (10.4) | 237 (8.2) | <0.001 (<0.0001) |
| Overweight, 25–29.9 | 819 (33.0) | 712 (17.5) | 616 (11.7) | 291 (9.3) | <0.001 (<0.0001) |
| Obese, ≥30 | 377 (33.8) | 410 (17.3) | 520 (13.0) | 299 (10.7) | <0.001 (<0.0001) |
| Rest electrocardiogram | | | | | |
| Normal | 492 (22.2) | 426 (9.2) | 504 (6.5) | 265 (5.4) | <0.001 (<0.0001) |
| Abnormal | 1,554 (37.8) | 1,240 (22.0) | 1,134 (17.9) | 564 (14.6) | <0.001 (<0.0001) |

*Continued on the next page*

for testing between 1991 and 1996, but it was only 22.6% among patients referred for testing between 2006 and 2009. In support of this notion, recent invasive and noninvasive angiographic studies indicate a lower contemporary prevalence of angiographically significant CAD among typical angina patients as compared to previous studies (26–28).

Third, progressively greater use of cardiac medications may have contributed to our findings. The increasing use of statins may be of particular relevance because their pleiotropic effects have been associated with ischemia reduction, including reversal of SPECT-MPI perfusion defects (29,30). However, the more aggressive use of statins does not account for the relatively comparable decline in SPECT-MPI abnormality between both patients taking and patients not taking statins in our cohort.

Fourth, temporal changes in patient referral patterns may have been influential. Just as the mean age of our patient population fell over time, so too physicians may now be

**Table 2 Continued**

| Clinical Parameters | 1991–1995 (n = 6,335) | 1996–2000 (n = 10,264) | 2001–2005 (n = 14,089) | 2006–2009 (n = 8,827) | p Values (Trend) |
|---|---|---|---|---|---|
| Medication use | | | | | |
| Statins | | | | | |
| No | — | 259 (12.4) | 1,116 (10.6) | 507 (8.3) | <0.001 (<0.0001) |
| Yes | — | 68 (14.8) | 522 (14.7) | 322 (11.8) | 0.003 (0.002) |
| Blood pressure medications | | | | | |
| No | — | 224 (11.7) | 691 (9.1) | 234 (5.7) | <0.001 (<0.0001) |
| Yes | — | 103 (16.3) | 947 (14.7) | 595 (12.7) | 0.003 (0.0006) |
| Aspirin | | | | | |
| No | — | 290 (12.4) | 1,145 (10.8) | 516 (8.3) | <0.001 (<0.0001) |
| Yes | — | 37 (17.9) | 493 (14.1) | 313 (12.0) | 0.009 (0.003) |
| Testing modality | | | | | |
| Exercise | 1,223 (27.5) | 681 (11.3) | 499 (7.0) | 155 (3.7) | <0.001 (<0.0001) |
| Pharmacological stress | 823 (43.8) | 985 (23.2) | 1,139 (16.5) | 674 (14.5) | <0.001 (<0.0001) |

Values are n (%). — = data were not available.
SPECT = single-photon emission computed tomography.

referring patients with milder intensity and/or duration of symptoms for cardiac stress testing. Also, although it could not be assessed in our study, it is possible that physicians now have a lower threshold for referring patients with more severe anginal symptoms directly to cardiac catheterization.

**The increasing use of pharmacological stress testing.** There was a progressively greater utilization of pharmacological testing over time. Notably, neither age nor the increasing weight of our patient population seemed to explain this trend because pharmacological testing increased in every age group and weight class. Potential explanations could include a lower threshold for converting poorly exercising patients to pharmacological stress, a greater tendency to use pharmacological stress due to convenience, and increasingly sedentary behavior or deconditioning among referred patients. Prior data in patients with normal SPECT-MPI have demonstrated higher mortality rates among those undergoing pharmacological testing versus exercise testing, even when matched on the basis of age, sex, and other clinical factors and excluding patients with pre-existing cardiac morbidities (31). In addition, our present data also indicate that pharmacological stress is associated with a greater likelihood of observing abnormal and ischemic SPECT-MPI studies.

Combined, these data indicate that patients undergoing pharmacological stress testing are at higher a priori risk and thus deserving of a lower threshold for testing than are patients who can exercise. Thus, prospective study is indicated to ascertain the causes for increasing use of pharmacological stress testing, to investigate why such patients are at increased ischemia risk, and to better ascertain the reasons for increased prognostic risk among even pharmacological patients without inducible myocardial ischemia (31).

