Exercise Tolerance in Asymptomatic Elderly Men With Fluoroscopically Detected Coronary Artery Calcification*

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Study objective: The value of detecting coronary artery calcification (CAC), by cardiac imaging, for the diagnosis of coronary artery disease (CAD) in asymptomatic middle-aged men has been demonstrated. However, the incidence of CAC increases with age. The functional significance of CAC remains unknown in asymptomatic elderly men. The purpose of this study is to explore whether CAC in asymptomatic aging men signifies the presence of cardiovascular dysfunction during exercise.

Design: This study was designed to address whether elderly asymptomatic men, selected because they have CAC, have reduced exercise tolerance due to functionally significant CAD.

Participants and setting: Thirty-eight asymptomatic male volunteers (ages 50 to 75 years, mean [± SD] 64 ± 7 years) with a normal resting ECG and at least one coronary risk factor, in a population study. Nineteen subjects had CAC detected by digital subtraction fluoroscopy in at least two major coronary arteries, and 19 subjects had no identifiable CAC.

Methods and results: Each subject underwent a symptom-limited incremental exercise test with 12-lead ECG monitoring and respiratory gas analysis. Four indexes of exercise oxygen transport were evaluated: peak oxygen uptake (Vo2), lactic acidosis threshold, peak Vo2/heart rate ratio, and Vo2 relative to a work rate increase. Eleven of 38 subjects (28%) were found to have reduced oxygen transport, which was defined as an abnormal reduction in more than two of the above four indexes of oxygen transport. Five of the 11 subjects with reduced oxygen transport had CAD, and 6 subjects did not (not significant). Only one subject with CAC had exercise ST depression.

Conclusion: Significant CAC in asymptomatic men over age 50 does not signify exercise limitation due to CAD.

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Key words: coronary artery disease; lactic acidosis threshold; oxygen pulse; peak oxygen uptake

Abbreviations: ATP = adenosine triphosphate; CAC = coronary artery calcification; CAD = coronary artery disease; HR = heart rate; LAT = lactic acidosis threshold; VCO2 = carbon dioxide output; VO2 = oxygen uptake; WR = work rate

Coronary artery disease (CAD) is the primary cause of mortality in the United States.1 More than one half of acute myocardial infarctions and sudden cardiac deaths occur in persons with previously unidentified CAD.2 Therefore, early diagnosis and treatment, including the modification of risk factors, is an essential element in reducing mortality and/or morbidity from CAD. A reliable noninvasive method for early detection of CAD is needed to identify subjects who are at the greatest risk so that they may be entered into a risk-modification program or may be treated.

The presence of coronary artery calcification (CAC) indicates the presence of the disease process of coronary atherosclerosis.3,4 A strong relationship has been demonstrated between CAC, as detected by radiologic techniques of cardiac imaging, and the presence of significant angiographic coronary artery narrowing.5-9 particularly in asymptomatic middle-aged men.10-12 However, the significant increase in the incidence of CAC with age4,13 may reduce the

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positive predictive value in an aging population. No study has addressed the question of whether asymptomatic aging men with CAC have an increased risk of functionally significant CAD. Therefore, this study was designed to explore whether cardiovascular dysfunction during exercise due to CAD is present in asymptomatic late middle-aged and elderly men with CAC.

Materials and Methods

Subject Recruitment

Thirty-eight male subjects over 50 years of age who were enrolled in the South Bay Heart Watch Program, which is a prospective, population-based cohort study conducted in the suburbs of Los Angeles, agreed to participate in this study. The South Bay Heart Watch Program population consists of asymptomatic adult volunteers who are over 45 years of age, who have at least one coronary risk factor, who have at least 6% risk of coronary heart disease events during a 6-year period, who have no history of exertional angina or myocardial infarction, and who do not have diagnostic Q waves, as defined by the Minnesota criteria.

The 38 subjects were chosen consecutively by a coordinator in this study, with the provision that they have either no calcification or calcification in at least two vessels. By design, the subjects were 50 to 75 years old (mean ± SD 64 ± 7 years); 19 subjects had definite calcific deposits in at least two major coronary arteries, and 19 subjects had no identifiable coronary calcification on their fluoroscopic studies. The two groups differed only on the basis of CAC. The investigators were blinded to which patients had CAC and which did not. All subjects agreed to participate in the study after its nature, purpose, and risks were explained. Once enrolled by the study coordinator, the subjects remained in the study, and no subject’s data were excluded from the analysis. Written informed consent was obtained from each subject. The protocol and procedures were reviewed and approved by the institution’s Human Subjects Committee.

