Journal of the American College of Cardiology
Vol. 54, No. 6, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.04.042

Cardiac Imaging

Achieving an Exercise Workload of ≥10 Metabolic Equivalents Predicts a Very Low Risk of Inducible Ischemia

Does Myocardial Perfusion Imaging Have a Role?

Jamieson M. Bourque, MD, MHS, Benjamin H. Holland, MD, Denny D. Watson, PhD, George A. Beller, MD

Charlottesville, Virginia

Objectives We sought to identify prospectively the prevalence of significant ischemia (≥10% of the left ventricle [LV]) on exercise single-photon emission computed tomography (SPECT) imaging relative to workload achieved in consecutive patients referred for myocardial perfusion imaging (MPI).

Background High exercise capacity is a strong predictor of a good prognosis, and the role of MPI in patients achieving high workloads is questionable.

Methods Prospective analysis was performed on 1,056 consecutive patients who underwent quantitative exercise gated ^{99m}Tc-SPECT MPI, of whom 974 attained ≥85% of their maximum age-predicted heart rate. These patients were further divided on the basis of attained exercise workload (<7, 7 to 9, or ≥10 metabolic equivalents [METs]) and were compared for exercise test and imaging outcomes, particularly the prevalence of ≥10% LV ischemia. Individuals reaching ≥10 METs but <85% maximum age-predicted heart rate were also assessed.

Results Of these 974 subjects, 473 (48.6%) achieved ≥10 METs. This subgroup had a very low prevalence of significant ischemia (2 of 473, 0.4%). Those attaining <7 METs had an 18-fold higher prevalence (7.1%, $p < 0.001$). Of the 430 patients reaching ≥10 METs without exercise ST-segment depression, none had ≥10% LV ischemia. In contrast, the prevalence of ≥10% LV ischemia was highest in the patients achieving <10 METs with ST-segment depression (14 of 70, 19.4%).

Conclusions In this referral cohort of patients with an intermediate-to-high clinical risk of coronary artery disease, achieving ≥10 METs with no ischemic ST-segment depression was associated with a 0% prevalence of significant ischemia. Elimination of MPI in such patients, who represented 31% (430 of 1,396) of all patients undergoing exercise SPECT in this laboratory, could provide substantial cost-savings. (J Am Coll Cardiol 2009;54:538–45)

The sequelae of coronary artery disease (CAD) continue to cause significant morbidity and impose high economic costs. Identifying those at the highest risk of major adverse cardiac events is imperative for guiding therapy and maximizing the benefits of revascularization. Noninvasive diagnostic imaging assists with this process and consequently has grown more than any other physician service under Medicare reimbursement (1). In 2005 alone, 9.3 million nuclear myocardial perfusion studies were performed at significant cost to the health care system (2). Improved pre-test risk stratification is essential to use this expensive imaging modality in a cost-effective manner. The incremental value of stress myocardial perfusion imaging (MPI) is small for patients with a low-risk stress test, a low-risk Duke Treadmill Score, or a high rate-pressure product without ST-segment depression (3–5).

See page 546

Exercise capacity measured in metabolic equivalents (METs) alone is a powerful predictor of cardiovascular events (6). Higher workloads achieved during exercise stress predict improved survival rates, irrespective of age and sex (6–8). A cutpoint of 10 METs achieved predicts low mortality, even in the setting of significant CAD (9,10). Its

From the Cardiovascular Division and the Cardiovascular Imaging Center, Department of Internal Medicine, University of Virginia Health System, Charlottesville, Virginia. Dr. Bourque is funded by National Institutes of Health National Research Service Award Training Grant T32 EB003841-04.

Manuscript received November 11, 2008; revised manuscript received April 8, 2009, accepted April 14, 2009.

association with the prevalence of significant ischemia by quantitative single-photon emission computed tomography (SPECT), as compared with the Duke Treadmill Score, would be of interest (11,12).

Accordingly, the primary objective of this study was to determine prospectively the relationship of cardiac workload attained to the prevalence and extent of myocardial abnormalities by gated SPECT in patients with known or an intermediate-to-high probability of CAD who achieved ≥85% of their maximum age-predicted heart rate (MAPHR). The hypothesis tested was that individuals reaching diagnostic heart rates (≥85% of their MAPHR) and ≥10 METs have a low prevalence of significant ischemia (≥10% of the left ventricle [LV]). A second hypothesis tested was that individuals achieving ≥85% of their MAPHR with lower workloads have a greater prevalence of ischemia. The third hypothesis was that patients reaching <85% of their MAPHR but ≥10 METs would still have a low prevalence of significant ischemia but greater than that seen in those attaining their target heart rate.

Methods

Prospectively collected data from the University of Virginia Nuclear Databank were analyzed in a cohort of consecutive patients undergoing exercise testing and SPECT imaging at the University of Virginia Medical Center.

