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Usefulness of Achieving 10 Metabolic Equivalents (METs) with a Negative Stress Electrocardiogram to Screen for High-Risk Obstructive Coronary Artery Disease in Patients Referred for Coronary Angiography after Exercise Stress Testing

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Abstract

Functional capacity in exercise stress testing is an independent predictor of cardiac events. Routine use of nuclear perfusion imaging increases radiation burden and cost. Our goal was to assess the clinical utility of exercise functional capacity with stress electrocardiogram (ECG) as an adjunct in predicting the presence of high-risk obstructive coronary artery disease (CAD) on diagnostic coronary angiography. We performed a retrospective study of patients who underwent exercise stress testing for the evaluation of chest pain and underwent diagnostic coronary angiography within the subsequent three months. High-risk CAD was defined as coronary artery diameter stenosis ≥70% in the proximal left anterior descending artery, ≥70% diameter stenosis in 3 major epicardial arteries, or ≥50% diameter stenosis in the left main artery. Univariable and multivariable analyses were performed to identify predictors of high-risk CAD. Of the 412 patients, 105 (25%) had high-risk CAD on coronary angiography. On multivariate logistic regression we found that positive stress ECG, abnormal stress imaging, left ventricular ejection fraction, and male sex were independent predictors of high-risk CAD. The strongest predictor was positive stress ECG (HR = 3.16, 95% CI 1.90 to 5.27, $p < 0.001$). Functional capacity measures alone were not independent predictors of high-risk CAD. Achieving ≥10 METs with a negative stress ECG resulted in 94% sensitivity and 97% negative predictive value in identifying high-risk CAD. This supports the strategy for provisional use of myocardial perfusion imaging in patients with low functional capacity and/or abnormal stress ECG to minimize cost and radiation exposure.

Keywords

functional capacity; high-risk CAD; exercise stress testing

Exercise stress testing remains an invaluable tool for the detection of obstructive coronary artery disease (CAD). Functional capacity in exercise stress testing is a measure of workload

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achievement and is reported as metabolic equivalents of task, or METS (equivalent to $3.5 \text{ ml O}_2 \text{ uptake} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at rest)¹, and is an independent predictor of cardiac events.^{2–6} Achievement of ≥ 10 METS is associated with a low prevalence of significant myocardial ischemia, questioning the need for additional noninvasive imaging in patients with good functional capacity.⁷ In the American College of Cardiology/American Heart Association guidelines, standard exercise treadmill testing without additional imaging is a Class I indication for the evaluation of chest pain in subjects with interpretable electrocardiograms (ECG).⁸ Nonetheless, the vast majority of exercise stress testing performed in this country includes additional imaging.⁹ Routine use of nuclear perfusion imaging accounts for $\sim 10\%$ of the radiation burden in this country and increases cost.¹⁰ Our goal was to assess the clinical utility of exercise functional capacity alone with stress ECG as an adjunct in predicting the presence of high-risk obstructive CAD on diagnostic coronary angiography.

Methods

The institutional review board of the University of Virginia approved the study. Its design was a retrospective cohort study analyzing medical records of patients who underwent coronary angiography within three months of exercise stress ECG testing from 2007 to 2011. 935 patients underwent exercise stress testing for with or without additional imaging for various indications during this period. A total of 412 of these patients underwent coronary angiography within 3 months of their stress test and were included in this analysis. There were no exclusions. The decision to undergo coronary angiography was made by discretion of the patient's provider. A three month inclusion window was chosen as a longer duration was felt to less likely reflect decisions based on the initial stress test. All subjects underwent exercise stress ECG testing using standard Bruce or modified Bruce protocols. The decision to hold anti-anginal medications prior to the test was at the discretion of the ordering physician. The test was symptom-limited unless stopped prematurely according to guideline recommendations.¹ Baseline demographics, medical co-morbidities, angiographic data, medications and exercise functional capacity as defined by maximal METS were obtained from the electronic medical record. Obstructive CAD was defined as the presence of at least one major epicardial artery with a diameter stenosis $\geq 70\%$, or the presence of $\geq 50\%$ diameter stenosis of the left main coronary artery on coronary angiography. High-risk CAD was defined as diameter stenosis $\geq 70\%$ in the proximal left anterior descending artery, $\geq 70\%$ diameter stenosis in 3 major epicardial arteries, or $\geq 50\%$ diameter stenosis in the left main artery.