**Study limitations and strengths.** Although the study sample in the present study was very large, 1 principle limitation is that the data reported herein constitute the experience from a single medical center, which may have been significantly affected by referral bias. Thus, there is a need to conduct similar temporal analyses in other stress test populations. Because our cohort was generally Caucasian, though it had decreased to 60% by the 2006 to 2009 period, caution should be applied in extrapolating our findings to other ethnic groups. We did not collect information regarding the chronicity or intensity of CAD risk factors, the severity of chest pain symptoms, or the distribution of physician specialties referring patients to our laboratory. The latter would be of potential interest for assessing whether changing frequencies in the distribution of referrals by cardiologists versus more general physicians helped contribute to our findings. During the course of our study, various technical innovations were introduced regarding our performance of SPECT-MPI, including the introduction of routine gated imaging for assessing regional wall motion and the combined use of both prone and supine imaging since the mid-1990s. However, these technical improvements, per se, are not likely to be a major cause for our findings because the frequency of abnormal SPECT-MPI studies declined continuously, both before and after these technical innovations took place. Concomitant quantitative analysis of our visually assessed scintigrams would have been of further interest in this regard, but could not be performed due to a lack of imaging storage of our early studies.

Our study also has considerable strengths, including our large consecutive sample of stress test patients, our consistent collection of the same baseline clinical data and scheme for interpreting stress-rest MPI studies, and generally the same interpreters for SPECT-MPI throughout the temporal span of our study.

**Clinical implications.** Two broad implications emanate from our findings. First, the declining frequency and severity of myocardial ischemia that was noted in our study may be reflecting a broader temporal change toward milder clinical presentations of CAD. Indeed, not only has the prevalence of cardiac death and myocardial infarction declined in the United States (1–3,5), but so too has the

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**Table 3** Temporal Prevalence of Abnormal SPECT According to Clinical Parameters in Propensity-Matched Patients

| Clinical Parameters | 1991–1995 (n = 1,000) | 1996–2000 (n = 1,000) | 2001–2005 (n = 1,000) | 2006–2009 (n = 1,000) | p Values (Trend) |
|---|---|---|---|---|---|
| Age group | | | | | |
| Mean age, yrs | 64.2 ± 12.6 | 64.0 ± 13.1 | 64.2 ± 13.2 | 64.4 ± 13.4 | 0.93 (1.00) |
| <55 | 32 (13.3) | 12 (4.7) | 13 (5.3) | 13 (5.5) | <0.001 (0.002) |
| 55–64 | 64 (28.0) | 32 (13.3) | 25 (9.2) | 25 (9.3) | <0.001 (<0.0001) |
| ≥65 | 219 (41.3) | 104 (20.6) | 87 (18.1) | 69 (13.9) | <0.001 (<0.0001) |
| Sex | | | | | |
| Female | 118 (25.9) | 47 (10.0) | 35 (7.9) | 28 (6.1) | <0.001 (<0.0001) |
| Male | 197 (36.2) | 101 (19.1) | 90 (16.2) | 79 (14.5) | <0.001 (<0.0001) |
| Ethnicity | | | | | |
| Caucasian | 250 (32.1) | 112 (15.2) | 94 (12.8) | 78 (11.3) | <0.001 (<0.0001) |
| African American | 34 (40.0) | 8 (10.3) | 16 (15.4) | 16 (10.6) | <0.001 (<0.0001) |
| Asian/Pacific Islander | 11 (26.2) | 5 (13.9) | 6 (16.2) | 4 (6.6) | 0.05 (0.01) |
| Hispanic/Latino | 3 (15.0) | 4 (11.8) | 8 (13.8) | 6 (8.1) | 0.71 (0.36) |
| Symptom class | | | | | |
| Asymptomatic | 83 (27.8) | 28 (9.7) | 39 (13.2) | 27 (8.4) | <0.001 (<0.0001) |
| Nonanginal chest pain | 69 (24.4) | 32 (11.1) | 26 (9.2) | 29 (10.9) | <0.001 (<0.0001) |
| Atypical angina | 66 (28.0) | 30 (13.0) | 18 (7.9) | 16 (6.8) | <0.001 (<0.0001) |
| Typical angina | 75 (56.0) | 43 (30.3) | 32 (23.7) | 25 (22.1) | <0.001 (<0.0001) |
| Dyspnea only | 22 (45.8) | 15 (30.6) | 10 (17.2) | 10 (15.6) | 0.001 (0.0001) |
| Coronary risk factors | | | | | |
| Family history | | | | | |
| No | 235 (31.9) | 103 (13.9) | 108 (15.0) | 92 (12.0) | <0.001 (<0.0001) |
| Yes | 80 (30.3) | 45 (17.2) | 17 (6.1) | 15 (6.5) | <0.001 (<0.0001) |
| Hypertension | | | | | |
| No | 141 (27.1) | 60 (11.1) | 50 (9.6) | 41 (8.1) | <0.001 (<0.0001) |
| Yes | 174 (36.3) | 88 (19.2) | 75 (15.6) | 66 (13.4) | <0.001 (<0.0001) |
| High cholesterol | | | | | |
| No | 196 (33.4) | 77 (13.3) | 63 (10.7) | 59 (10.3) | <0.001 (<0.0001) |
| Yes | 119 (28.8) | 71 (16.8) | 62 (15.2) | 48 (11.2) | <0.001 (<0.0001) |
| Smoking | | | | | |
| No | 261 (31.5) | 121 (14.7) | 110 (13.1) | 95 (11.1) | <0.001 (<0.0001) |
| Yes | 54 (31.4) | 27 (15.5) | 15 (9.4) | 12 (8.2) | <0.001 (<0.0001) |
| Diabetes | | | | | |
| No | 256 (29.5) | 110 (12.5) | 97 (11.0) | 79 (9.1) | <0.001 (<0.0001) |
| Yes | 59 (45.0) | 38 (31.4) | 28 (24.1) | 28 (20.6) | <0.001 (<0.0001) |
| Mean weight | 165.0 ± 35.8 | 165.6 ± 37.9 | 166.4 ± 38.4 | 166.3 ± 38.4 | 0.99 (0.76) |
| Mean body mass index | 26.2 ± 4.6 | 26.1 ± 4.9 | 26.1 ± 5.1 | 26.1 ± 5.1 | 0.54 (0.19) |
| Rest electrocardiogram | | | | | |
| Normal | 77 (21.7) | 37 (7.6) | 42 (7.6) | 45 (7.9) | <0.001 (<0.0001) |
| Abnormal | 238 (36.9) | 111 (21.6) | 83 (18.4) | 62 (14.5) | <0.001 (<0.0001) |
| Testing modality | | | | | |
| Exercise | 189 (27.2) | 76 (10.9) | 70 (10.1) | 46 (6.9) | <0.001 (<0.0001) |
| Pharmacological | 126 (41.5) | 72 (23.6) | 55 (17.7) | 61 (18.3) | <0.001 (<0.0001) |