Study cohort. This prospective study cohort comprised 2,794 consecutive patients who underwent ^{99m}Tc SPECT MPI between February 2006 and January 2007. After excluding those who underwent pharmacologic stress or achieved <10 METs and <85% of their MAPHR, our final study cohort included 1,056 subjects (Fig. 1). Patients reaching <10 METs and <85% of their MAPHR were not studied, because it is well-recognized that such patients are at high risk for CAD and future cardiac events due to deconditioning and other factors. Imaging provides added diagnostic and prognostic information in this patient population (13).

Patients achieving ≥85% of their MAPHR (n = 974) were subdivided into 3 groups (<7 METs [n = 267], 7 to 9 METs [n = 234], and ≥10 METs [n = 473]). To test the third hypothesis, a second group of 82 individuals who attained ≥10 METs but <85% of their MAPHR was also examined.

Clinical information collection and management. Clinical information was collected from patients at the time of their exercise test and entered into the University of Virginia Nuclear Databank, including demographic data, comorbidities, physical examination, and baseline electrocardiogram (ECG) findings. Exercise test parameters and SPECT results (volumes, perfusion, and function) were also recorded (14,15). Protocol approval and waiver of informed consent were obtained from the University of Virginia Institutional Review Board.

Exercise testing. All subjects underwent exercise treadmill stress with electrocardiographic monitoring with standard exercise protocols; 1,033 of 1,056 (99%) exercised according to a Bruce or modified Bruce protocol. The decision of whether to stop anti-ischemic medication before testing was left up to the discretion of the referring physician. Testing was symptom-limited unless prematurely terminated for reasons recommended in the exercise testing guidelines (16). Exercise workload was defined as the total METs achieved (17). Ischemic ST-segment depression was defined as ≥1 mm horizontal or down-sloping depression of the ST-segment ≥80 ms after the J-point for 3 consecutive beats.

Abbreviations and Acronyms

CAD = coronary artery disease

ECG = electrocardiogram

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

MAPHR = maximum age-predicted heart rate

MET = metabolic equivalent

MI = myocardial infarction

MPI = myocardial perfusion imaging

SPECT = single-photon emission computed tomography

Radionuclide SPECT imaging. Subjects underwent ^{99m}Tc sestamibi rest-stress gated-SPECT MPI with either a 1- or 2-day protocol (for a body mass index ≥36 kg/m^2). With the 1-day protocol, patients received first 10 mCi of ^{99m}Tc sestamibi at rest, and images were acquired after a 60-min delay. They subsequently received 30 mCi of ^{99m}Tc sestamibi at peak stress with gated-SPECT imaging performed after a 30-min delay. The 2-day protocol differed in that subjects received 30 mCi of ^{99m}Tc sestamibi (45 mCi in

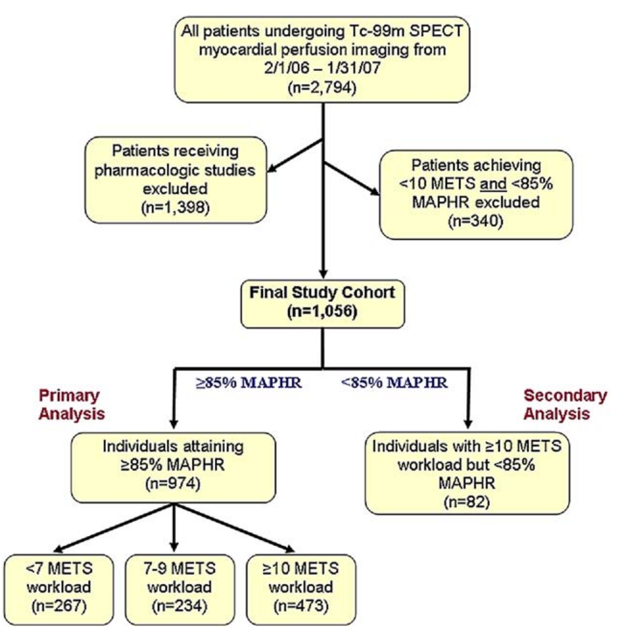

Figure 1 **Study Cohort Derivation Flowchart**

MAPHR = maximum age-predicted heart rate; MET = metabolic equivalent; SPECT = single-photon emission computed tomography.

JACC Vol. 54, No. 6, 2009
August 4, 2009:538–45

patients with a body mass index >45 kg/m^2) before both rest and stress imaging.

Images were acquired with a dual-head GE Infinia camera (GE Medical Systems, Milwaukee, Wisconsin) with low-energy, high-resolution collimators. Each camera head rotated through 60 projections at 30 to 40 s/projection to acquire 180° of data with a standard ^{99m}Tc energy window. The data from the 2 heads were combined to give 360° of coverage. No scatter or attenuation correction was used.

Nuclear imaging interpretation. Myocardial perfusion studies were initially read clinically by experienced nuclear cardiology specialists with visual and quantitative image analysis (14). All borderline or abnormal studies were reclassified by the consensus of 2 additional readers blinded to additional patient information. The University of Virginia quantification program provides continuous measurement of relative percent tracer uptake in each of 17 standard segments. Segments were flagged as normal or abnormal, on the basis of normal databases. Reversibility was flagged by computer-based analysis of variance derived from the normal databases. Systolic and diastolic volumes and body surface area normalized volumes were also calculated (14).