We examined whether functional capacity provided significant clinical utility in predicting the presence of high-risk obstructive CAD, together with other clinical variables such as sex, age, and traditional cardiac risk factors. Continuous variables were presented as medians (25th, 75th percentiles) and were compared using T-tests where appropriate. Categorical variables were given as percentages and compared using Chi-square analysis and Fisher's Exact Testing where appropriate. Interactions between key markers of interest, such as between high-risk obstructive CAD, functional capacity, stress testing and comorbidities, were compared by univariable logistic regression. A total of 16 candidate variables were studied, including prior myocardial infarction, diabetes mellitus, hyperlipidemia, obesity, tobacco use, chronic obstructive pulmonary disease, hypertension, peripheral vascular

disease, congestive heart failure, positive stress ECG, abnormal stress imaging, sex, age, maximal METS, left ventricular ejection fraction, and achievement of 10 METS. For the multivariable model, variables from the univariable analysis with a p-value < 0.10 were included. The alpha level of significance was set at <0.05. Statistical analyses were performed using SAS version 9.4 (Cary, NC).

Results

Of the 935 patients who underwent exercise stress ECG from 2007 to 2011, 412 also had coronary angiography performed within 3 months of exercise stress testing and were included in our analysis. Of the 412 patients, 403 (98%) exercised according to a Bruce or modified Bruce protocol, 387 (94%) underwent stress imaging (357 with SPECT, and 30 with echocardiography) and 105 (25%) were found to have high-risk CAD on coronary angiography. The baseline characteristics of the patient population separated according to the presence or absence of high-risk CAD on coronary angiography are shown in Table 1.

Of the 16 candidate variables, 7 variables had p-values <0.10. Positive stress ECG (p<0.001), abnormal stress imaging (p=0.01), male sex (p=0.01) and age (0.04) were statistically significant predictors of high-risk CAD in the univariable analysis (Table 2). Two models were created using only one of the functional capacity variables (maximal METS achieved or achieving 10 METS) to minimize interdependence. Neither of these variables were found to be independent predictors of high-risk CAD based on the multivariate analysis (Table 2). Positive stress ECG, abnormal stress imaging, left ventricular ejection, and male sex were all independent predictors of high-risk CAD. The strongest predictor was positive stress ECG (Hazard ratio = 3.16, 95% CI 1.90–5.27, p <0.001). Receiver operating characteristic curve generated a c-statistic of 0.72 for this model.

A total of 247 (60%) of the patients had any obstructive CAD on coronary angiography, and 105 (25%) had high-risk CAD. With regard to functional capacity, a total of 103 (25%) patients achieved 10 METS during exercising stress testing, and of these, 20 (19%) had high-risk CAD on coronary angiography (Table 3). High-risk CAD patients had significantly more abnormal stress imaging (myocardial perfusion imaging or echocardiogram) and positive stress ECG results. There was no difference between those with and without high-risk CAD in achieving 10 METS (Table 4). As shown in Table 3 and Figure 1, only 1 patient achieved 10 METS with no evidence of ST segment depression on ECG but was subsequently found to have high-risk CAD on coronary angiography (a 36 year old man with a family history of premature CAD who achieved 12.9 METS and had ST elevation in lead aVR and chest pain during exercise). In sensitivity-specificity testing we found 80% sensitivity and 47% specificity when using positive or negative stress ECG findings alone. However, when focusing on those with a negative stress ECG and incorporating functional status as 10 METS or < 10 METS, we found 94% sensitivity, 37% specificity, and 97% negative predictive value. While the majority of patients in our cohort had additional stress imaging performed (94%), Figure 1 illustrates the implications of a strategy of achieving 10 METS and stress ECG for screening high risk CAD. In this cohort, ~ 16% of patients would not have needed additional imaging if using this strategy.

