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Influence of Age and Gender on the Presence of Coronary Calcium Detected by Ultrafast Computed Tomography

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Objectives. **This study sought to determine the relation between coronary calcification detected with ultrafast computed tomography and lumen narrowing defined with angiography and evaluated whether this relation is influenced by age and gender.**

Background. **Ultrafast computed tomography has been shown to be a sensitive method for detection of coronary calcification associated with atherosclerotic disease, but the relation between the extent of coronary calcification and degree of lumen narrowing and the possible influence of gender or age, or both, on this relation have not been clarified.**

Methods. **Seventy men and 70 women were studied with ultrafast computed tomography for analysis of coronary calcification and coronary angiography. Coronary atherosclerosis was considered present if any lumen irregularity was noted on angiography, and obstructive coronary artery disease was defined as a lumen diameter narrowing ≥70%.**

Results. **Coronary calcification had a sensitivity of 88% for identification of patients with atherosclerotic disease and 97% for those with obstructive disease, with corresponding specificities of 55% and 41%, respectively. The sensitivity of coronary calcium for detection of atherosclerotic disease in women <60 years old was 50%, significantly less than the 97% sensitivity in women >60 years old and the 87% sensitivity in men <60 years old ($p < 0.05$ for each comparison). Logistic regression analysis revealed a 1.81-fold increase in the likelihood of detecting coronary calcification in the atherosclerotic lesions of men compared with those in women (95% confidence interval 1.12 to 2.93, $p = 0.016$) when controlled for age and severity of coronary disease by angiography.**

Conclusions. **Atherosclerotic lesions in women are less likely to have coronary calcium than lesions with a similar degree of lumen narrowing in men. Differences in the pattern of coronary calcification between men and women may provide insight into the gender differences observed in the clinical development of symptomatic coronary artery disease.**

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Calcific deposits in the coronary arteries are markers of atherosclerotic disease (1–10). Because calcific deposits are radiopaque, numerous radiographic techniques have been used in the search for a noninvasive screening test for coronary artery disease. Cine fluoroscopy of the heart has been utilized to image calcific deposits associated with severe obstructive coronary disease (3,4). More recently, interest in coronary calcification as a marker of atherosclerosis has been stimulated by advances in radiographic imaging that permit increased resolution of vascular calcification. Ultrafast computed tomography, an innovation in tomographic scanning that permits images to be obtained with 3-mm slice thickness and 100-ms acquisition time, has previously been shown (5) to detect coronary calcium with a nearly twofold greater sensitivity than fluoroscopy. The present study was performed to evaluate the utility of ultrafast computed tomography for 1) detection of atherosclerotic coronary artery disease in patients referred for cardiac catheterization, 2) evaluation of the influence of age and gender on the relation between the extent of vascular calcification and severity of atherosclerosis assessed with coronary angiography, and 3) investigation of the relation between the extent of coronary calcification and the incidence of obstructive coronary disease.

Methods

The study cohort included patients who had undergone both an ultrafast computed tomographic examination for coronary calcification and coronary angiography from June 1990 to October 1992. Patients with previous coronary artery bypass surgery were excluded from consideration. Patients were included for analysis if computed tomographic scans were performed within 9 months of catheterization; 90% of patients were scanned within 1 month of catheterization.

Detection of coronary calcium with ultrafast computed tomography. The ultrafast computed tomographic examination was performed with an Imatron C-100 scanner. A scout preview image identified the main stem bronchial bifurcation

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as the starting point for acquisition of 40 transverse 3-mm thick slices to image the entire heart. The acquisition time for each slice was 100 ms gated to 80% of the RR interval. The images were acquired in two sets of 20 axially contiguous 3-mm thick scans. Each set of 20 scans was obtained during maximal inspiration over ~30 s. Images were reconstructed to a 512 × 512-matrix with a 26-cm reconstruction circle.