To compare the results more easily with other published studies, each segment was categorized into normal, mild, moderate, and severe defects and absent tracer uptake (scores 0 to 4). Segmental scores were categorized by each reader who chose a score on the basis of both the quantitative perfusion data and a qualitative visual assessment. The semi-quantitative summed stress, rest, and difference values were calculated from these segmental scores. The 5 apical segments were weighted at 40% of the value of nonapical segments to correct the standard 17-segment model so that each unit of myocardial volume was given equal weight. Finally, the "percent myocardial ischemia" was obtained by dividing the difference between summed stress and summed rest scores by the maximum possible difference. This score, although misnamed by tradition, does provide a logical semi-quantitative measure, which combines both extent and severity of LV inducible ischemia (11,12).

Outcomes. The primary outcome for our analysis was the prevalence of ≥10% LV ischemia on MPI. This value was used as the cutpoint for significant ischemia on the basis of a prior report of revascularization benefit in patients demonstrating ≥10% LV ischemia (11). The mean %LV ischemic burden and the percentages of patients with 0%, 1% to 4%, 5% to 9%, and ≥10% LV ischemia, as categorized in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial nuclear substudy, were ascertained (18). The prevalence of varying degrees of LV ischemia was determined in the subgroups of patients achieving either <7, 7 to 9, or ≥10 METs. The prevalence of fixed defects in these groups was documented as well. The influence of ischemic ST-segment depression on this workload–ischemia relationship was also investigated.

Statistical analysis. Descriptive statistics are given as medians with 25th and 75th percentiles and compared by analysis of variance with Tukey's studentized range testing and *t* tests for continuous variables and as numbers of patients with percentages and comparisons by Pearson chi-square or Fisher exact testing for categorical variables. The level of significance was 0.05 for all analyses.

Univariable logistic regression analyses of possible predictors of ≥10% LV ischemia (Table 1) were performed. Variables with p values <0.10 were entered into a multivariable logistic regression model predicting ≥10% LV ischemia. The C-statistic represents the discriminative power of the logistic equation (1.0 represents perfect prediction). All statistics were performed with SAS version 9.1 (SAS Institute, Cary, North Carolina).

Results

Study population characteristics. Patients reaching ≥85% of their MAPHR had a 22.4% prevalence of known CAD, with 132 of 974 patients (13.6%) having had a prior

Table 1 Baseline Characteristics in Patients Achieving ≥85% of Their MAPHR Relative to Workload Attained

Characteristic	<7 METs Achieved (n = 267)	7–9 METs Achieved (n = 234)	≥10 METs Achieved (n = 473)	p Value
Age, yrs	64 (53, 72)	60 (50, 67)	53 (46, 61)	<0.001
Male	121 (45.3)	109 (46.6)	325 (68.7)	<0.001
Chest pain	168 (62.9)	149 (63.7)	333 (70.4)	0.061
Hypertension	197 (73.8)	157 (67.1)	204 (43.1)	<0.001
Diabetes mellitus	66 (24.7)	41 (17.5)	49 (10.4)	<0.001
Hyperlipidemia	157 (58.8)	139 (59.4)	258 (54.6)	0.357
Current tobacco use	84 (31.5)	64 (27.4)	114 (24.1)	0.094
Known CAD	59 (22.1)	64 (27.4)	95 (20.1)	0.092
History of MI	39 (14.6)	37 (15.8)	56 (11.8)	0.293
Prior revascularization	51 (19.1)	56 (23.9)	80 (16.9)	0.083
Abnormal resting ECG	46 (17.2)	27 (11.5)	35 (7.4)	<0.001
Same-day beta-blocker use	18 (6.7)	12 (5.1)	24 (5.1)	0.604

Values are expressed as median (25th, 75th percentiles) or n (%).
CAD = coronary artery disease; ECG = electrocardiogram; MAPHR = maximum age-predicted heart rate; MET = metabolic equivalent; MI = myocardial infarction.

Table 2 Exercise Test Variables in Patients Achieving ≥85% of Their MAPHR Relative to Workload Attained

Exercise Test Parameter	<7 METs Achieved (n = 267)	7–9 METs Achieved (n = 234)	≥10 METs Achieved (n = 473)	p Value
Exercise duration (min)	6 (5, 6)	7 (7, 8)	10 (9, 12)	<0.001
Maximum predicted HR	93 (89, 99)	94 (89, 99)	96 (90, 101)	0.012
Maximum systolic BP (mm Hg)	197 (175, 218)	198 (172, 221)	197 (174, 215)	0.593
Maximum diastolic BP (mm Hg)	87 (76, 99)	86 (76, 98)	85 (76, 95)	0.323
Rate pressure product ($\times 10^3$)	28.8 (25.1, 32.8)	29.4 (25.9, 33.8)	31.0 (27.5, 34.7)	0.388
≥1 mm ST-segment depression on ECG	35 (13.1)	35 (15.0)	43 (9.1)	0.048
Chest pain during stress	42 (15.7)	35 (15.0)	40 (8.5)	0.004
Duke treadmill score	4 (1, 6)	7 (3, 7)	9 (7, 11)	<0.001