Discussion

The majority of exercise stress testing performed in this country includes additional imaging which increases radiation burden and cost⁹ despite the fact that ACC/AHA guidelines recommend standard exercise treadmill testing without additional imaging as a Class I indication for the evaluation of chest pain in subjects with interpretable electrocardiograms.⁸ In an era of increasing attention to cost-effective healthcare, maximizing the utility of non-invasive and invasive cardiovascular testing is becoming increasingly important. We found that 16% of our patients undergoing exercise stress testing actually did not require additional stress imaging.

Higher workloads achieved during exercise stress testing predict improved survival rates. In men, functional capacity is a better predictor of mortality than other established risk factors for CAD.² While patients with high-risk CAD derive the greatest benefit from revascularization,^{11,12} prior models focus on predictors of any obstructive CAD, not high-risk CAD. Previously, we have shown that functional capacity is important in that achievement of high functional capacity (≥ 10 METS) during exercise stress testing was associated with decreased rates of cardiac death (0.1%/year) and non-fatal myocardial infarction (0.7%/year),¹³ and compared to patients who achieved a high functional capacity, those with low functional capacity (< 7 METS) had an 18-fold higher prevalence of significant left ventricular ischemia.⁷

Our cohort included patients with intermediate to high probability for obstructive CAD since the majority were men with a high incidence of comorbidities, and given that they were referred for coronary angiography. This is further supported by the finding that ~60% had obstructive CAD of some degree. A large national registry has reported a much lower presence (38%) of obstructive CAD for patients referred for invasive coronary angiography.¹⁴ This may be due, at least in part, to the fact that our cohort was at higher risk of severe CAD.

Of the 103 patients that achieved ≥ 10 METS, 20 (19%) had high-risk CAD on coronary angiography. Only one of these patients did not have ST depression on stress ECG. This patient was young and perhaps more likely to achieve a high functional capacity. Previously we found that the mean age of patients who achieved ≥ 10 METS with low-risk of inducible ischemia was 53 years old.⁷ Perhaps a higher METS cut-off would be needed to predict low-risk CAD in younger patients. Our findings are also consistent with prior work showing that no patients without ST depression on exercise stress testing had high-risk (≥ 10 % left ventricular ischemia) on myocardial perfusion imaging.⁷

In our multivariable analysis, a positive stress ECG and male sex were stronger predictors of high-risk CAD than abnormal stress imaging. We contend that for patients who can exercise and achieve a diagnostic stress test, exercise stress ECG is an effective way to identify those with high-risk CAD, with 94% sensitivity and 97% negative predictive value. This is supported by a class I indication in current guidelines.⁸ Up to 70% of myocardial perfusion imaging studies ordered for CAD detection are normal,¹⁵ further supporting the idea of provisional use of myocardial perfusion imaging only for patients who achieve < 10 METS

and/or have a negative or non-diagnostic stress ECG to minimize costs and radiation exposure.¹⁶ Our findings are consistent with a prior study reporting a sensitivity of 81% and a specificity of 62% for high-risk CAD.¹⁷

Our study has limitations. First, it is a single-center, retrospective analysis with a small number of patients and it is possible that factors other than what we collected may have influenced the results such as body habitus, musculoskeletal disease, and preparedness for the test. Second, we do not have information regarding long-term clinical outcomes. Third, we do not have information regarding fractional flow reserve assessment of indeterminate lesions seen on coronary angiography.

In conclusion, the combination of high functional capacity and absence of ischemic ECG changes on exercise stress testing effectively screens for high-risk CAD, supporting the strategy of provisional use of stress imaging for patients with low functional capacity and/or abnormal stress ECG changes to minimize cost and radiation exposure.

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Figure 1.

Implications of a strategy to use stress electrocardiogram (ECG) results and achievement of 10 METS to identify patients with high-risk coronary artery disease (CAD). In patients with angiographically documented high-risk CAD (top panel) only one (represented by the white section) achieved ≥ 10 METS and had a negative stress ECG. In patients without angiographically documented high-risk CAD (bottom panel), using a provisional imaging strategy in only patients who did not achieve 10 METS or achieved ≥ 10 METS and had a positive stress ECG (dark gray section) would have avoided additional imaging in ~16% (light gray section).