Measurement of coronary calcium was performed with a densitometric program available on the Imatron scanner. Images were reviewed by an experienced observer for lesions defined as areas of increased density overlying the coronary arteries. A region of interest was placed around each lesion, and the peak density was recorded. In accordance with previously published studies (5,7), calcium was defined as present in pixels where the attenuation equaled or exceeded 130 Hounsfield units (HU). A scaling factor was assigned to the peak pixel attenuation within a lesion as follows: 130 to 199 HU = 1; 200 to 299 HU = 2; 300 to 399 HU = 3; ≥400 HU = 4. A calcium score for each lesion was calculated as the scaling factor multiplied by the area in mm^2 of the lesion. The calcium score for each artery was the sum of scores of all lesions within that artery, and the total calcium score for each patient was the sum of calcium scores of the left main, left anterior descending, circumflex and right coronary arteries. Coronary calcium was considered present when the calcium score was >1.

Coronary angiography. Coronary angiography was performed using standard Judkins or Sones techniques, including multiple views of each coronary artery to visualize the entire distribution of the artery. Each angiogram was reviewed by an experienced angiographer uninformed of the results of the coronary calcium scan. The results of coronary angiography were classified as obstructive for arteries with >70% lesions and as diseased for arteries with any lumen irregularities or stenosis.

Statistical methods. A two-tailed *t* test was performed to test for differences in the mean values of two groups. Contingency analysis was used to evaluate for differences in detection of coronary calcium in subgroups defined by age and gender. Multiple logistic regression was utilized to evaluate the relation among age, gender and coronary atherosclerosis or the presence of coronary calcification in individual arteries. A random effects logistic binomial model accounted for the fact that multiple arteries are grouped within a single patient (11). A probability level of $p \leq 0.05$ was considered significant. Averages are expressed as ±1 SD.

Results

Identification of patients with coronary artery disease using ultrafast computed tomography. The study group included 140 patients (70 men, mean age [±SD] 56 ± 12 years; 70 women, mean age 60 ± 12 years). Forty-two men were <60 years old, and 28 were ≥60 years old. Twenty-nine women were <60 years old, and 41 were ≥60 years old. The women were significantly older ($p < 0.05$).

Table 1. Risk Factor Profile

Risk Factor	Overall	Women	Men	p Value (men vs. women)
Hypertension	53.6%	64.3%	42.8%	<0.05
Diabetes mellitus	24.3%	32.9%	15.7%	<0.05
Smoking	17.9%	15.7%	20.0%	NS
Hyperlipidemia	12.9%	8.6%	17.1%	NS
Family history of CAD	5.7%	4.3%	7.1%	NS

The prevalence of risk factors for coronary atherosclerosis is shown for the entire study group and in groups defined by gender. CAD = coronary artery disease.

Risk factors in the study patients are summarized in Table 1. Overall, there was no significant difference in the average number of risk factors in men (1.3 ± 0.9) compared with women (1.0 ± 1.0). Indications for cardiac catheterization included chest pain (58.8%), evaluation for noncardiac surgery (12.3%), congestive heart failure (12.3%), abnormal exercise test (5.3%), valvular disease (4.4%), evaluation after myocardial infarction (3.5%) and pulmonary hypertension (3.5%). On the basis of an angiographic finding of ≥70% stenosis as the definition of significant coronary artery disease, single-, double- and triple-vessel disease was found in 22 (15.7%), 24 (17.1%) and 13 patients (9.3%), respectively. Overall, the prevalence of an obstructive lesion in this study was 42.8%, and the presence of coronary atherosclerosis (any angiographic evidence of lumen irregularity, stenosis or obstruction) was 70.0%. Average ejection fraction was 63.6 ± 18.0%.

The results are summarized in Table 2. Fifty-eight of 60 patients with obstructive disease (lumen diameter narrowed ≥70%) in at least one artery had coronary calcium. Thirty-three of 80 patients without obstructive disease had no coronary calcium (Table 2). Therefore, the sensitivity for detection of a patient with obstructive coronary disease with coronary calcium was 97%, and the specificity was 41%. When obstructive disease was defined by a stenosis ≥50%, the sensitivity was 96%, and the specificity was 44%.

Eighty-six of 98 patients with angiographic disease (lumen irregularity, stenosis or obstruction) had coronary calcification (Table 2). Twenty-three of 42 patients without angiographic evidence of atherosclerotic disease did not have coronary calcium. Accordingly, the sensitivity and specificity of coronary calcium for detection of atherosclerotic disease on the basis of angiography were 88% and 55%, respectively.