Values are mean ± SD or n (%).
SPECT = single-photon emission computed tomography.

severity of myocardial infarction (4). At the same time, however, the overall prevalence of CAD remains high in society, even among young individuals (32,33). Notably, we performed concomitant coronary artery calcium (CAC) scans in a sample of 1,195 of the patients who underwent exercise SPECT-MPI in our laboratory (34). Among the 1,119 patients with normal exercise SPECT-MPI studies, 78% had evidence of atherosclerosis as detected by CAC scanning and 31% had CAC scores >400. Similar results have been noted by Chang et al. (35). Thus, despite the current decline in the frequency of inducible myocardial ischemia, overall plaque burden remains quite high in stress testing cohorts.

Second, the declining frequency of inducible myocardial ischemia, particularly among exercising patients without typical angina, suggests a need to refine the future diagnostic workup of patients with suspected CAD. Interestingly in this regard, repeated study has now demonstrated a thresh-

**Table 4 Temporal Risk-Adjusted OR for Having an Abnormal SPECT Study**

| Variables | All Patients | 1991–1995 | 1996–2000 | 2001–2005 | 2006–2009 |
|---|---|---|---|---|---|
| Age per 5 yrs | 1.25 (1.2–1.3), <0.001 | 1.24 (1.2–1.3), <0.001 | 1.24 (1.2–1.3), <0.001 | 1.20 (1.17–1.23), <0.001 | 1.21 (1.2–1.3), <0.001 |
| Sex | | | | | |
| Female | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Male | 2.47 (2.3–2.6), <0.001 | 2.53 (2.2–2.9), <0.001 | 2.89 (2.5–3.3), <0.001 | 2.69 (2.4–3.0), <0.001 | 2.62 (2.2–3.1), <0.001 |
| BMI per 5 kg/m$^2$ | 1.06 (1.04–1.1), <0.001 | 1.10 (1.03–1.2), 0.004 | 1.08 (1.02–1.1), 0.009 | 1.09 (1.05–1.1), <0.001 | 1.10 (1.05–1.2), <0.001 |
| Ethnicity | | | | | |
| Caucasian | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| African American | 0.91 (0.8–1.0), 0.06 | 0.99 (0.8–1.2), 0.95 | 0.83 (0.7–1.02), 0.08 | 1.12 (1.0–1.3), 0.17 | 1.13 (0.9–1.4), 0.21 |
| Asian/Pacific Islander | 0.79 (0.7–0.9), 0.004 | 0.95 (0.7–1.3), 0.75 | 1.03 (0.7–1.4), 0.87 | 0.89 (0.7–1.2), 0.44 | 0.66 (0.5–0.97), 0.04 |
| Hispanic/Latino | 0.77 (0.7–0.9), <0.001 | 1.00 (0.7–1.5), 1.00 | 0.81 (0.6–1.1), 0.21 | 1.01 (0.8–1.3), 0.91 | 0.90 (0.7–1.2), 0.45 |
| Patient status | | | | | |
| Outpatient | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Inpatient | 1.23 (1.1–1.3), <0.001 | 1.12 (1.0–1.3), 0.11 | 1.01 (0.9–1.2), 0.93 | 1.42 (1.3–1.6), <0.001 | 1.58 (1.3–1.9), <0.001 |
| Emergency department | — | — | — | 0.70 (0.4–1.1), 0.16 | 1.20 (0.8–1.9), 0.41 |
| Patient symptoms | | | | | |
| Asymptomatic patient | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Nonanginal chest pain | 1.01 (0.9–1.1), 0.81 | 0.81 (0.7–0.9), 0.009 | 1.02 (0.8–1.2), 0.81 | 0.88 (0.7–1.1), 0.21 | 0.82 (0.6–1.1), 0.25 |
