Original Article

Using Workload to Predict Left Main Coronary Artery Stenosis in Candidates for Coronary Angiography

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Abstract

Background: *Coronary angiography, albeit a safe procedure, may cause serious complications especially in patients with left main stenosis (LMS). This study was designed to investigate the efficacy of workload achieved by exercise tolerance test (ETT) in predicting LMS in candidates for coronary angiography.*

Methods: *A total of 743 patients with a positive ETT who subsequently underwent cardiac catheterization were retrospectively studied. Different risk factors were compared among the patients with and without LMS. A multivariate forward stepwise logistic regression analysis was used to identify the main predictors of LMS.*

Results: *Among our 743 patients, 72% were male and 41(5.5%) had LMS≥50%. Patients with LMS, by comparison with those without LMS, were older and were more likely to be male and had higher percentages of ejection fraction less than 35% (EF≤35%), history of myocardial infarction, and lower metabolic equivalent (METs). After adjusting for important variables, we found that EF≤35%, METs, and the male sex were significant independent predictors of LMS (P<0.0001, P=0.024, and P=0.006, respectively). When the patients were divided into two groups in terms of METs≤7 and METs>7, LMS was found in 8.3% and 3.6%, respectively (P=0.006). The risk of having LMS in the men with METs≤7 was higher than that in those with METs>7 (OR=3, P=0.003, 95% CI=1.50-6.00). Among the patients with LMS, stenosis≥70% was found in 44% in METs≤7 and 18.8% in METs>7.*

Conclusion: *Lower METs correlated with an increased likelihood of significant LMS in the patients, especially if they were male, who had a positive exercise test and were suspected of coronary artery disease. It is, therefore, advisable that patients with METs≤7 receive due attention during coronary angiography.*

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Introduction

Coronary angiography may result in life-threatening complications. The coronary angiography-related mortality rate varies from 0.02 to 0.11 percent,[1,2] and independent risk factors of the complications of coronary arteriography include unstable angina, coronary multivessel disease, left main coronary artery disease, and heart failure.[1] Patients with left main coronary stenosis (LMS) have a 2-fold higher risk of complications from coronary angiography and require care when the procedure is performed.[1] In agreement with those results, our experiment on more than 45000 angiographies showed an angiography-related mortality rate of 0.04% (16 patients), 9 cases of which had left main artery lesion (56%). For this reason, investigators have attempted to find

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noninvasive tests that will predict patients with significant narrowing of the left main coronary artery.

Although previous studies attempted to quantitate the severity of coronary disease by examining various aspects of the exercise tolerance test (ETT),[3,4,5] the results were not simply used in practice with respect to the existence of LMS. Introducing criteria with which those at a higher risk of LMS during coronary angiography can be identified will reduce the mortality risk. Given the wide use of ETT as a screening test prior to angiography, the present study sought to investigate weather LMS could be predicted using workload achieved by ETT.

Methods

Patient selection: In this cross-sectional study, we retrospectively investigated data on 743 patients who had a positive treadmill exercise test and subsequently underwent cardiac catheterization between 2003 and 2005. All the tests were ordered by physicians, and decision to interrupt medications before the treadmill exercise test was at the discretion of the attending physician.

Clinical data: Data were prepared using the angiography data base, in which the data were obtained through a comprehensive interview and examination by cardiologists prior to the exercise test. A trained nurse was responsible for taking the blood pressure (with a mercury device), height, and weight of each patient. All the blood tests were done after 12 hours of overnight fasting by calorimetry. Patients already taking hypertensive medication or those whose average of two blood pressure readings at least five minutes apart in the sitting posture was≥140/90 mmHg were labeled as hypertensive.[6] Also, patients with a history of taking antihyperlipidemic drugs, total cholesterol≥200 mg/dl, or low density lipoprotein≥130 mg/dl were defined as hypercholestrolemic.[7] Diabetes mellitus was diagnosed to be present if a patient had a definite history of diabetes with records of treatment or fasting plasma glucose≥126 mg/dl or two-hour post-load glucose≥200 mg/dl, based on the guideline of the American Diabetes Association, 2003.[8] Angina class of each patient was determined according to the NYHA classification.

Myocardial infarction or sudden death before the age of 55 years in the father or any other male first-degree relative, or before the age of 65 years in the mother or any other female first-degree relative was considered a positive family history of premature coronary artery disease (CAD).[9] A smoker was defined as a person who regularly smoked cigarettes or who had stopped smoking within the past one month.[10] Finally, an opium user was defined as a person who reported the use of opium at least once or more in his or her life.

Exercise test: All the patients were exercised on the treadmill according to the Bruce and modified Bruce protocol under cardiologist supervision. Exclusion criteria for the exercise test in this database were: those who could not exercise for any reason, those with significant valvular or congenital heart disease, acute myocardial infarction in recent seven days, percutaneous or coronary surgery intervention, decompensated heart failure, advanced atrioventricular block, and high risk unstable angina.

