Long-term effects of smoking and smoking cessation on exercise stress testing: Three-year outcomes from a randomized clinical trial

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Background The long-term effects of smoking and smoking cessation on markers of cardiovascular disease (CVD) prognosis obtained during treadmill stress testing (TST) are unknown. The purpose of this study was to evaluate the long-term effects of smoking cessation and continued smoking on TST parameters that predict CVD risk.

Methods In a prospective, double-blind, randomized, placebo-controlled trial of 5 smoking cessation pharmacotherapies, symptom-limited TST was performed to determine peak METs, rate-pressure product (RPP), heart rate (HR) increase, HR reserve, and 60-second HR recovery, before and 3 years after the target smoking cessation date. Relationships between TST parameters and treatments among successful abstainers and continuing smokers were evaluated using multivariable analyses.

Results At baseline, the 600 current smokers (61% women) had a mean age of 43.4 (SD 11.5) years and smoked 20.7 (8.4) cigarettes per day. Their exercise capacity was 8.7 (2.3) METs, HR reserve was 86.6 (9.6)%, HR increase was 81.1 (20.9) beats/min, and HR recovery was 22.3 (11.3) beats. Cigarettes per day and pack-years were independently and inversely associated with baseline peak METs ($P < .001$), RPP ($P < .01$, pack-years only), HR increase ($P < .05$), and HR reserve ($P < .01$). After 3 years, 168 (28%) had quit smoking. Abstainers had greater improvements than continuing smokers (all $P < .001$) in RPP (2,055 mm Hg beats/min), HR increase (5.9 beats/min), and HR reserve (3.7%), even after statistical adjustment (all $P < .001$).

Conclusions Smokers with a higher smoking burden have lower exercise capacity, lower HR reserve, and a blunted exercise HR response. After 3 years, TST improvements suggestive of improved CVD prognosis were observed among successful abstainers. (Am Heart J 2012;163:81-87.e1.)

Cigarette smoking is a powerful risk factor for cardiovascular disease (CVD) morbidity and mortality.[1,2] The mechanisms by which smoking increases CVD risk are not well understood.[3,4] Observational studies have demonstrated that exercise capacity is significantly impaired in smokers and that reduced smoke exposure may improve exercise parameters.[5,6] However, smoking cessation is associated with weight gain,[7-9] which affects exercise capacity,[10,11] and today's smokers are considerably heavier than those in past studies.[12-14] Therefore, the long-term effects of smoking cessation on exercise physiology are unclear in today's smokers. Several parameters measured during treadmill stress testing (TST) are predictive of future CVD events and mortality, including exercise capacity, rate-pressure product (RPP), peak heart rate (HR) increase, HR reserve, and 60-second HR recovery.[15-21] To our knowledge, the effects of smoking cessation and continued smoking on exercise parameters have not been investigated longitudinally in a contemporary cohort of smokers. The purpose of this study was to evaluate the long-term effects of smoking cessation and continued smoking on TST parameters that predict CVD risk.

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Methods

Study participants and design

This study was approved by the Institutional Review Board at the University of Wisconsin School of Medicine and Public Health. All subjects provided written informed consent to participate in a 3-year longitudinal, randomized, double-blinded, placebo-controlled trial that evaluated the efficacy of 5 smoking cessation pharmacotherapies and the natural history of continued smoking and smoking cessation on CVD risk.[22] This

report describes a prespecified analysis of data from the baseline and year 3 (final) study visits. Major inclusion criteria included being 18 years or older, smoking 10 or more cigarettes per day (cpd), and expired carbon monoxide (CO) higher than 9 ppm. Major exclusion criteria were blood pressure (BP) higher than 160/100 mm Hg, myocardial infarction within past 4 weeks, heavy alcohol use, use of contraindicated medications, and current pregnancy or breastfeeding.[22]