Values are expressed as n (%) or median (25th, 75th percentiles).
BP = blood pressure; HR = heart rate; other abbreviations as in Table 1.

myocardial infarction (MI). Table 1 shows that the patients who achieved higher workloads were younger, more often male, and had significantly lower rates of diabetes and hypertension. For variables with $p < 0.05$, all pair-wise comparisons were statistically significant between those reaching ≥10 METs and both those attaining <7 and 7 to 9 METs except an abnormal resting ECG, which was only significant between <7 and ≥10 METs. Only age and diabetes mellitus had statistically significant differences among all 3 groups. There were no significant differences in the proportion with prior known CAD or MI. Symptoms possibly related to ischemia (i.e., chest pain or dyspnea) were reported in 77.4% (754 of 974) of the overall cohort with no significant differences among groups on the basis of exercise capacity ($p = 0.65$).

Exercise and stress parameters. The physiologic parameters, symptoms, and stress-ECG findings are provided in Table 2. In patients reaching ≥85% MAPHR, 117 (12%) had chest pain during the test, and 93 (80%) of these had normal scans. The prevalence of exercise chest pain (40 of 473, 8.5%) and ST-segment depression (43 of 473, 9.1%) were both significantly lower in individuals attaining ≥10 METs than in the lower workload subgroups.

The small change in the percentage of the MAPHR achieved was not clinically significant and was only statistically significant when comparing <7 and ≥10 METs (93% vs. 96%). No other physiologic parameters varied by exercise workload. The median Duke Treadmill Score was significantly different across all 3 workload levels (<7 METs: 4.3; 7 to 9 METs: 7.0; ≥10 METs: 9.0, $p < 0.001$ among each of the 3 groups). A low-risk Duke Treadmill Score is considered ≥5.0, and an intermediate score is ≥−10.0 but <5.0 (15). In this study, the median Duke Treadmill Score fell in the low-risk range for those attaining ≥7 METs and in the intermediate-risk category for those reaching <7 METs. The median Duke Treadmill Score was in the same risk category for patients achieving ≥10 METs and those reaching 7 to 9 METs. However, the prevalence of ≥10% LV ischemia was significantly different between the 2 workload groups.

SPECT imaging results. The relationship between cardiac workload and SPECT imaging findings are presented in Table 3. All variables with a global $p \leq 0.05$ had

Table 3 Myocardial SPECT Imaging Results Versus Exercise Capacity in Patients Achieving ≥85% of Their MAPHR

Characteristic	<7 METs Achieved (n = 267)	7–9 METs Achieved (n = 234)	≥10 METs Achieved (n = 473)	p Value
Perfusion				
Fixed perfusion defects	46 (17.2)	28 (12.0)	31 (6.6)	<0.001
Any reversible ischemia	55 (20.6)	39 (16.7)	19 (4.0)	<0.001
Mean % LV ischemic (SD)	1.8 (4.4)	1.3 (4.1)	0.2 (1.4)	<0.001
LV ischemia				<0.001
0%	212 (79.4)	195 (83.3)	454 (96.0)	
1%–4%	17 (6.4)	20 (8.6)	12 (2.5)	
5%–9%	19 (7.1)	9 (3.9)	5 (1.1)	
≥10%	19 (7.1)	10 (4.3)	2 (0.4)	<0.001
Volumes and function				
ESVI	12 (8, 17)	11 (8, 17)	14 (10, 18)	0.614
ESVI ≥25	32 (12.1)	24 (10.4%)	40 (8.5)	0.283
EDVI	43 (37, 52)	43 (37, 53)	47 (40, 55)	0.145
Ejection fraction	65 (58, 70)	66 (61, 71)	65 (60, 69)	0.203

Values are expressed as n (%) or median (25th, 75th percentiles).
EDVI = end-diastolic volume index; ESVI = end-systolic volume index; LV = left ventricular; SPECT = single-photon emission computed tomography; other abbreviations as in Table 1.

JACC Vol. 54, No. 6, 2009
August 4, 2009:538–45

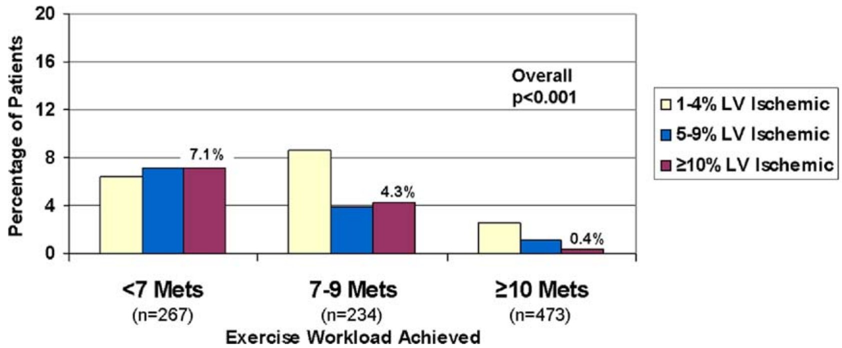

Figure 2 Prevalence of LV Ischemia by Exercise Capacity

The 974 individuals reaching 85% of their maximum age-predicted heart rate were divided by exercise workload achieved (horizontal axis). The vertical axis represents the percentage of subjects with each percentage of left ventricular (LV) ischemia. MET = metabolic equivalent.