Metabolic equivalent (METs) was used to express the estimated workload. The term MET refers to unit of oxygen uptake in a sitting, resting person, and 1 MET is equivalent to 3.5 ml O_2/kg/min of body weight. Measured volume of O_2 in ml O_2/min/kg divided by 3.5 ml O_2/kg/min determines the number of METs associated with activity.[11] Exercise testing was stopped if exertional hypotension, malignant ventricular arrhythmias, marked ST depression (≥3 mm), ST elevation≥1.0 mm in noninfarct leads without diagnostic Q wave (other than V1 or aVR), and limiting chest pain were reported. The positive exercise ECG was determined by conventional criteria (≥1 mm of horizontal or downsloping ST segment depression at 80 ms after the end of QRS complex (from the J point) in three consecutive beats.

First, we categorized the patients according to their METs into 4 groups of ≤5, 5-7, 8-12, and>12 METs to show the relationship between METs and different results of coronary angiography. Then, to investigate the relationship between METs and LMS or sex, we combined the first two groups as METs≤7 and the other two groups as METs >7.

Angiography data: Cardiac catheterization was performed≤90 days after the exercise test using standard techniques and was recoded in multiple projections for the left and right coronary arteries. Diagnoses of CAD were determined after coronary artery catheterizations, all of which were done by cardiologists with over 5 years of experience in the field of cardiac angiography (each cardiologist had performed more than 500 angiographies per year). The diagnoses were based on the cardiologists' visual assessments.

CAD was defined as the presence of≥50% stenosis in the coronary arteries; single vessel disease (SVD): stenosis of one of left anterior descending artery or left circumflex artery or right coronary artery or main branches of each; two-vessel disease (2VD): stenosis in two coronary arteries other than left main artery; three-vessel disease (3VD): stenosis in three coronary arteries other than left main artery; and left main stenosis (LMS): stenosis in left main artery regardless of existence of stenosis in other arteries. The extent of atherosclerosis was assessed with a "clinical vessel score" on a scale of 0-3 based on the system of Oberman et al.[12]

Statistical analysis: Numerical variables were presented as mean±standard deviation and were compared using the Student's t-test. Categorical variables were summarized by percentages and were compared using the chi-square (or Fisher's exact test if required) or Mantel-Haenszel chi-square test for trend. A multivariate forward stepwise logistic regression model for the risk factors that could predict LMS was established. Variables were included into the multivariate model if the P value was found to be less than or equal to 0.15 in the univariate analysis. The associations of independent predictors with LMS in the final model were expressed as odds ratios (OR) with 95% confidence intervals (CIs). Model discrimination was measured using the c statistic, which is equal to the area under the Receiver Operating Characteristics (ROC) curve. Model calibration was estimated using the Hosmer-Lemeshow (HL) goodness-of-fit statistic (higher P values imply that the model fits the observed data better). For the statistical analysis, the statistical software SPSS version 13.0 for Windows (SPSS Inc, Chicago, IL) and the statistical package SAS version 9 for Windows (SAS Institute Inc, Cary, NC, USA) were used. All P values were 2-tailed, with statistical significance defined by P≤0.05.

Results

The group of 743 patients comprised 537 (72.3%) men and 206 (27.7%) women at a mean age of 55.84±9.36 years. The prevalence of left main coronary stenosis≥50% was 5.5% (41 patients; 95%CI=3.9%-7.1%). The distribution of the patients in the 4 METs groups based on the results of coronary angiography is shown in Table 1, which demonstrates that the presence of LMS increased as METs decreased. This trend was significant according to the Mantel-Haenszel chi-square test (P=0.008).

In the second analysis, we divided the patients into two groups: with LMS and without LMS. A comparison of the clinical characteristics of the patients with and without LMS after angiography (Table 2) showed that the proportion of the male sex in those with LMS was higher than that of the ones without LMS (87.8% vs. 71.4%, P=0.020) and that patients with LMS were older (mean age of 58.8±10.5 years in those with LMS vs. 55.6±9.2 in the ones without LMS, P=0.03). The proportion of the patients with EF≤35% was lower in the LMS group, and this group also had a significantly lower mean of METs (7.4±2.3 vs. 8.6±2.7 METs, P=0.006).

When we divided the patients into two groups in terms of METs≤7 and METs>7, 11.3% of men and 2.8% of women among the patients who achieved METs≤7 had stenosis≥50% in the left main artery. This difference was significant (OR=4.4, 95%CI=1.30-15.18, P=0.010). The frequency of LMS also was higher in the male patients with METs≤7 compared with the male patients with METs>7 (OR=3, 95% CI=1.50-6.02, P=0.003), while the female patients with METs≤7 were only 1.4 times more likely to have LMS (95% CI=0.23-8.55, P=0.99,) compared with the women with METs >7.