Influence of gender and age on detection of coronary calcium in patients with angiographic disease. To determine whether gender influences the detection of coronary atherosclerotic disease in association with age, coronary calcium detection was evaluated in men and women according to age >60 or <60 years (Fig. 1). The sensitivity of coronary calcium for detection of any evidence of atherosclerotic disease in women <60 years old was 50%, significantly less than the 97% sensitivity in women ≥60 years old and the 87% sensitivity in men <60 years old ($p < 0.05$). The specificity of coronary calcium for detection of any atherosclerotic disease in women

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Table 2. Detection of Atherosclerotic Disease in Patients With Coronary Calcium

	All Pts	Men		Women	
		Age <60 yr	Age ≥60 yr	Age <60 yr	Age ≥60 yr
Obstructive disease					
Sens (%)	97	95	100	75	100
Spec (%)	41	45	15	72	15
PPV (%)	55	61	58	30	55
NPV (%)	94	91	100	95	100
+CAD, +Ca (n)	58	19	15	3	21
+CAD, −Ca (n)	2	1	0	1	0
−CAD, +Ca (n)	47	12	11	7	17
−CAD, −Ca (n)	33	10	2	18	3
Any lumen irregularity					
Sens (%)	88	87	96	50	97
Spec (%)	55	58	33	76	20
PVV (%)	82	84	92	60	79
NPV (%)	66	64	50	68	67
+CAD, +Ca (n)	86	26	24	6	30
+CAD, −Ca (n)	12	4	1	6	1
−CAD, +Ca (n)	19	5	2	4	8
−CAD, −Ca (n)	23	7	1	13	2

Number (n) of patients (Pts) with various thresholds of coronary artery disease (CAD) by detection of coronary calcium (Ca). Lumen irregularity = all degrees of stenosis and obstruction as threshold for detection of disease; Obstructive disease = ≥70% diameter lumen narrowing as threshold for detection of disease. PPV (NPV) = positive (negative) predictive value; Sens = sensitivity; Spec = specificity; + = presence; − = absence.

<60 years old was 76%, significantly greater than the 20% in women ≥60 old ($p < 0.001$) but similar to the 58% specificity in men >60 years old (p = NS).

The sensitivity of coronary calcium for detection of obstructive disease was 75% in women <60 years old (n = 4), 100% in women ≥60 years old and 95% in men <60 years old (p = NS for all comparisons). The specificity of coronary calcium for obstructive disease in women <60 years old was 72%, significantly greater ($p < 0.05$) than the 15% specificity in women ≥60 years old.

Comparison of coronary calcium and angiography on an artery-to-artery basis. The presence or absence of coronary calcium detected by ultrafast computed tomography was compared with the angiographic findings in the same artery of each patient. These results are summarized in Table 3. Overall, the sensitivity was less, and the specificity was greater, for detection of angiographic disease in a given artery than for detection of disease anywhere in the coronary bed.

Influence of gender and age in detection of coronary calcium in the same artery containing angiographic disease. No significant differences were found in the sensitivity or specificity of coronary calcium for the detection of atherosclerotic disease on the basis of gender alone.

To determine whether gender influences the detection of coronary atherosclerotic disease in an artery by artery basis in association with age, coronary calcium detection was evaluated in men and women according to age groups >60 or <60 years