statistically significant differences between those reaching ≥10 METs and those attaining <7 and 7 to 9 METs. Individuals who achieved ≥85% of their MAPHR with higher exercise workloads had a markedly lower prevalence of perfusion abnormalities ($p < 0.001$) (Fig. 2). Subjects with ≥10 METs exercise capacity had a more than 5-fold lower prevalence of reversible ischemic defects and 2.6-fold fewer fixed perfusion defects compared with those attaining a poor workload (<7 METs).

Those who achieved ≥10 METs had a low percentage of any ischemia (19 of 473, 4%) and significant ischemia (2 of 473, 0.4%), defined as ≥10% of the LV. The latter represents a more than 17-fold decrease compared with the prevalence of ≥10% LV ischemia in those attaining <7 METs (19 of 267, 7.1%). The percentage of subjects with significant LV dysfunction (EF <35%) was also lower in those attaining ≥10 METs (0.7% vs. 3.1%, $p = 0.007$).

Value of the ST-segment response on the exercise ECG. Figure 3 shows that, of the 430 patients who achieved ≥10 METs with no ischemic ST-segment depression, only 3 (0.7%) had 5% to 9% LV ischemia. The prevalence of ≥10% LV ischemia was 0%. Of the 43 patients who achieved ≥10 METs with ischemic ST-segment depression, 2 (4.7%) had 5% to 9% LV ischemia, and 2 had ≥10% LV ischemia ($p = 0.016$ and $p < 0.001$, respectively, compared with those without ST-segment depression). As shown in Figure 3, the prevalence of LV ischemia by SPECT was higher in patients failing to reach ≥10 METs. Of the 70 patients attaining <10 METs with ST-segment depression, 14 (20%) had ≥10% LV ischemia. For those in this group that attained <7 METs, 28.6% (10 of 35) had ≥10% LV ischemia.

Logistic regression modeling. Diabetes, hyperlipidemia, and tobacco use were not significant predictors of ≥10% LV ischemia on univariable logistic regression analysis. The remaining variables from Table 1 were entered into a multivariable logistic regression model predicting significant LV ischemia (≥10%) in subjects attaining ≥85% of their MAPHR (Table 4). The predictive accuracy of this model is very high, with a C-statistic of 0.92. Lower exercise capacity (<10 METs) gave the largest increased odds of ≥10% LV ischemia when present. Pre-specified testing revealed no interactions between cardiac workload and age, male sex, decreased LVEF, and ischemic ST-segment depression ($p = 0.925$, $p = 0.921$, $p = 0.645$, and $p = 0.829$, respectively).

Influence of higher workload in patients attaining <85% MAPHR. Of all the patients in the original study cohort achieving ≥10 METs, 14.8% (82 of 555) reached <85% of their MAPHR. This subgroup had a higher rate of beta-

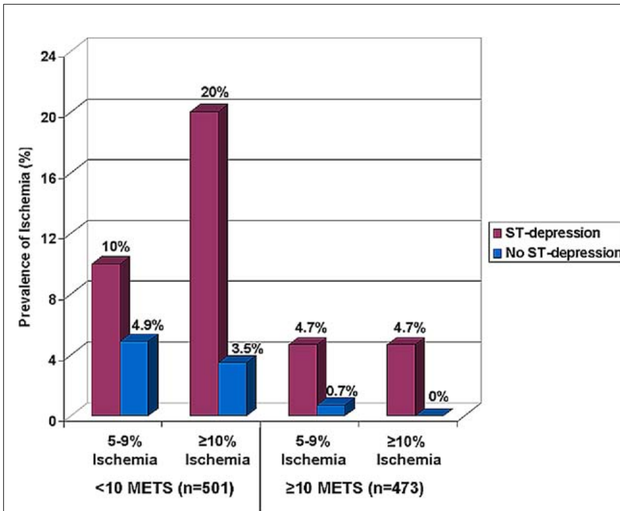

Figure 3 Relationship of Ischemic ST-Segment Depression on the Exercise ECG and Workload Achieved to the Percentage of LV Ischemia

The 974 subjects reaching ≥85% of their maximum age-predicted heart rate were divided by the exercise workload attained and the presence of ischemic ST-segment depression. The vertical axis represents the prevalence of 5% to 9% and ≥10% LV ischemia. ECG = electrocardiogram; other abbreviations as in Figure 2.