| Atypical angina | 0.86 (0.8–0.9), <0.001 | 1.22 (1.05–1.4), 0.01 | 1.23 (1.05–1.4), 0.01 | 0.96 (0.8–1.1), 0.59 | 0.81 (0.7–0.99), 0.04 |
| Typical angina | 3.68 (3.3–4.1), <0.001 | 2.48 (2.1–3.0), <0.001 | 3.57 (3.0–4.3), <0.001 | 4.95 (3.9–6.3), <0.001 | 3.93 (2.6–6.0), <0.001 |
| Dyspnea | 1.22 (1.1–1.4), <0.001 | 1.22 (0.9–1.6), 0.15 | 1.79 (1.5–2.2), <0.001 | 1.43 (1.2–1.7), <0.001 | 1.32 (1.03–1.7), 0.03 |
| CAD risk factors | | | | | |
| Family history | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.15 (1.1–1.2), 0.001 | 1.00 (0.9–1.1), 0.98 | 1.10 (1.0–1.3), 0.18 | 0.96 (0.8–1.2), 0.67 | 0.89 (0.7–1.2), 0.39 |
| Hypertension | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.13 (1.1–1.2), <0.001 | 1.27 (1.1–1.4), <0.001 | 1.27 (1.1–1.4), <0.001 | 1.16 (1.02–1.3), 0.02 | 1.35 (1.1–1.6), 0.003 |
| History of high cholesterol | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.07 (1.005–1.1), 0.04 | 1.16 (1.03–1.3), 0.01 | 1.22 (1.1–1.4), 0.001 | 1.31 (1.2–1.5), <0.001 | 1.09 (0.9–1.3), 0.32 |
| Smoking | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.54 (1.4–1.7), <0.001 | 1.27 (1.1–1.5), 0.003 | 1.34 (1.1–1.6), 0.001 | 1.23 (1.0–1.5), 0.05 | 1.32 (1.01–1.7), 0.04 |
| History of diabetes | | | | | |
| No | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Yes | 1.74 (1.6–1.9), <0.001 | 1.57 (1.3–1.8), <0.001 | 1.87 (1.6–2.2), <0.001 | 1.75 (1.5–2.0), <0.001 | 1.66 (1.4–2.0), <0.001 |
| Heart rate per 5 beats/min | 1.06 (1.05–1.08), <0.001 | 1.07 (1.04–1.09), <0.001 | 1.05 (1.03–1.07), <0.001 | 1.06 (1.04–1.09), <0.001 | 1.06 (1.03–1.09), <0.001 |
| SBP per 5 mm Hg | 1.03 (1.02–1.035), <0.001 | 1.01 (1.0–1.03), 0.08 | 1.03 (1.02–1.04), <0.001 | 1.003 (1.0–1.02), 0.71 | 1.00 (0.98–1.02), 0.98 |
| DBP per 5 mm Hg | 1.07 (1.05–1.08), <0.001 | 0.99 (0.96–1.01), 0.35 | 1.04 (1.01–1.07), 0.002 | 1.04 (1.02–1.07), 0.001 | 1.01 (0.97–1.05), 0.62 |
| Rest ECG | | | | | |
| Normal | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Abnormal | 2.30 (2.2–2.5), <0.001 | 1.56 (1.4–1.8), <0.001 | 2.10 (1.8–2.4), <0.001 | 2.37 (2.1–2.7), <0.001 | 1.90 (1.6–2.2), <0.001 |
| Stress mode | | | | | |
| Exercise | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Pharmacological stress | 1.43 (1.3–1.5), <0.001 | 1.56 (1.4–1.8), <0.001 | 1.83 (1.6–2.1), <0.001 | 1.93 (1.7–2.2), <0.001 | 2.63 (2.1–3.2), <0.001 |
| Medication use | | | | | |
| No lipid medications | — | — | — | 1.00 | 1.00 |
| Use of lipid medications | — | — | — | 1.16 (1.0–1.4), 0.07 | 1.02 (0.8–1.3), 0.88 |
| No HBP medications | — | — | — | 1.00 | 1.00 |
| Use of HBP medications | — | — | — | 1.01 (0.9–1.2), 0.91 | 1.29 (0.99–1.7), 0.06 |
| No aspirin | — | — | — | 1.00 | 1.00 |
| Use of aspirin | — | — | — | 1.02 (0.9–1.1), 0.80 | 1.09 (0.9–1.3), 0.29 |

