

Coronary artery calcium, exercise tolerance, and CHD events in asymptomatic men

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Received 27 September 2005; received in revised form 7 December 2005; accepted 14 December 2005

Available online 24 January 2006

Abstract

Coronary artery calcium (CAC) scores ≥ 100 are predictive of CHD events in asymptomatic men. Exercise tolerance of ≥ 10 METs predicts lower event rates in CHD patients; however, its relationship with events in individuals with subclinical atherosclerosis is less known. Participants were 710 asymptomatic men from the Aerobics Center Longitudinal Study whose exercise tolerance (ET) was quantified (< 10 or ≥ 10 METs) and whose CAC score was ≥ 100 as measured by electron beam tomography. During 3.5 years of follow-up 59 CHD events occurred. The age-adjusted hazard ratio (HR) of CHD events was 0.26 (95% CI=0.15–0.45) in men whose ET was ≥ 10 METs compared with men whose ET was < 10 METs. Adjustment for CHD risk factors and abnormal exercise ECG did not change the association between ET and CHD. The extent of underlying atherosclerosis did not influence the association between ET and CHD; for example, the HR for CHD events in the ≥ 10 MET group among men with CAC scores < 400 and ≥ 400 was 0.16 (95% CI=0.05–0.56) and 0.23 (95% CI=0.11–0.46), respectively. In asymptomatic men with subclinical coronary atherosclerosis, an ET of ≥ 10 METs identifies patients at lower risk for manifest CHD.

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Keywords: Coronary heart disease; Coronary calcium; Electron beam tomography; Exercise testing; Primary prevention; Cardiovascular fitness

1. Introduction

Coronary artery calcium (CAC), measured by electron beam tomography (EBT), is directly associated with the number and severity of diseased vessels and is recognized as a noninvasive measure of subclinical coronary atherosclerosis [1]. CAC scores predict CHD events in asymptomatic individuals [2–5], although a consensus on clinically relevant levels of CAC is lacking [1]. Extant data [2,3] suggest that a sharp increase in CHD event rates occurs at a CAC score of ~ 100 . In our study [5], the relative risk of

coronary death and nonfatal myocardial infarction (MI) is 3.9 ($P < 0.05$) and 19.1 ($P < 0.0001$) in men whose CAC score was 1–99 and ≥ 100 , respectively, compared to men with no detectable CAC. These data and other published observations suggest that a CAC score of 100 may define a clinically relevant level of subclinical disease and identify individuals who should receive intensive primary prevention therapy.

Higher levels of exercise tolerance are associated with lower risk of CHD events in individuals with established disease, independent of traditional risk factors [6–13]. In patients with clinical manifestations of CHD, an exercise tolerance of ~ 10 metabolic equivalents (METs, 1 MET = resting metabolic rate = 3.5 mL O₂ uptake \cdot kg⁻¹ \cdot min⁻¹) is associated with significantly lower CHD morbidity and mortality than

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is observed in individuals with lower exercise tolerance, irrespective of the underlying extent of CHD or ischemic sequelae [10–13].

Recent cross-sectional studies in symptomatic individuals referred for cardiac assessment indicate that EBT-derived CAC scores combined with either ischemic exercise ECG responses or myocardial perfusion defects may provide superior diagnostic accuracy for identifying significant obstructive coronary artery disease than the CAC scores or exercise test responses alone [14–16]. The focus of these studies was on the diagnostic rather than the prognostic use of EBT and exercise test responses. It is not known whether quantifying exercise tolerance provides prognostic value for CHD risk prediction in asymptomatic individuals with evidence of subclinical atherosclerotic coronary disease. Therefore, the current study was undertaken to test the hypothesis that higher exercise tolerance would be associated with a lower incidence of CHD events in asymptomatic individuals with significant subclinical coronary atherosclerosis based on the presence of CAC scores ≥ 100 .