Table 4 Multivariable Logistic Regression Analysis Predicting ≥10% Ischemia of the Left Ventricle

Variable	Chi-Square	Odds Ratio	95% Confidence Interval	p Value
<10 METs exercise capacity	8.9	10.1	2.2–46.0	0.003
ST-segment depression ≥1 mm on exercise ECG	18.8	7.1	2.9–17.4	<0.001
Chest pain during stress	6.1	3.2	1.3–8.0	0.014
Male sex	4.6	3.0	1.1–8.2	0.033
Ejection fraction (↓ by 5%)	3.9	1.3	1.0–1.7	0.048

Global Wald chi-square = 58.2, c = 0.92.
↓ = decrease; other abbreviations as in Table 1.

blocker use on the day of testing (18.3% vs. 5.1%, $p < 0.001$) and a 2.2-fold higher prevalence of known CAD (43.9% vs. 20.1%, $p < 0.001$) compared with the 473 patients achieving ≥85% of MAPHR and ≥10 METs.

Table 5 shows that subjects attaining ≥10 METs of workload but <85% MAPHR were approximately 4 times more likely to have fixed and ischemic perfusion defects than patients achieving ≥10 METs and ≥85% of their MAPHR. Ischemia of ≥10% of the LV was also more prevalent in those reaching <85% of their MAPHR, but the difference was not statistically significant (2.4% vs. 0.4%, $p = 0.11$). As shown in Table 5, the <85% MAPHR group showed a higher percentage of patients with an end-systolic volume index ≥25 (25.9% vs. 8.5%, $p < 0.001$) and a lower median LVEF (61% vs. 65%, $p < 0.001$).

Discussion

Exercise workload is an important prognostic variable derived from the exercise stress test. Good exercise capacity has been associated with decreased mortality, MI, and revascularization, even in those with ischemic ST-segment depression (6,8,9,17,19,20). Moreover, exercise duration is 1 of the 3 components of the Duke Treadmill Score. High levels of exercise workload and low-risk Duke Treadmill Scores are associated with a lack of benefit with revascularization and a decreased prognostic impact of ischemia with respect to cardiac death and nonfatal MI (3,4). A high rate-pressure product without ST-segment depression also identifies a low-risk group (5). Exercise capacity was shown to be a better predictor of all-cause mortality than maximum exercise heart rate and even the angiographic severity of CAD (6,9).

However, these prior studies have certain limitations, including small sample sizes, inclusion of lower-risk subjects with a low incidence of cardiovascular risk factors, a lack of symptom documentation, and the exclusion of patients with CAD or prior MI. Many of these analyses were retrospective, analyzed only all-cause mortality, and did not determine the value of MPI to further risk-stratify.

The study population in this report comprised individuals referred for combined exercise ECG testing and MPI at the outset, thereby reducing bias from selective referral. The majority of these patients were symptomatic and had known CAD or multiple risk factors (one-quarter had diabetes) consistent with an intermediate to high risk of CAD.

A cutpoint of 10 METs was chosen, because prior studies have shown low rates of all-cause mortality, cardiac death, nonfatal MI, and revascularization in individuals reaching this level of workload (19–21). Among the patients with diagnostic exercise heart rates, there was a very low rate of myocardial ischemia (4%) in those reaching an exercise workload ≥10 METs. Only 2 of the 473 patients (0.4%) attaining ≥85% of their MAPHR and ≥10 METs had significant ischemia, which was defined as ≥10% of the LV myocardium. This finding is especially important, because Hachamovitch et al. (11,12) showed a survival benefit with revascularization only in patients with ischemia involving ≥10% of the LV. Although their study is subject to the limitations of a retrospective analysis, it suggests that 10% LV ischemia might be the optimal threshold for revascularization. Moreover, in the COURAGE nuclear substudy, the rate of death or MI was high (39.3%) for individuals with residual ischemia of ≥10% of the LV (18). In the present study, patients reaching <7 METs had a >17-fold increase in the prevalence of ≥10% LV ischemia.

The low prevalence of ≥10% LV ischemia and decreased benefit of perfusion imaging in the group with increased workload are consistent with the outcomes in patients with a low-risk Duke Treadmill Score (4,15). Some key differences between analyzing workload alone versus the Duke Treadmill Score are worth mentioning. The prevalence of moderate-to-severe perfusion defects appears higher in patients with a low-risk Duke Treadmill Score (16% to 20%) (3,4) versus the prevalence of such defects for those

Table 5 SPECT Imaging Results by MAPHR Achieved in Patients Attaining ≥10 METs

Characteristic	≥85% MAPHR Achieved (n = 473)	<85% MAPHR Achieved (n = 82)	p Value
Perfusion			
Fixed defects	31 (6.6%)	21 (25.6%)	<0.001
Reversible ischemia	19 (4.0%)	15 (18.3%)	<0.001
≥10% LV ischemia	2 (0.4%)	2 (2.4%)	0.106
Volumes and function			
ESVI >25	40 (8.5%)	21 (25.6%)	<0.001
Ejection fraction, median (25th, 75th percentiles)	65 (60, 69)	62 (56, 67)	0.001

Abbreviations as in Tables 1 and 3.

reaching ≥10 METs in the present study (0.4%). This difference is not unexpected. Although individuals achieving 7 to 9 METs in this study had a median Duke Treadmill Score in the low-risk range, they had a higher rate of significant perfusion abnormalities. Moreover, chest pain, 1 of the components of the Duke Treadmill Score, is subjective and often not reflective of ischemia (22). The majority of individuals reaching ≥85% MAPHR with exercise chest pain in the present study had normal scans (80%).