CAC Detection

All subjects had undergone digital subtraction cardiac fluoroscopy to detect CAC on entry to the study. Digital subtraction fluoroscopy was done in the 60° left anterior oblique projection while the patient held his breath for between 2 and 5 s. Fluoroscopic images were digitized, on-line, and were processed with a digital cardiac imaging unit (Philips Medical Systems; Shelton, CT). Exposure factors included a pulse width of 16 ms, a peak of 50 to 80 kV, and a milliamperage of 50 to 90 mA for the x-ray tube current. The pixel matrix format was 512 × 512. A mask image was acquired over 5 frames and was obtained immediately before a run of between 15 and 20 frames at 15 frames/s. Immediately after the acquisition of each frame of the image, the digital cardiac imaging unit subtracted the blurred mask image and stored the resulting subtracted image on digital disk. A cardiologist blinded to clinical and exercise data visually interpreted the fluoroscopic studies and identified the presence of calcification in the major epicardial arteries. Two independent observers reviewed the subtraction images and evaluated them using a semiquantitative visual score from 0 (no calcific deposit in the arteries) to 3 (definitely containing calcific deposit throughout most of the proximal 2 cm of the arteries). A score of at least 2 (definitely containing calcific deposits) defined CAC. Any calcification in the distribution of any coronary artery defined an abnormal study. This method had been shown to have good interstudy reliability and interobserver reproducibility. The prevalence of calcific deposits in at least one major coronary artery was 62.0% in this study population of subjects over the age of 50 years. In order to more sensitively detect associations between abnormal fluoroscopic results and abnormal exercise results, 19 subjects who had at least two calcified arteries were selected for the experimental group and 19 matched subjects without evidence of coronary calcification were selected for the control group.

Exercise Protocol

Each subject performed a progressively increasing work rate (WR) exercise test in the seated position on a calibrated, electronically braked cycle ergometer (Godart; Groningen, The Netherlands) in an air-conditioned laboratory at least 2 h after a light lunch. After 3 min of unloaded pedaling at 60 rpm, the WR was increased linearly (ramp pattern) by 15 or 20 W/min. The WR increment was chosen based on the examiner’s estimate of the subject’s work capacity as determined from data on age, height, and history of physical activity. The WR increment size was designed so that the incremental period of the test would last 8 to 12 min. The test was terminated if the subject was unable to maintain a pedaling frequency above 45 rpm, if the subject reached the age-predicted peak heart rate (HR; 220 minus the age of an individual subject), or if the physician detected evidence of deteriorating cardiovascular function such as significant ST segment depression or frequent premature beats.

Measurements

Subjects breathed room air through a mouthpiece, while carbon dioxide and oxygen concentrations at the mouthpiece were measured continuously with a mass spectrometer and while inspired and expired gas flow were measured continuously by a linearized turbine flowmeter. After the consideration of transport delay and mass spectrometer response time, the calculation of oxygen uptake (VO2) on a breath-by-breath basis was performed as previously described. Subsequently, 10-s averaging was performed off-line. The 12-lead ECG was continuously monitored (ELI-XR; Mortara Instruments; Milwaukee, WI) and was recorded every minute at a paper speed of 25 mm/s. The ST segment trend of each lead was obtained after the study. HR was also continuously monitored using a CC5 lead configuration. Brachial arterial BP was measured every minute by auscultation using a sphygmomanometer during rest, exercise, and recovery. All parameters were monitored for at least 10 min of recovery.

Parameters of Cardiovascular Function

We calculated the following four parameters from the exercise test to evaluate the capacity of the cardiovascular system to transport oxygen to the exercising muscles: (1) peak VO2 (20-21); (2) lactic acidosis threshold (LAT) (20-21); (3) peak VO2/HR (peak oxygen pulse, which is equal to stroke volume × arteriovenous oxygen difference at peak VO2) (22); and (4) rate of aerobic regeneration of adenosine triphosphate (ATP) as related to increasing WR above the LAT (ΔVO2/ΔWR) (23,24).