2. Methods

Participants were 710 men in the Aerobics Center Longitudinal Study who were asymptomatic, free of known CHD, and had an EBT-derived CAC score ≥ 100 . EBT scans were completed at the Cooper Clinic, Dallas, TX, during the period 1995–2001 as part of a comprehensive preventive medical examination (~50%), or on the basis of physician (~30%) or self-referral (~20%). The study methods have been described in detail elsewhere [5,6,17]. Body mass index (BMI, kg/m^2) was computed from measured height and weight. Resting blood pressure was determined with standard auscultation methods. Blood lipids and glucose were measured following a 12-h fast using standardized bioassays. Prevalent hypertension, diabetes, and dyslipidemia were determined by clinical definitions for blood pressure ($\geq 140/\geq 90$ mmHg), glucose (≥ 126 mg/dL), and abnormal lipids (total cholesterol ≥ 240 mg/dL or triglyceride ≥ 200 mg/dL, or HDL < 40 mg/dL), respectively. A self-reported history of physician diagnosis of these conditions also was used to identify the presence of each risk factor. Based on medical record review, a sensitivity and specificity of 98% and 99%, respectively, has previously been shown for the self-reported history of chronic disease in the overall population from which the participants in the current study were drawn [18]. Current smoking status (yes/no) was self-reported as any cigarette smoking at the time of baseline examination. MET levels of exercise tolerance (< 10 or ≥ 10 METs) were estimated from the final speed and grade [19] of a maximal treadmill exercise test using a modified Balke protocol [6]. Patients began walking at 3.3 mph (88 m/min) with no elevation. The incline was increased to 2% after the first minute, and was increased 1% each minute thereafter until the 25th minute. For participants who were still able to exercise beyond 25 min, the

elevation was maintained at 25%, and the speed was increased by 0.2 mph (5.4 m/min) each minute until volitional exhaustion. A 12-lead electrocardiogram and blood pressure was monitored throughout the test and recovery period. Participants were verbally encouraged to achieve a maximal effort. We used a 10-MET exercise tolerance cut-point because this value has been shown to discriminate degrees of prognosis in men with clinically manifest CHD [7,10,11,13], it approximates the median level of exercise tolerance in the study sample, and because it resulted in an adequate distribution of events in the exposed and unexposed groups for analysis. Using an Imatron EBT scanner (GE Imatron, San Francisco, CA), 3-mm thick slices were obtained with 2-mm table (3×2) increments that were synchronized to end-diastole in the cardiac cycle during a breath-holding protocol. The CAC score was calculated according to the Agatston method [17,20]. CHD events were defined as coronary death, nonfatal MI, and coronary revascularization (PCI, CABG). Deaths were identified using the National Death Index; CHD mortality was defined using the International Classification of Diseases, 9th edition revised, codes 410.0–414.0. Nonfatal MI and revascularization history were ascertained from a mail-back questionnaire to which a 70% response rate was obtained. Respondents and nonrespondents were similar on baseline CHD risk factors and CAC scores. In the larger study from which the current sample is drawn, 99 of the CHD events have been adjudicated using medical record review by investigators blinded to the EBT results. A total of 95% of events were verified as reported. Of the misreported events, three were cardiac catheterizations without revascularization and two were peripheral revascularization procedures. Of the adjudicated events, all of the CHD deaths and MIs were confirmed.

The distribution of CAC scores was skewed; therefore, log transformed scores were used for analyses. Student's *t*-tests and the Wilcoxon test were used to compare continuous variables [21]. Chi-square tests were used to compare categorical variables [21]. Person-years of exposure were calculated from the date of EBT scanning to the date of death, the date of an event reported on the mail-back survey, or December 31, 2001. Incidence rates were computed as the number of cases divided by person-years of exposure. Cox proportional hazards regression [22] was used to quantify the strength of association between exercise tolerance and CHD events. Hazard ratios (HR) and 95% confidence intervals (CI) were computed for CHD events according to CAC scores and exercise tolerance. Likelihood ratio tests [21] were used to determine whether exercise tolerance added to CHD risk prediction beyond CAC scores. The Likelihood ratio test compares the likelihood of an observed outcome from a simpler model (e.g., CAC alone) with that from a more complex model (e.g., CAC plus exercise tolerance), and it is based on a chi-square distribution with degrees of freedom equal to the number of additional parameters in the complex model. *P*-values are two-sided with statistical significance set at $P < 0.05$.

Table 1
Baseline characteristics by event status at follow-up (mean \pm S.D.)

Characteristic	CHD	No CHD
N	59	651
Age (year)	58.9 \pm 8.8	58.3 \pm 8.4
BMI (kg/m ²)	28.0 \pm 4.3	26.7 \pm 3.5
Maximal METs	9.5 \pm 2.3*	10.9 \pm 2.2
CAC scores (median)	708*	306
Dyslipidemia (%)	72.9*	58.8
Hypertension (%)	61.0	48.4
Diabetes (%)	10.2	6.9
Current smoker (%)	15.3	10.6

BMI, body mass index; CAC, coronary artery calcium.

* $P < 0.05$.