No differences in LVEF or cardiac volumes were observed with decreasing exercise workload. This suggests that the degree of myocardial ischemia affects exercise capacity more than LV systolic function or volumes. This is consistent with the finding of a lesser relationship between extent of fixed defects and workload achieved. These patients achieving ≥10 METs but <85% MAPHR had more perfusion defects, a higher prevalence of significant ischemia, and higher end-systolic volumes than those attaining ≥10 METs and ≥85% of their MAPHR. Thus, the MAPHR achieved provides important additional information to exercise capacity with respect to predicting the prevalence of significant ischemia. This is not surprising, because chronotropic incompetence during a treadmill test is a marker of increased future cardiovascular mortality (13).

The model examining the predictors of ≥10% LV ischemia was highly predictive (c = 0.92) and demonstrated that reduced exercise capacity is 1 of the 2 most significant markers of significant LV ischemia. Not reaching ≥10 METs was associated with a 10-fold increase in the risk of having ≥10% LV ischemia on SPECT imaging. The other significant predictor was the presence of ischemic ST-segment depression. As mentioned previously, not 1 patient achieving ≥85% of MAPHR and ≥10 METs of workload without ischemic ST-segment depression had ≥10% LV ischemia. It seems unlikely that any supplemental prognostic information that might influence management decisions could be expected from myocardial SPECT imaging as an adjunct to the exercise ECG in this subgroup. For example, in patients achieving a workload of ≥10 METs without exercise-induced ischemic ST-segment depression, optimal medical therapy would likely first be instituted according to practice guidelines.

New protocols should be explored in which patients would be referred for exercise ECG with only conditional SPECT myocardial perfusion imaging. Those individuals reaching the target heart rate and ≥10 METs of workload without ischemic ST-segment depression would not be injected with tracer. Although the appearance of significant ST-segment depression solely during the recovery period would complicate this approach, such an occurrence is unlikely. Very few patients achieving their target heart rate with high workloads show ST-segment depression only during recovery (23). Similarly, patients with an abnormal blood pressure response or nonsustained ventricular tachycardia might benefit from myocardial imaging despite reaching a high workload.

Cost implications. Diagnostic imaging is the fastest growing cost for Medicare and has been targeted by the Office of the Inspector General for a medical appropriateness assessment (24,25). SPECT MPI makes up a substantial portion of these costs, with an estimated $1.2 billion in allowed charges on stress nuclear SPECT in 2006 alone. This represents a 10.5% increase from 2004. In this study, 31% (430 of 1,396) of all patients referred for exercise SPECT myocardial perfusion imaging over a 12-month period achieved ≥10 METs of exercise workload without exercise ischemic ST-segment depression. Assuming the mix of patients in this study is roughly representative of the national referral pattern and these savings are projected to the more than 9.3 million SPECT studies performed each year, the cost savings could be potentially quite substantial (2,26–28).

Study limitations. One possible limitation is that the percentage of LV ischemia rather than hard clinical events was used as the end point of the study. This might not be a major limitation, because prognosis for patients with significant LV ischemia (≥10% of the LV) has been well-established. Similarly, the hard cardiac event rate for patients with normal exercise SPECT scans is very low (<1%/year). The prevalence of balanced ischemia due to left main and/or 3-vessel CAD yielding "normal" perfusion scans should rarely occur in a cohort of patients achieving ≥85% of MAPHR and ≥10 METs of workload with no ischemic ST-segment depression.

The low rate of ≥10% LV ischemia limits the number of variables that can be tested in the multivariable logistic regression model. Including too many predictors can lead to model over-fitting. Candidate variables were limited, and univariable logistic regression analysis was performed to minimize this risk.

Conclusions

This analysis suggests that the achievement of ≥10 METs is associated with a very low prevalence of ≥10% LV ischemia on MPI. No patient achieving ≥85% of MAPHR and ≥10 METs without exercise ST-segment depression had this degree of ischemia by SPECT. This group represented 31% of all patients undergoing exercise stress SPECT over a 12-month period. Patients attaining 7 to 9 and <7 METs had a progressively higher prevalence of ≥10% LV ischemia, despite reaching their target exercise heart rate. By multivariable analysis, low exercise capacity was associated with 10-fold increased odds of having ≥10% LV ischemia. These observations in a large consecutive series of patients referred for exercise SPECT imaging suggest that additional risk stratification with MPI might be eliminated in individuals who achieve ≥85% of their maximum age-predicted heart rate and ≥10 METs without ischemic ST-segment depression. This would lead to substantial cost savings.

Reprint requests and correspondence: Dr. Jamieson M. Bourque, Cardiovascular Imaging Center, Cardiovascular Division, Department of Medicine, University of Virginia Health System, Box 800662, 1215 Lee Street, Charlottesville, Virginia 22908. E-mail: jamieson2@gmail.com.