Table 1

Baseline characteristics of patients with and without high-risk coronary artery disease on coronary angiography

Variable	High-Risk Coronary Artery Disease		P value
	Yes (n=105)	No (n=307)	
Age (years)	72 ± 10	69 ± 12	0.04
Men	86 (82%)	210 (68%)	<0.01
Body Mass Index (kg/m ²)	30.0 ± 6.2	29.6 ± 5.5	0.50
Diabetes mellitus	39 (37%)	98 (32%)	0.34
Hypertension	90 (86%)	256 (83%)	0.65
Hyperlipidemia	91 (87%)	255 (83%)	0.44
Smoker	51 (49%)	138 (45%)	0.57
Prior myocardial infarction	31 (30%)	72 (23%)	0.24
Prior heart failure	14 (13%)	37 (12%)	0.73
Peripheral vascular disease	8 (8%)	27 (9%)	0.84
Chronic obstructive pulmonary disease	8 (8%)	18 (6%)	0.49
Medications:			
Aspirin	89 (85%)	245 (80%)	0.31
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker	57 (54%)	171 (56%)	0.82
Beta-blocker	58 (55%)	160 (52%)	0.65
Calcium channel blocker	15 (14%)	52 (17%)	0.65
Nitrates	26 (25%)	65 (21%)	0.50
Statin	74 (70%)	214 (70%)	0.90

Values are mean ± SD or count (percentage). Hypertension is defined by a prior documentation of blood pressure > 140/90mm Hg or current use of antihypertensive medication. Hyperlipidemia is defined by a prior documentation of total cholesterol > 200 mg/dl or low-density lipoprotein > 130 mg/dl or high-density lipoprotein < 40mg/dl or current use of lipid-lowering agent.

Univariable and multivariable logistic regression analysis predicting high-risk coronary artery disease (Global Wald $X^2=42.66$, $c=0.72$).

Table 2

Predictors	Univariable			Multivariable		
	X^2	Hazard Ratio (95% CI)*	P value	X^2	Hazard Ratio (95% CI)	P value [†]
Positive stress ECG	20.2	2.84 (1.80–4.49)	<0.001	19.5	3.16 (1.90–5.27)	<0.001
Abnormal stress imaging	7.75	2.55 (1.32–4.92)	0.01	3.95	2.07 (1.01–4.22)	0.047
Male sex	6.86	2.09 (1.20–3.63)	0.01	5.68	2.12 (1.14–3.93)	0.017
Age	4.33	1.02 (1.00–1.04)	0.04			
Maximal METS	3.31	0.92 (0.83–1.007)	0.07			
LV ejection fraction	3.2	0.98 (0.96–1.00)	0.07	3.93	0.974 (0.95–1.00)	0.047
10 METs	2.63	0.64 (0.37–1.10)	0.10			

* CI=confidence interval; ECG=electrocardiogram; LV=left ventricular; METS=metabolic equivalents.

[†] P-values are two-tailed with values <0.05 considered statistically significant.

Table 3

High-risk coronary artery disease according to functional capacity and stress ECG results

	High-Risk CAD on coronary angiography		
	No	Yes	Total
10 METS, normal ECG	35	1	36
10 METS, abnormal ECG *	48	19	67
< 10 METS, normal ECG	60	15	75
< 10 METS, abnormal ECG *	164	70	234
Total	307	105	412

* Abnormal ECG: defined as positive or non-diagnostic, CAD=coronary artery disease; ECG=electrocardiogram; METS=metabolic equivalents

Table 4

Exercise stress testing data

Variable	With high-risk CAD N=105	Without high-risk CAD N=307	P value
Exercise stress ECG			<0.001
Positive	63 (60%)	106 (35%)	
Non-diagnostic	26 (25%)	106 (35%)	
Negative	16 (15%)	95 (31%)	
Abnormal stress imaging	88 (88%)	213 (74%)	<0.001
Achieved 10 METS	20 (19%)	83 (27%)	0.12

CAD=coronary artery disease; ECG=electrocardiogram; METS=metabolic equivalents.