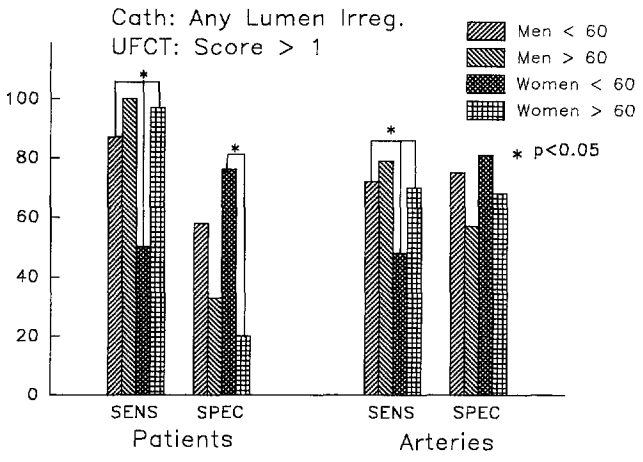

Figure 1. Sensitivity (SENS) and specificity (SPEC) for identification of atherosclerotic disease by detection of coronary calcium in subgroups defined by gender and age. Data are presented separately for detection of disease in patients (calcium anywhere in the coronary tree regardless of the site of angiographic coronary disease) and in arteries (calcium in the same artery that contains the angiographic disease). Detection of coronary calcium in women <60 years old had a lower sensitivity than that in younger men and older women for detection of atherosclerotic disease. Cath = any evidence of atherosclerotic disease found with coronary angiography; Irreg. = irregularities; UFCT = coronary calcification detected with ultrafast computed tomography.

of age (Table 3). The sensitivity of coronary calcium for detection of the particular coronary artery with angiographic disease in women <60 years old was 48%, less than the 70% sensitivity in women ≥60 years old and less than the 72% sensitivity in men <60 years old ($p \leq 0.05$ for both comparisons) (Table 3). The specificity for detection of angiographic disease in arteries of women <60 years old was 81%, similar to

Table 3. Detection of Coronary Arteries With Atherosclerotic Disease in the Same Artery Containing Coronary Calcium

	All Pts	Men		Women	
		Age <60 yr	Age ≥60 yr	Age <60 yr	Age ≥60 yr
Obstructive disease					
Sens (%)	85	82	93	83	82
Spec (%)	63	62	46	78	61
PPV (%)	36	43	35	17	35
NPV (%)	94	91	95	99	93
+CAD, +Ca (n)	94	36	25	5	28
+CAD, −Ca (n)	17	8	2	1	6
−CAD, −Ca (n)	168	47	46	24	51
−CAD, −Ca (n)	281	77	39	86	79
Any lumen irregularity					
Sens (%)	71	72	79	48	70
Spec (%)	72	75	57	81	68
PVV (%)	66	76	70	38	62
NPV (%)	76	71	68	86	75
+CAD, +Ca (n)	173	63	50	11	49
+CAD, −Ca (n)	71	25	13	12	21
−CAD, +Ca (n)	89	20	21	18	30
−CAD, −Ca (n)	227	60	28	75	64

Abbreviations as in Table 2.

Table 4. Logistic Regression Analysis of Variables Associated With Presence of Coronary Calcification

Variable	Odds Ratio	95% CI	p Value
Age (yr)	1.044	1.023–1.066	<0.001
Male gender	1.812	1.119–2.934	0.016
<50% stenosis	2.854	1.679–4.853	<0.001
50–69% stenosis	7.880	3.027–20.51	<0.001
70–89% stenosis	27.18	8.616–85.77	<0.001
90–95% stenosis	18.99	3.786–95.25	<0.001
96–100% stenosis	9.796	4.477–21.44	<0.001

A multiple logistic regression model was constructed with the presence of calcium as a dependent variable and age, male gender and angiographic findings as independent variables. Age, male gender and all grades of angiographic disease were found to influence significantly the likelihood of coronary calcification. CI = confidence interval.

the 68% specificity in women ≥60 years old and the 75% specificity in men <60 years old (p = NS for all comparisons).

To evaluate further the relations among gender, age and coronary disease on the presence of coronary calcification, a multiple logistic regression model was constructed with the presence or absence of coronary calcium as a dependent variable and age, gender and grade of angiographic disease as independent variables (Table 4). In this analysis, the odds ratio of male gender for increasing the likelihood of calcification was 1.81 (95% confidence interval [CI] 1.12 to 2.93, p = 0.016), and the odds ratio for age was 1.04 (95% CI 1.02 to 1.07, p < 0.001). As shown in Table 4, the presence of all grades of angiographic disease increased the likelihood of coronary calcification.

Relation of coronary calcium to the severity of atherosclerotic disease. The relation between the extent of calcification and severity of lumen narrowing (Fig. 2) was significant (chi-square 185.3, p < 0.0001). The percent of arteries with ≥70% stenosis for coronary calcium score ranges is further illustrated in Figure 3. These data show that although an association exists between calcium scores and the incidence of obstructive disease, there is considerable overlap between the calcium score groups. Grouping the calcium score ranges as 0, 1 to 499 and 499+ resulted in a distribution of obstructive disease of 6%, 30% and 58%, respectively, that was significantly associated (chi-square 292, p < 0.0002).