1. Peak VO2 was defined as the VO2 attained during the 20-s period just before the exercise was terminated. This parameter is reduced when the cardiac output has not increased to a normal maximal level that was secondary to impaired cardiac function, other organ dysfunction, anemia, or lack of subject motivation.
2. The VO₂ at the LAT was determined by the V-slope method, as described by Beaver et al. In this method, carbon dioxide output (VCO₂) is plotted as a function of VO₂ with equal scaling of VO₂ and VCO₂. The LAT is identified as the VO₂ at which the VCO₂ starts to increase faster than VO₂ (the slope becomes steeper than 1). This parameter will be reduced if the capillary PO₂ falls to its lowest (critical) value in the exercising muscle capillary bed at an inordinately low WR.

3. Peak VO₂/HR (oxygen pulse) was calculated from VO₂ divided by HR at the peak of exercise. VO₂/HR at maximal exercise equals the maximal stroke volume × the arteriovenous oxygen difference. Therefore, VO₂/HR at maximal exercise will be reduced if either of these factors are reduced. Because the arteriovenous oxygen difference reaches the same maximum in normal subjects and in patients with heart disease, a reduction in peak oxygen pulse generally signifies that the stroke volume is reduced if the patient is not significantly anemic.

4. Aerobic regeneration of ATP to perform physical work (ΔVO₂/ΔWR) above the LAT was calculated by least squares linear regression from the VO₂ data between 60 s after the LAT had been reached to 20 s before the end of the increasing WR period of the exercise test. The first 60 s and the last 20 s of the response were excluded from the calculation for the reasons described by Hansen et al. A reduction in ΔVO₂/ΔWR above the LAT signifies the failure of cardiovascular transport of oxygen to the exercising muscle or the inability of the muscle to consume oxygen to maintain the aerobic regeneration of ATP.

Criteria of Abnormal Response

Three experienced observers, blinded to the CAC data, used the following criteria in the assessment of the exercise tests: Positive ST depression was defined as horizontal or downsloping ST segment depression ≥ 0.1 mV at 80 ms after the J point in at least one ECG lead and lasting for > 30 s of the exercise. An abnormal peak VO₂ response was defined as < 83% of the predicted value for the particular age, gender, and size; an abnormal LAT was defined as any value for LAT less than the lower 95% confidence limits for age, gender, and size of the predicted normal values; an abnormal ΔVO₂/ΔWR ratio was defined as < 0.5 mL/W.

The number of abnormal parameter(s) detected from among the four indexes defined earlier yielded an exercise score of from 0 to 4. Exercise performance was considered to be impaired if the exercise score was more than 2.

Statistical Analysis

The unpaired t test was used for intergroup comparison. The χ² test for independence was used for the relationship between...
CAC and impaired exercise tolerance, and the χ² test for goodness of fit was used for comparison of the prevalence of abnormal values in four exercise parameters. Significance for the test was regarded to be p < 0.05.

**RESULTS**

Nineteen of the 38 subjects had CAC, and the other 19 subjects did not, as described by the study design. There were no significant differences in age and in the number of coronary risk factors between the two groups, as shown in Table 1.

Twenty-seven subjects stopped exercising due to leg fatigue or to shortness of breath. One subject (with diabetes but without CAC) stopped exercising because of calf pain with physical evidence of obstructive peripheral artery disease, and one subject (with CAC) stopped exercising because of knee pain (Table 1). Seven subjects reached their predicted maximal HR and, thus, had their exercising stopped by the investigators. One subject with CAC was asked to stop exercising because of frequent ventricular premature beats, and another subject without CAC was stopped because of paroxysmal supraventricular tachycardia.

No subject had chest pain or an abnormal BP response during the test period. Only one subject with CAC had exercise-induced ST segment depression, and that subject stopped exercising due to leg fatigue without chest pain.

The average values, given as percentages of the predicted values for the cardiorespiratory parameters of the two groups combined (38 subjects total), were 84% for peak VO₂, 94% for HR, 90% for peak VO₂/HR, and 91% for LAT. The absolute values (±SD) for each group are given in Table 1.