3. Results

During a mean \pm S.D. follow-up of 3.5 \pm 1.4 years and 2280 person-years of exposure, 59 CHD-related events occurred (1 CHD death, 11 nonfatal MIs, and 47 revascularizations). Men who developed manifest CHD had a higher prevalence of CHD risk factors and a lower exercise tolerance at baseline than men who remained event free (Table 1). Baseline CAC scores were higher ($P < 0.001$) in CHD cases than among event-free men. Sixty-two percent of study participants had an exercise tolerance of ≥ 10 METs (Table 2). Men in both groups were similar in age and smoking status, but the prevalence of the other CHD risk factors was significantly higher in men in the <10 -MET group compared with ≥ 10 -MET group. Median CAC scores were higher though not significantly different in the <10 -MET group (CAC = 396) compared with the ≥ 10 -MET group (CAC = 298, $p = 0.21$).

We used Cox regression to compute multivariable adjusted point and interval estimates of association for CAC and exercise tolerance with CHD events (Table 3). After adjusting for age, each 100-unit increase in CAC was, on average, associated with a 3.1% (95% CI = 1.3–5.2%) higher risk of CHD events. CAC remained a significant predictor of CHD events after including CHD risk factors and maximal METs in the regression model. Likewise, exercise tolerance was significantly associated with the incidence of CHD

Table 2
Baseline characteristics by exercise tolerance (mean \pm S.D.)

Characteristic	<10 METs	≥ 10 METs
N	265	445
Age (year)	57.7 \pm 8.8	58.7 \pm 8.1
BMI (kg/m ²)	28.8 \pm 4.3*	26.3 \pm 2.9
Maximal METs	8.5 \pm 1.4*	12.2 \pm 1.6
CAC scores (median)	396.3	298.6
Dyslipidemia (%)	70.5*	53.7
Hypertension (%)	58.9*	43.8
Diabetes (%)	13.9*	4.9
Current smoker (%)	14.7*	6.9

BMI, body mass index; CAC, coronary artery calcium.

* $P < 0.05$.

events. After adjusting for age, each 1-MET increment in exercise tolerance was, on average, associated with a 31% (95% CI = 39–22%) lower risk of CHD events. Additional adjustment for CHD risk factors and CAC scores had little influence on the inverse association between exercise tolerance and CHD risk. In regression models that included age and CHD risk factors, maximal METs added significantly to CHD event prediction based on CAC scores alone (Likelihood ratio_{d.f.=1} = 27.9, $P < 0.001$).

We next examined the association between CHD risk and a clinically relevant definition of exercise tolerance (<10 METs versus ≥ 10 METs). The age-adjusted event rate was lower ($P < 0.001$) in men whose exercise tolerance was ≥ 10 METs (14.1 per 1000 person-years) compared to that in men whose exercise tolerance was <10 METs (48.2 per 1000 person-years). The age-adjusted risk of CHD events was 74% lower (95% CI = 55–85%, $P < 0.001$) for men in the ≥ 10 -MET group compared to that in men in the <10 -MET group (Table 4). As was seen in the analysis of METs as a continuous variable, adjustment for CHD risk factors and CAC scores had little effect on the strength of association between exercise tolerance and CHD events. In a subset of men for whom exercise ECG data was available for analysis ($n = 635$; 54 CHD cases), the presence of an abnormal ECG response also did not materially change the multivariable association between exercise tolerance and CHD risk (RR = 0.36, 95% CI = 0.19–0.67). The influence of BMI was examined in 565 men (48 CHD cases) and similarly did not weaken the association between exercise tolerance and CHD events (HR = 0.25, 95% CI = 0.13–0.50).

To determine whether the amount of detectable CAC, and thus the severity of subclinical atherosclerotic coronary disease, influences the association between exercise tolerance and CHD events, an additional analysis was performed using a CAC cut-point of 400 [1,23]. The severity of the underlying atherosclerosis did not alter the significant protective association between exercise tolerance and CHD events. In men with a CAC < 400 (15 events) the HR for CHD events in the ≥ 10 -MET group was 0.16 (95% CI = 0.05–0.56) and 0.23 (95% CI = 0.11–0.46) in men with CAC ≥ 400 (44 events).

Table 3
Risk of CHD events for coronary artery calcium scores and for maximal MET levels of exercise tolerance

	HR ^a	95% CI	P-value
CAC (per 100 units)	1.03	1.01–1.05	<0.001
Adjusted for CHD risk factors	1.04	1.02–1.06	<0.001
Adjusted for above and maximal METs	1.02	1.01–1.05	0.01
Maximal METs (per 1 MET)	0.69	0.61–0.78	<0.001
Adjusted for CHD risk factors	0.69	0.61–0.79	<0.001
Adjusted for above and CAC	0.70	0.61–0.80	<0.001

HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease; MET, metabolic equivalent (1 MET = 3.5 mL O₂ uptake·kg⁻¹·min⁻¹); CAC, coronary artery calcium score. CHD risk factors were smoking, hypertension, dyslipidemia, and diabetes.