Discussion

Vascular calcification has long been recognized as accompanying coronary atherosclerosis (1–7). Pathologic studies have demonstrated that coronary calcification is a specific marker of the presence of atherosclerotic disease (2,7,8). The radiopaque nature of calcific deposits has fostered interest in radiographic detection of coronary calcification as a method for noninvasive detection of coronary artery disease. Conventional chest X-ray film and fluoroscopy were shown to image vascular calcification of the coronary bed (2–4). However, the clinical utility of these techniques has been limited because of the reduced sensitivity for small calcific deposits associated with coronary atherosclerosis (5).

Detection of coronary calcification with ultrafast computed tomography with 8-mm thick slices was first reported by Tanenbaum et al. in 1989 (6). These initial observations were extended in a larger cohort of patients by Agatston et al. (5), who, with 3-mm thick slices, demonstrated the high sensitivity of coronary calcium for detection of clinical coronary disease and showed an age relation of the sensitivity and specificity using coronary calcification. Simons et al. (7) confirmed the high sensitivity of coronary calcium for detection of obstructive disease in excised hearts that underwent both ultrafast computed tomographic scanning and histopathologic evaluation. The significance of coronary calcification detected with ultrafast computed tomography for identification of atherosclerotic disease in vivo was confirmed by Goel et al. (9) with intracoronary ultrasound; they showed that evidence of atherosclerosis

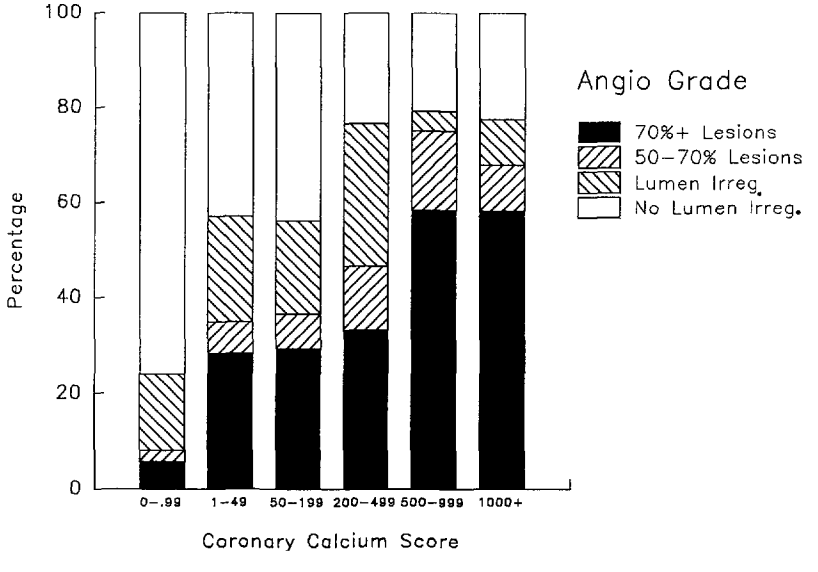

Figure 2. Distribution of angiographic (Angio) disease observed with ranges of coronary calcium scores. Irreg. = irregularities.

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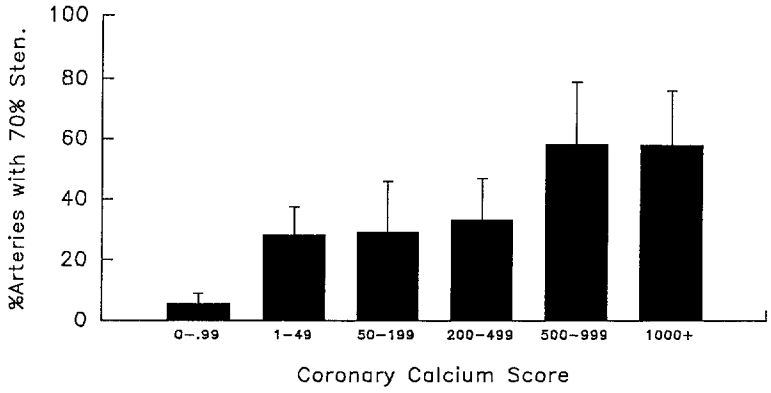