Figure 1 and Table 1 show comparisons of peak VO₂, LAT, peak VO₂/HR (oxygen pulse), and ΔVO₂/ΔWR for the 19 subjects with CAC and for the 19 subjects without CAC. There were no significant differences between the two groups in any parameters. The values of the peak double product (an indirect measure of myocardial oxygen demand) vs the peak VO₂ overlapped in the two groups, as shown in Figure 2. The relationship between exercise score and CAC is shown in Table 2. Exercise performance was impaired in 6 of 19 subjects with CAC and in 5 of 19 subjects without CAC. Thus, there was no significant difference in the prevalence of impaired exercise tolerance.
between subjects with CAC in at least two vessels and subjects without CAC.

Figure 3 shows the relationship between exercise score and age for subjects with and without CAC. There was no age-related trend in exercise score or in prevalence of CAC.

Eighteen of 38 subjects (47%) in this study had abnormal values for peak \( \text{VO}_2 \), 16 of 38 subjects (42%) had abnormal values for LAT, 12 of 38 subjects (32%) had abnormal values for peak \( \text{VO}_2/\text{HR} \), and 11 of 38 subjects (29%) had abnormal values for \( \Delta \text{VO}_2/\Delta \text{WR} \). Figure 4 shows which parameters contributed to the abnormal exercise score. There was no significant difference in the prevalence of abnormal values for each parameter between subjects with CAC in at least two vessels and subjects without CAC (Figs 1 and 4), except that only a reduced peak \( \text{VO}_2 \) or reduced LAT accounted for an abnormality with exercise score 1.

**DISCUSSION**

In contrast to what we expected to find, CAC, as detected by digital subtraction fluoroscopy, did not identify those subjects with impaired exercise tolerance due to CAD in asymptomatic men 50 years of age and older. The deposition of calcium in coronary arteries is an indicator of the age of the atheroma. CAC detected by radiologic techniques can predict significant CAD in asymptomatic middle-aged men. It has been demonstrated in a necropsy

**Table 2—Incidence of Reduced Exercise Performance in Subjects With and Without CAC**

<table>
<thead>
<tr>
<th>Exercise score</th>
<th>CAC (+)*</th>
<th>CAC (-)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 2 )</td>
<td>13</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>( &gt; 2 )</td>
<td>6</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>19</td>
<td>38</td>
</tr>
</tbody>
</table>

*CAC (+) = subjects with CAC; CAC (-) = subjects without CAC.

**Figure 2.** Peak double product (DP), calculated as beats per minute (bpm) \( \times \) systolic BP (mm Hg), as a function of peak \( \text{VO}_2 \) for subjects with CAC in at least two vessels (●) and subjects without (○) CAC.

**Figure 3.** Exercise score as related to age for subjects with CAC in at least two vessels (●) and subjects without (○) CAC. The exercise score is the number of measured parameters of aerobic function that was found to be abnormal for each subject.

**Figure 4.** Number of subjects with abnormal parameters of aerobic function for each exercise score for subjects with CAC in at least two vessels (below diagonal) and subjects without CAC (above diagonal). Row "N" shows the number of subjects in whom the indicated parameter was normal for each group.
study that the greater the degree of calcification, the more likely is the presence of significant coronary artery obstruction, while the relationship between the extent of CAC and the severity of stenotic lesion is nonlinear with large confidence limits. Thus, it would be reasonable to expect a higher incidence of significant CAD in subjects with CAC, even if the subjects are elderly.

However, the prevalence of CAC increases with age and reaches about 50 to 90% in the seventh and eighth decades, suggesting that CAC may occur as a result of aging and not necessarily to significant CAD. The predictive accuracy of CAC for functionally significant CAD in asymptomatic elderly populations is unknown. If clinical manifestations occur in only a small fraction of subjects with CAC, calcification would be considered a “benign” association of aging. Thus, it is important to test the functional significance of CAC as related to age.

In this study, coronary arteriography was not performed because subjects were enrolled from an asymptomatic population of 50- to 75-year-old men. Thus, we did not know the coronary artery anatomy and the extent to which the atheroma encroached on the lumen of the blood vessel. However, we did evaluate the functional capacity of the cardiovascular system with gas exchange techniques and electrocardiography during all levels of a subject’s exercise capacity. Exercise-induced ischemia due to CAD would produce an ST segment depression of the ECG and a left ventricular mechanical dysfunction, which would result in a reduction of exercise capacity and in abnormalities of gas exchange variables even though resting cardiac function is normal.