Study procedures

Participants were recruited from communities near and around Madison, WI, from January 2005 to June 2007. Baseline clinical visits included measurements of anthropometric data, fasting laboratory testing, completion of validated questionnaires and interviews, and TST. Smoking burden was defined as current cigarette smoking (cpd) and pack-years (cpd × years smoked). Recent smoke exposure was determined by exhaled CO levels. Smoking status was assessed by self-reported 7-day point-prevalence abstinence and and was confirmed by an expired CO level of less than 10 ppm. Three self-reported measures of environmental smoke exposure were evaluated at baseline: whether smoking was allowed inside the home, whether the subject lives with a partner/spouse who smokes, and whether smoking was allowed in the workplace.[23] Fasting blood samples were obtained by venipuncture and refrigerated. Plasma aliquots were isolated by centrifugation and frozen at −70°C. Physical activity was assessed by the International Physical Activity Questionnaire.[24]

Exercise testing

TST was conducted using a modified Balke protocol by an exercise physiologist, under physician supervision, using standards from the American Heart Association and American College of Sports Medicine.[25-27] Patients were asked to perform symptom-limited maximal exercise. At each stage of exercise, including peak exercise and 1 minute after exercise cessation, HR, BP, and estimated work load in metabolic equivalents (METs; 1 MET = 3.5 ml O_2 uptake/kg body weight/min) were determined.[15] After achieving the maximum work load, participants performed a minimum 3-minute cool-down at walking speed. All studies were interpreted for the presence of ischemia by a single physician, and peak METs, RPP (peak HR × peak systolic BP), HR increase, HR reserve (maximum HR/[220 − age in years], expressed as a percentage), and 60-second HR recovery (maximum HR − HR at 60 seconds) were calculated.

Data analysis

Analyses were performed with SPSS software (Version 17.0, SPSS, Inc., Chicago, IL). Continuous variables were described as means (SD); categorical variables were presented as percentages. Because the cessation treatment condition was not significantly related to any TST variable or changes, it was not covaried. For the baseline analysis, Pearson and point-biserial correlations were used to identify univariate associations among TST parameters (peak exercise capacity, HR, RPP, HR increase, HR reserve, and HR recovery), smoking parameters (cpd, pack-years, CO), and participant characteristics. Separate multivariable analyses were performed to determine variables that were independently associated with each baseline exercise parameter, prior to the initiation of cessation therapy. All models included age, sex, resting HR, resting systolic and diastolic BP, diagnosis of diabetes mellitus (based on self-report or hemoglobin A_{1C} >6.5%), use of β-blockers, and use of any antihypertensive medication. Separate models were created for each smoking cessation parameter.

Next, we analyzed changes in TST parameters among participants who returned for their 3-year visit. *t* Test and χ^2 tests were used to evaluate differences in subject characteristics, TST parameters, and smoking parameters between those who returned and did not return for a 3-year visit and between abstainers and those who continued smoking. Multivariable regression analyses were used to determine variables that independently predicted changes in TST parameters. All models were adjusted for age, sex, resting HR, resting systolic and diastolic BP, use of β-blockers, body mass index, change in weight, quartile of moderate-vigorous leisure time activity, presence of a home smoking ban, and any other changes in variables that were correlated ($P < .10$) with changes in the TST parameter. HR reserve and its changes also were modeled as binary variables (≤12 vs >12 beats/min).

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Results

Subject characteristics

Subject characteristics at baseline and the 3-year follow-up visit are in Table I. At baseline, the 600 current smokers (61% women) were 43.4 (11.5) years old and smoked 20.7 (8.3) cpd with a smoking burden of 26.7 (19.0) pack-years. BPs were normal (116.3 [14.3]/70.3 [10.3] mm Hg). Exercise capacity was 8.7 (2.3) METs with a peak RPP of 25,954.9 (5,431.4) mm Hg × beats/min, HR reserve of 86.6 (9.6)%, and 60-second HR recovery of 22.7 (11.3) beats. Only 27 (4.5%) subjects had ST segment changes suggestive of ischemia. Only 26 (4.3%) subjects were taking β-blockers (12 for hypertension); 4 (0.7%) were taking rate-lowering calcium-channel blockers (3 for hypertension), and 26 (4.3%) were taking antihypertensive medications (including individuals on β- or calcium-channel blockers for hypertension). Diabetes mellitus was present in 13 (2.2%) subjects. There were no differences between the treatment arms in the distributions of any demographic, anthropomorphic, smoking, TST, or laboratory parameters evaluated.

Baseline TST parameters and their relationships with smoking parameters

Baseline correlations between smoking and TST parameters are in Table II. Exercise capacity was correlated