Figure 3. Percent of arteries with various thresholds of coronary calcium scores containing ≥70% stenosis (Sten.). **Error bars** are the upper 95% confidence limits.

is invariably present at the site of calcific plaques identified with ultrafast computed tomography. The present study extends these observations in describing the relation between coronary calcification and the presence and severity of angiographic disease in a gender-balanced study group.

Evaluation of end points for detection of coronary artery disease. The presence and extent of coronary calcification were evaluated against two definitions of coronary disease. The first definition was the presence of any angiographic disease. This broad description, which encompasses the full range of angiographically demonstrable atherosclerotic disease, is an important end point based on mounting evidence that acute ischemic syndromes frequently evolve from nonobstructive atherosclerotic lesions (12). The second definition of coronary disease considered the presence of an obstructive lesion, defined as a coronary artery with a lumen diameter narrowing ≥70%. This definition was used to evaluate the significance of coronary calcification for detection of atherosclerotic lesions which are most likely to evoke myocardial ischemia under conditions of increased myocardial oxygen demand.

Gender differences in detection of coronary artery disease. Although the present study includes a higher percent of women than previous investigations involving ultrafast computed tomography, many findings are consistent with those of other investigators. The conclusions of Breen et al. (10) and Agatston et al. (5) that coronary artery calcification is a sensitive marker for the presence of coronary artery disease and that coronary artery calcium is not highly specific for the presence of an obstructive lesion are confirmed in the present study. Agatston et al. (5) also showed a distinct influence of age on the relation between coronary calcification detected by ultrafast computed tomography and coronary artery disease: Sensitivity improves with age, and specificity declines with age. This study demonstrates that coronary atherosclerosis in men is more likely to be associated with calcification than similarly diseased arteries in women. The finding of an increased likelihood of coronary calcification in men (1.81-fold compared with that in women) is particularly significant in light of the higher prevalence of coronary risk factors and the older age of the women in the study group. We believe that this study is the first to demonstrate the biological phenomenon linking gender and coronary calcification. The influence of gender on coronary calcification appears to impact the ability of ultrafast computed tomography to identify disease in gender-defined groups. However, the actual extent of differences in sensitivity and specificity on the basis of gender needs to be confirmed in larger studies.

Women >60 years old have a calcification pattern indistinguishable from that in men of any age. The finding that younger women have a unique pattern of calcification, which more closely resembles the male pattern only after women reach 60 years of age, raises questions regarding the possible link between coronary calcification patterns and the clinical manifestations of cardiac disease in which gender differences in clinical coronary disease are minimized in the postmenopausal years (13). In a study of asymptomatic subjects, Janowitz et al. (14) concluded that screening for atherosclerotic disease with ultrafast computed tomography might be particularly beneficial in younger women. Our finding of reduced sensitivity in younger women does not support this hypothesis. Furthermore, the reduced sensitivity of coronary calcium to detect angiographic disease in men (35 to 50 years) has recently also been reported (15). These data suggest that evaluation of the utility of coronary calcification with ultrafast computed tomography should be made in the context of gender and age.

A patient with an obstructive coronary lesion is highly likely to have calcification detected somewhere in the coronary tree. However, in many cases, calcium is detected in an artery that does not contain an obstructive lesion, and, conversely, no calcium may be found in an artery with obstructive disease. Accordingly, coronary calcium was evaluated for identification of patients with atherosclerotic disease (calcium in any coronary artery regardless of the site of angiographic disease) as well for identification of the particular artery with atherosclerotic involvement (calcium in the same artery with angiographic disease). These two end points serve distinct and important functions. Identification of patients with atherosclerotic disease, regardless of whether angiographic disease is present at the site of calcium deposition, is the most important end point in screening patients for coronary artery disease. Analysis of the match between calcium and angiographic disease in a particular artery permits a more direct evaluation

of the pathophysiologic links between coronary calcium and angiographically demonstrable atherosclerotic disease.