Recently, the gas exchange response to exercise has been applied widely for a measurement of the functional capacity of the cardiovascular system. Cardiovascular dysfunction should be reflected in an imbalance in the supply and demand of oxygen under exercise stress, because the cardiovascular system has a central role in supporting cellular respiration. In a normal subject during a 6- to 12-min incremental exercise test, the anaerobic component is likely to be a small portion of the total energy need. In contrast, in patients with cardiovascular disease with impairment in oxygen delivery, the anaerobic component is likely to be a larger portion of the total energy requirement as symptom-limited maximal exercise is approached. This reduced capacity for oxygen transport to the exercising muscle not only reduces the \( V_{O_2 \max} \), anaerobic threshold, and oxygen pulse, but also limits the rate of increase in aerobic ATP regeneration above the LAT (\( \Delta V_{O_2} / \Delta \text{WR} \)). Although abnormalities in these parameters may not specify the etiology of the cardiovascular dysfunction, CAD is the central component in the United States of a broad spectrum of cardiovascular diseases that progress dramatically as age advances. The two groups in this study differed only on the basis of CAC. Therefore, if the prevalence of reduced exercise tolerance and gas exchange abnormalities had been higher in subjects with CAC compared with those without CAC, it would be reasonable to expect a higher prevalence of functionally significant CAD in subjects with CAC. CAD that limits oxygen transport to the exercising muscles has been described as having characteristic ECG and gas exchange abnormalities. Subclinical diseases other than CAD, such as myopathic heart disease, peripheral vascular disease, ventilatory disorders, or anemia, might have reduced the exercise performance in some subjects. However, the prevalence of such subclinical diseases would not have been different between the two groups. None of the subjects had a history of lung disease, and there was no physical evidence of airway dysfunction during exercise.

A subject’s sensitivity to gas exchange abnormalities, when added to ECG recording during exercise testing, is not known. However, maximal exercise capacity would be expected to be reduced if the degree of exercise-induced ischemia is of sufficient magnitude to impair the function of the cardiac pump, even in asymptomatic subjects. Because of limited activity, many elderly persons with flow-limiting CAD do not experience the exertional angina so common in younger patients with the disease. In addition, pain perception sometimes reduces in elderly subjects. Therefore, an “asymptomatic” elderly person may not have a normal exercise capacity. In this study, only one subject with CAC had ST segment depressions at maximal exercise. The prevalence of positive exercise ST segment depression has been reported in 10 to 13% of asymptomatic men. Langou et al reported that the prevalence of positive exercise ST segment depression was 4% in subjects without CAC and 35% in subjects with CAC in asymptomatic middle-aged men. The prevalence of positive exercise ST segment depression in the current study was too low to contrast the two groups.

Our results show no differences in the parameters of oxygen utilization during exercise and in exercise ST segment depression at maximal WR in subjects with densely calcified coronary arteries, compared with subjects without any CAC. In addition, the values for HR, BP, and double product at the maximal WR did not differ between the two groups. The peak double product can be used to characterize cardiovascular performance, and it is reduced in many patients with significant CAD. Thus, this study suggests that CAC, detected by radiologic tech-
niques in asymptomatic elderly subjects, would not be an indication for further evaluation for the presence of CAD and for restricting physical activity.

Fluoroscopic imaging and exercise testing examine different aspects of the same pathologic process. The former assesses anatomy, the latter physiology. It is possible that elderly asymptomatic individuals with coronary calcification may carry an increased mass of atherosclerotic coronary tissue without hemodynamic impairment, even during exercise. Since it is known that plaques, which do not impede flow, can rupture and cause catastrophic events, it is possible that anatomic imaging using radiographic techniques like digital fluoroscopy or electron beam CT may be useful for screening for future catastrophic events.\(^1\)

CAD is common in the elderly and is the most common cause of death in persons older than 65 years of age in the United States.\(^3\) Based on the Framingham Heart Study,\(^4\) more than half of all patients currently hospitalized for an acute myocardial infarction are older than 65.\(^5\) In addition, although overall mortality due to CAD in the United States declined significantly during the 1970s, mortality rates for patients over 65 years of age have not shown the same rate of decline observed in younger patients.\(^6\) For the prevention and the treatment of CAD, diagnostic and therapeutic interventions will be needed, even in elderly asymptomatic subjects. Our results, however, suggest that detection of CAC may have limited value in predicting functional CAD in asymptomatic male subjects over 50 years of age.

**References**