^a All models are adjusted for age.

Table 4
Risk of CHD events by exercise tolerance

Exercise tolerance	N (events)	Person-years	HR ^a (95% CI)	HR ^b (95% CI)	HR ^c (95% CI)
<10 METs	265 (38)	787	1.0 referent	1.0 referent	1.0 referent
≥10 METs	445 (21)	1490	0.26 (0.15–0.45)	0.30 (0.17–0.53)	0.27 (0.15–0.50)

HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease; MET, metabolic equivalent (1 MET = 3.5 mL O₂ uptake kg⁻¹ min⁻¹); CAC, coronary artery calcium score.

^a Adjusted for age.

^b Adjusted for age, smoking, dyslipidemia, diabetes, and hypertension.

^c Adjusted for covariables above and CAC scores.

4. Discussion

These prospective data indicate that in asymptomatic men with subclinical coronary atherosclerosis, CAC scores and maximal exercise tolerance are both significant independent predictors of CHD events after adjustment for age and conventional CHD risk factors. Furthermore, maximal MET levels of exercise tolerance add significant prognostic information to CAC scores, and an exercise tolerance ≥10 METs is associated with lower risk for CHD-related events, independent of CHD risk factors, abnormal exercise ECG responses, and CAC scores. The cardioprotection associated with a ≥10-MET exercise tolerance was also observed among study participants who had evidence of greater subclinical atherosclerosis (CAC scores ≥400).

Observational data from our study [5] and others [2–4] suggest that CAC scores, particularly CAC ≥100, can be used to identify asymptomatic adults at risk for future CHD events. The findings reported herein indicate that even in men with CAC scores ≥100, incremental CAC scores were associated with significant increased risk of incident CHD events after accounting for conventional CHD risk factors and exercise tolerance. Cross-sectional studies have suggested that exercise test responses combined with EBT-derived CAC scores may enhance the identification of significant obstructive coronary artery disease in symptomatic individuals referred for cardiovascular assessment [14–16]. Our prospective findings suggested that in asymptomatic men with evidence of subclinical atherosclerosis, maximal exercise tolerance added significantly to the prediction of CHD events based on CAC scores and conventional CHD risk factors. To our knowledge this is the first epidemiological study to demonstrate that maximal exercise tolerance adds prognostic value to CAC scores in identifying asymptomatic men at risk for incident CHD events.

Exercise tolerance is among the most powerful predictors of CHD events in patients with coronary artery disease [7–13]. The finding that a ≥10-MET exercise tolerance is associated with a lower rate of CHD-related events in men with documented subclinical atherosclerosis is similar to observations in individuals with clinically manifest coronary disease [7,10–13]. For example, in coronary patients with abnormal echocardiograms, McCully et al. [13] reported a 90% 5-year event-free survival rate among coronary patients

with a ≥10-MET exercise tolerance. Even in patients with highly ischemic exercise electrocardiograms, Thompson et al. [12] observed an 86% lower likelihood of death or MI in patients with a ≥10-MET exercise tolerance compared to those who exercised <7 METs. In men with multivessel CHD and low left ventricular ejection fraction, De Feyter et al. [10] showed that a ≥10-MET exercise tolerance was associated with no cardiac deaths and a 2% recurrent MI rate compared to rates of 9% and 9%, respectively, in patients whose exercise tolerance was <10 METs. Finally, Weiner et al. [11] reported that surgical intervention did not provide additional survival benefit over medical therapy in patients with an exercise tolerance of ≥10 METs, but greatly improved survival in patients whose exercise tolerance was <5 METs. It is clear from the available data that a ≥10-MET exercise tolerance identifies individuals with a greatly improved prognosis in a secondary prevention setting.

The present study extends these previous findings to asymptomatic men at high risk for coronary events based on elevated CAC by demonstrating an improved prognosis associated with a ≥10-MET exercise tolerance. The overall event rate in this cohort of men with CAC scores ≥100 was 2.3% per year, which suggests a relatively high CHD risk status by conventional standards [24]. Men with an exercise tolerance ≥10-METs had an annualized event rate of 1.3%, consistent with low to intermediate CHD risk; whereas the event rate was 4.1% per year in men with a <10-MET exercise tolerance, consistent with a high CHD risk status [24]. Our observations suggest that in individuals with subclinical coronary atherosclerosis, based on the presence of CAC, promoting higher exercise tolerance may reduce the future risk of experiencing a CHD-related event.