Diagnostic utility of coronary calcification for detection of atherosclerosis. This study confirms previous work (5,7,10) highlighting the very strong negative predictive value of an ultrafast computed tomographic study for detection of *obstructive* coronary disease, which was 94% in the current study. In contrast, the negative predictive value of a scan for detection of lumen irregularities was only 76%. Therefore, although negative scan results provide strong evidence against the finding of a high grade coronary stenosis, the possibility of coronary atherosclerosis cannot be excluded by the absence of coronary calcification. The implication of these findings on the utility of screening for coronary artery disease with ultrafast computed tomography is dependent on the as yet undetermined prognostic information provided by detection of "lumen irregularities" versus obstructive disease.

The specificity of ultrafast computed tomography for detection of obstructive atherosclerotic coronary disease is low (41% in patients, 63% in arteries), similar to that observed for detection of lumen irregularities on the angiogram indicative of atherosclerotic disease (55% in patients, 72% in arteries). This finding implies that a positive result from coronary calcium screening may have little predictive value with regard to the extent of angiographic coronary disease. This study did find a weak association between the amount of calcium detected and the degree of angiographic disease; however, the relation observed was inadequate for determination of the angiographic severity of disease from the calcium score. In this data set, 6% of arteries without calcium had obstructive disease compared with 30% of arteries with a calcium score of 1 to 500 and 58% of arteries with a score >500. Unfortunately, the range of these calcium scores is very wide and may not be applicable to subgroups of patients defined by age and gender.

Study limitations. The low sensitivity in younger women may be related to the limited resolution available with current scanning methodology. The current technique assumes constant lung volume in successive scans, which results in perfect slicing of the heart by precise ECG gating and 3-mm table movement. This complex procedure may have significant limitations in the detection of small calcium deposits that would be expected early in the atherosclerotic disease process. The possibility exists that the differences in detection of coronary calcium on the basis of gender may be attributed in part to the smaller diameter of coronary arteries and associated plaques in women compared with men.

Our study cohort is a biased group in that most patients were referred for coronary angiography to determine the etiology of a chest pain syndrome or to evaluate suspected coronary disease because of the presence of multiple risk factors or an abnormal exercise test result, or both. Accordingly, the relation between coronary calcification and atherosclerotic coronary disease identified in this study may not apply to the population at large. Evaluation of the diagnostic accuracy of coronary calcium detected with ultrafast computed tomography for detection of angiographically confirmed coronary disease in a truly unselected population is unlikely to be performed because of the ethical issues involved in submitting apparently healthy subjects to the risks of coronary angiography.

Nevertheless, the 42.8% prevalence of obstructive coronary disease observed in this study is comparable to that in other study groups evaluated for noninvasive detection of coronary artery disease. The prevalence of angiographically proved "significant" coronary artery disease in a review of 16 such studies ranged from 30% to 81%, with an average of 60.4 ± 14.3% (16). Additionally, the prevalence of any evidence of atherosclerotic disease in the present study was 70.0%, a value that closely resembles the prevalence of coronary atherosclerosis observed in autopsy studies of a similar age range of patients studied after accidental deaths (17). Confirmation of the present findings of the influence of gender on the detection of coronary disease with ultrafast computed tomography will require additional studies in groups of patients with both a higher and lower prevalence of disease. Furthermore, the occurrence of menopause was not noted in this study, and, therefore, any possible relation between the number of years after menopause and coronary calcium cannot be addressed.

Summary. Our findings demonstrate that patients without evidence of coronary calcification detected by ultrafast computed tomography are highly unlikely to have obstructive coronary artery disease. The high sensitivity of ultrafast computed tomography for detection of obstructive disease holds considerable promise, therefore, as a tool for coronary artery disease screening. However, coronary calcium appears less sensitive for detection of angiographically proved disease in young women than in older women or men of any age. This finding requires further study to determine whether gender-related differences in calcification are related to known gender differences in the clinical manifestation of ischemic heart disease. The potential application of ultrafast computed tomography to screen for coronary artery disease could result in detection of nonobstructive atherosclerotic plaques, which may serve to identify patients in whom risk factor modification may be particularly beneficial.

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