Table 1. Coronary angiography results in different METs groups

		Coronary Angiography Result				
METs group	No	NCA (%)	SVD (%)	2VD (%)	3VD (%)	LMS (%)
≤5	94	14 (14.8)	12 (12.8)	22 (23.4)	37 (39.4)	9 (9.6)
5-7	208	41 (19.7)	26 (12.5)	41 (19.7)	84 (40.4)	16 (7.7)
7-12	381	132 (34.6)	65 (17.1)	71 (18.6)	99 (26.0)	14 (3.7)
≥13	60	27 (45.0)	8 (13.3)	13 (21.7)	10 (16.7)	2 (3.3)

METs, Metabolic equivalent; No, Number; NCA, Normal coronary artery; SVD, Single vessel disease; 2VD, Two vessels disease; 3VD, Three vessels disease; LMS, Left main stenosis

Table 2. Characteristics of Patients with and without left main stenosis*

Variable	LMS+	LMS-	P value
Age (yr)	58.8 ± 10.5	55.6 ± 9.2	0.03
METs	7.38 ± 2.3	8.57 ± 2.7	0.01
Male sex	87.8	71.4	0.02
Smoking	39.0	28.1	0.15
Diabetes	29.3	24.0	0.45
Hypertension	43.9	42.7	0.87
Hyperlipidemia	70.7	55.8	0.07
History of MI	18.9	8.1	0.03
Angina class III or VI	17.9	19.5	0.99
Family history of CAD	22.5	23.3	0.99
Opium user	14.6	10.6	0.43
EF≤35%	15.8	3.6	0.01
BMI (kg/m2)	27.5 ± 3.8	26.64 ± 3.8	0.34

*All values are presented as mean±SD or percentage (%)
LMS+, With left main stenosis; LMS-, Without left main stenosis; METs, Metabolic equivalent; MI, Myocardial infarction; CAD, Coronary artery disease; EF, Ejection fraction; BMI; Body mass index

In the patients with LMS, LMS≥70% was found more frequently in those having METs≤7 compared with those having METs>7 (44% vs. 18.8%), although this difference was not strongly significant (P=0.096). The majority (78.5%) of cases with angiographic evidence of LMS≥70% had METs ≤7.

In the final investigation, to show the main predictors of LMS, we included age, gender, hypercholesterolemia, smoking, history of MI, EF≤35%, METs, and body mass index in a multivariate forward stepwise logistic regression analysis. Three risk factors remained in the model: EF≤35% (OR=5.5, 95%CI=2-13.4, P<0.0001), METs (OR=0.83, 95%CI=0.7-0.9, P=0.0068), and the male sex (OR=2.90, 95%CI=1.1–7.7, P=0.0246). The final model had good discrimination (c statistic, 0.71; 95%CI, 0.7-0.8) and calibration (Hosmer-Lemeshow statistic, P=0.1940). These results showed that the occurrence of left main coronary stenosis≥50% increased as ejection fraction and workload capacity decreased.

Discussion

Significant stenosis of the left main coronary artery has a poor prognosis and puts the patients at a higher risk of mortality and morbidity during angiography.[13,14] In this study, we included all the patients with a positive exercise test to determine how well the existence of LMS can be predicted among patients referred for a treadmill exercise test with suspected coronary artery disease. To our knowledge, a few studies have dealt uniquely with LMS in this area.[5,15]

Moris PA and colleagues[16] reported that METs is an independent predictor of the existence of three-vessel or left main disease but not the presence of coronary artery disease. Only 55% of their cases who had METs<5 showed existence of CAD. The first finding of the present study supports the conclusion that workload at which the ischemic changes are determined is important in the evaluation of the presence of CAD inasmuch as we found that METs≤5 showed an 85.1% chance of having stenosis in at least one coronary artery.

A few studies have thus far confirmed a positive relationship between workload and existence of left main disease.[2,3,17] In our study, a workload equal to or less than 7 METs indicated an 8.3% chance of detecting left main stenosis confirmed by the angiographic findings. In contrast, when the workload was raised to greater than 7 METs, this chance decreased to less than half (3.6%).

Schneider RM et al.[15] demonstrated a 35% predictive value for left main disease in patients with medically refractory and disabling angina pectoris who had stage I or stage II positive treadmill tests. Our data did not demonstrate a relationship between severe chest pain (angina class III and VI) and prevalence of LMS. This maybe due to the fact that some of our patients with disabling angina who were high risk for ETT were excluded.

The diagnostic accuracy of ETT is less in women than in men.[11] Our study showed that in the patients who achieved METs≤7, women had 4.4 times lesser chance of stenosis≥50% in the left main artery compared with their male counterparts. However, in our data, only 5 of 41 patients with LMS were female and 3 of them (60%) had METs≤7; this number was not enough to warrant a separate analysis. These findings suggests that a low workload may increase the probability of the existence of LMS among women with METs≤7 compared with those having METs>7.

Regarding the relationship between the severity of LMS and workload, it seems that patients with lower METs have a higher risk of LMS≥70%; although maybe due to the small number of patients having LMS, this correlation was not significant in the univariate analysis. It is very important to note that 78.5% of the patients with LMS≥70% appeared with a workload equal to or less than 7 METs.

In conclusion, our data clearly support the concept that workload at which the ischemic changes are determined is important in the evaluation of the severity of the disease and that a positive treadmill test in METs≤7 predicts an increased likelihood of significant left main coronary stenosis in patients referred for coronary angiography with suspected coronary artery disease. It is advisable that patients with METs≤7, who are high risk for LMS and for whom aggressive techniques are inevitable, receive especial preparations such as standby CABG and PCI prior to angiography in addition to a careful management of the procedural process.

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