REFERENCES

1. Brindis RG, Douglas PS, Hendel RC, et al. ACCF/ASNC appropriateness criteria for single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI): a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group and the American Society of Nuclear Cardiology. J Am Coll Cardiol 2005;46:1587–605.
2. Thomas GS. ASNC news. J Nucl Cardiol 2007;14:136–8.
3. Hachamovitch R, Berman DS, Kiat H, Cohen I, Friedman JD, Shaw LJ. Value of stress myocardial perfusion single photon emission computed tomography in patients with normal resting electrocardiograms: an evaluation of incremental prognostic value and cost-effectiveness. Circulation 2002;105:823–9.
4. Poornima IG, Miller TD, Christian TF, Hodge DO, Bailey KR, Gibbons RJ. Utility of myocardial perfusion imaging in patients with low-risk treadmill scores. J Am Coll Cardiol 2004;43:194–9.
5. Christian TF, Miller TD, Bailey KR, Gibbons RJ. Exercise tomographic thallium-201 imaging in patients with severe coronary artery disease and normal electrocardiograms. Ann Intern Med 1994;121: 825–32.
6. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793–801.
7. Goraya TY, Jacobsen SJ, Pellikka PA, et al. Prognostic value of treadmill exercise testing in elderly persons. Ann Intern Med 2000; 132:862–70.
8. Snader CE, Marwick TH, Pashkow FJ, Harvey SA, Thomas JD, Lauer MS. Importance of estimated functional capacity as a predictor of all-cause mortality among patients referred for exercise thallium single-photon emission computed tomography: report of 3,400 patients from a single center. J Am Coll Cardiol 1997;30:641–8.
9. Weiner DA, Ryan TJ, McCabe CH, et al. Prognostic importance of a clinical profile and exercise test in medically treated patients with coronary artery disease. J Am Coll Cardiol 1984;3:772–9.
10. Morris CK, Ueshima K, Kawaguchi T, Hideg A, Froelicher VF. The prognostic value of exercise capacity: a review of the literature. Am Heart J 1991;122:1423–31.
11. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation 2003;107: 2900–7.
12. Hachamovitch R, Rozanski A, Hayes SW, et al. Predicting therapeutic benefit from myocardial revascularization procedures: are measurements of both resting left ventricular ejection fraction and stress-induced myocardial ischemia necessary? J Nucl Cardiol 2006;13: 768–78.
13. Elhendy A, Mahoney DW, Khandheria BK, Burger K, Pellikka PA. Prognostic significance of impairment of heart rate response to exercise: impact of left ventricular function and myocardial ischemia. J Am Coll Cardiol 2003;42:823–30.
14. Watson DD, Smith WH II. The role of quantitation in clinical nuclear cardiology: the University of Virginia approach. J Nucl Cardiol 2007;14:466–82.
15. Mark DB, Shaw L, Harrell FE Jr., et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. N Engl J Med 1991;325:849–53.
16. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). J Am Coll Cardiol 1997;30: 260–311.
17. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. Circulation 2003;108:1554–9.
18. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008;117:1283–91.
19. LaMonte MJ, Fitzgerald SJ, Levine BD, et al. Coronary artery calcium, exercise tolerance, and CHD events in asymptomatic men. Atherosclerosis 2006;189:157–62.
20. Thompson CA, Jabbour S, Goldberg RJ, et al. Exercise performance-based outcomes of medically treated patients with coronary artery disease and profound ST segment depression. J Am Coll Cardiol 2000;36:2140–5.
21. Bhat A, Desai A, Amsterdam EA. Usefulness of high functional capacity in patients with exercise-induced ST-depression to predict a negative result on exercise echocardiography and low prognostic risk. Am J Cardiol 2008;101:1541–3.
22. Gasperetti CM, Burwell LR, Beller GA. Prevalence of and variables associated with silent myocardial ischemia on exercise thallium-201 stress testing. J Am Coll Cardiol 1990;16:115–23.
23. Soto JR, Watson DD, Beller GA. Incidence and significance of ischemic ST-segment depression occurring solely during recovery after exercise testing. Am J Cardiol 2001;88:670–2.
24. Levin DC, Parker L, Intenzo CM, Sunshine JH. Recent rapid increase in utilization of radionuclide myocardial perfusion imaging and related procedures: 1996–1998 practice patterns. Radiology 2002;222:144–8.
25. Health Care Financing Administration. HHS/OIG fiscal year 2000 work plan. Office of Inspector General Projects. Washington, DC: U.S. Department of Health and Human Services.
26. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol 2002;40:1531–40.
27. Hannoush H, Shaar K, Alam S, Nasrallah A, Sawaya J, Dakik HA. Analysis of referral patterns, predictive accuracy, and impact on patient management of myocardial perfusion imaging in a new nuclear cardiology laboratory. J Nucl Cardiol 2003;10:148–53.
28. Hachamovitch R, Hayes S, Friedman JD, et al. Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans: what is the warranty period of a normal scan? J Am Coll Cardiol 2003;41:1329–40.

Key Words: coronary artery disease ▪ exercise capacity ▪ radionuclide imaging ▪ risk prediction.