Values are OR or OR (95% CI), p values. — = data were unavailable. Adjusted for age, sex, body mass index, chest pain symptom, ethnicity, inpatient versus outpatient status, stress test mode, family history, hypertension, high cholesterol, diabetes, and smoking. Tests for interactions between every predictor and epoch (second, third, fourth versus first) in the overall cohort revealed interactions between epoch and the following variables: age, ethnicity, inpatient versus outpatient status, chest pain symptom, family history, hypertension, hyperlipidemia, smoking, diabetes, heart rate, SBP, DBP, abnormal rest ECG, lipid-lowering medications, blood pressure medications, aspirin usage, and pharmacological test type.

ECG = electrocardiogram; DBP = diastolic blood pressure; HBP = high blood pressure; OR = odds ratio(s); SBP = systolic blood pressure; other abbreviations as in Table 1.

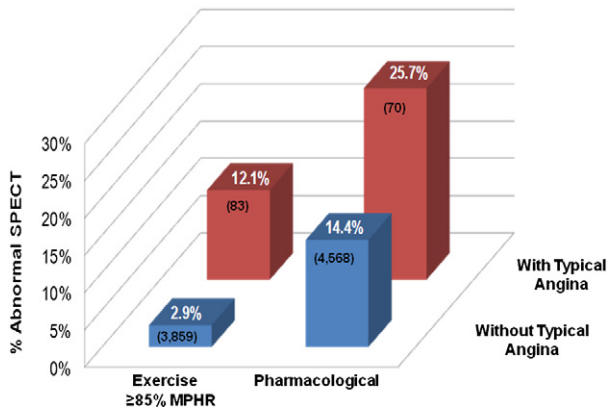


**Figure 2** **Recent Frequency of Abnormal SPECT-MPI Studies**

Frequency of abnormal single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) studies among recently studies patients (between 2006 and 2009) according to whether patients had presence or absence of typical angina at the time of referral for stress testing and whether testing was performed using exercise or pharmacological stress. The analysis excludes 247 patients who did not achieve 85% of maximal predicted heart rate (MPHR). The values in parentheses are the number of patients.

old relationship between CAC scores and the likelihood of inducible myocardial ischemia (36–39). Accordingly, CAC scanning has the potential to serve as a useful means for triaging patients toward cardiac stress testing when CAC scores are high and away from stress testing when CAC scores are low. Among those patients who are exercise candidates, assessment of patients' functional capacity may provide additional triaging information in light of data from Bourque et al. (40,41) that demonstrate that achievement of a high workload during treadmill exercise electrocardiography is associated with a very low frequency of inducible myocardial ischemia by SPECT-MPI imaging and cardiac events among such patients. Conceivably then, CAC scanning, with or without treadmill exercise electrocardiography, could serve as potentially low-cost alternative to more expensive imaging tests for the initial workup of relatively lower-risk diagnostic patients. Thus, prospective clinical trials now appear indicated to assess whether utilization of such lower-cost alternatives provides comparable or improved diagnostic workup and subsequent management of patients with suspected CAD while incurring lower overall healthcare costs.

**Reprint requests and correspondence:** Dr. Daniel S. Berman, Cedars-Sinai Medical Center, 8700 Beverly Building, Room 1258, Los Angeles, California 90048. E-mail: bermand@cshs.org.

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**Key Words:** coronary artery disease risk factors ■ myocardial ischemia ■ perfusion ■ prognosis.