Strengths of this study are use of CAC scores derived from standardized EBT methodology, assessment of exercise tolerance by maximal exercise testing, measured clinical risk factors, and >2000 person-years of exposure in a sample of men free of baseline CHD. The current findings were derived from men who are Caucasian, educated, and of middle-to-upper socioeconomic status. Although this may lower generalizability, the homogeneity of demographic factors may enhance internal validity by reducing potential confounding by these characteristics. Additional limitations include insufficient data on medication usage and the presence of incomplete data on exercise ECG responses and BMI.

The relatively short follow-up period resulted in only one coronary death. Thus, the reported data largely reflect the association of exercise tolerance with the incidence of non-fatal MI and revascularizations. While these outcomes were obtained from self-reported questionnaire data, the method of ascertaining nonfatal endpoints in the current study is similar to that used in other large studies of CAC and CHD [2–4]. Nevertheless, these limitations require that caution be used when interpreting and generalizing the observations reported here.

The fact that higher exercise tolerance was associated with fewer first MIs or cardiac revascularizations in the presence of significant subclinical coronary artery disease has important clinical implications. Higher exercise tolerance in the presence of a significant atherosclerotic burden likely reflects better endothelial function and coronary vasomotor reserve [25,26], and thus a relatively lesser degree of static and dynamic coronary obstruction. Therefore, cardiac function, as reflected by the results of symptom-limited maximal exercise tolerance tests, appears to be an important prognostic indicator to consider along with the anatomical distribution of coronary atherosclerosis determined by EBT-derived CAC scores, whether high or low. Additional studies are needed to describe this relationship in women.

Since all men in this study had elevated CAC scores, the higher number of revascularizations cannot be simply referral bias stimulated by the CAC measurement itself. It is also unlikely that the revascularizations were a result of findings during the baseline exercise tolerance test. The median time to revascularization was 1.5 years among all men, 11 months among men in the <10-MET group (31 revascularizations), and 1.9 years among men in the ≥ 10 -MET group (16 revascularizations). Only 8% of all revascularizations occurred within 2 months of the baseline exam. It is improbable that men with significant evidence of high-grade obstructive coronary artery disease based on the baseline exercise stress test alone or with confirmation by nuclear imaging would have waited a year or more for invasive intervention.

Higher exercise tolerance may also be associated with lower levels of vascular inflammation, a marker of disease activity that identifies a prothrombotic milieu [27]. An inverse association between exercise tolerance and C-reactive protein, a marker of subclinical inflammation, has previously been reported in a sample of asymptomatic men from the overall study population from which the current sample was drawn [28]. It is plausible that even in the presence of significant subclinical atherosclerosis, higher levels of cardiovascular fitness attenuate CHD risk by promoting a less vulnerable environment around existing coronary lesions.

The small number of events precluded the use of expanded MET categories to examine the dose–response characteristics between exercise tolerance and CHD events. Use of a 10-MET exercise tolerance cut-point may lead to the question of whether individuals with underlying atherosclerotic coronary disease can achieve this level of conditioning. More than 50% of our population sample of men with CAC scores ≥ 100 had

an exercise tolerance of ≥ 10 METs at baseline. In another study approximately 40% of men who were on average 60 years old and had clinically diagnosed cardiovascular disease were reported to have close to and above 10-MET exercise tolerance [7]. Clinical exercise training studies [29,30] and randomized controlled trials [31,32] have shown that men with established coronary artery disease can improve their baseline level of exercise tolerance to ≥ 10 METs in response to the prescribed exercise intervention. The exercise training characteristics used in these studies have generally been in accord with current recommendations on the type and dose of physical activity for primary and secondary CHD prevention [19,33].

We conclude that in asymptomatic men with subclinical coronary atherosclerosis maximal exercise tolerance may add additional prognostic information to EBT-derived CAC scores for the identification of individuals at high risk of manifesting clinical CHD events. An exercise tolerance level of ≥ 10 METs identifies patients who are at lower risk for developing clinical manifestations of CHD across a range of CAC scores ≥ 100 . This level of cardiovascular fitness is achievable through regular, moderate-intensity aerobic physical activity [34] and may be a reasonable goal in exercise programs recommended for prevention of manifest CHD [33] in individuals with CAC scores ≥ 100 .

Acknowledgments

This study is supported by NIH grants AG06945 and HL62508, and by the Communities Foundation of Texas, on recommendation of Nancy Ann and Ray L. Hunt. We thank Dr. Kenneth Cooper for establishing the Aerobics Center Longitudinal Study, the Cooper Clinic physicians and technicians for collecting the baseline data, and Melba Morrow, M.A., for editorial assistance.

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